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Poster presentation

Differential effects on HIV replication and T cell activation following direct inhibition of CDK9 or flavopiridol (FVP) treatment in primary peripheral blood lymphocytes

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HIV Tat is a viral transactivator that strongly stimulates the processivity of RNA polymerase II (RNAP II) via recruitment of the cyclin T1/CDK9 transcription elongation factor, which phosphorylates the C-teminal domain of RNAP II and negative elongation factors. We have investigated the effects of limiting CDK9 activity with recombinant lentiviruses expressing a dominant negative form of CDK9 (dnCDK9) in human cells including Peripheral Blood Lymphocytes (PBLs). Our results show that direct inhibition of CDK9 activity potently inhibits HIV replication in single-round infection assays with little to undetectable effects on RNAP II transcription, overall RNA synthesis, proliferation and viability. In PBLs, direct inhibition of CDK9 activity blocks HIV replication but does not prevent T cell activation, as shown by cell surface and cell cycle markers, and DNA synthesis. We have also compared the effects of dnCDK9 to FVP, a general CDK inhibitor that potently inhibits CDK9. In contrast to dnCDK9, FVP interferes with key cellular processes at concentrations that inhibit HIV replication with potency similar to dnCDK9. In particular, FVP inhibits T cell activation markers and DNA synthesis in PBLs at the minimal concentrations required to inhibit HIV-1 replication. Our data supports the notion that FVP affects cellular activities by combinatorial inhibition of various CDKs, including two distinct RNAP II kinases. Our results imply that small pharmacological compounds targeting CDK9 with enhanced selectivity could be developed into effective anti-HIV therapeutic drugs.