

**EFFECTS OF PHARMACOLOGICAL CYCLIN-DEPENDENT KINASE INHIBITORS ON VIRAL TRANSCRIPTION AND REPLICATION**

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Cyclin-dependent kinases (cdk) are required for replication of adeno-, papilloma- and other viruses that replicate only in dividing cells, and surprisingly also for replication of HIV, HSV, and other viruses that can replicate in non-dividing cells [1-3]. Two low-molecular weight pharmacological cdk inhibitors (PCIs), flavopiridol and roscovitine, appear to be non-toxic in human clinical trials against cancer [4-7], and it has been proposed that they may be useful drugs against viruses that replicate in cycling and non-cycling cells. PCIs inhibit cdks by competing with the ATP co-substrate. Purine-type PCIs, such as roscovitine and purvalanol, preferentially inhibit the cdks involved in cell cycle regulation (cdk1-4/6/7) or neuronal functions (cdk5), whereas flavopiridol inhibits cdks involved in cell cycle regulation or in transcription (cdk7/9). Other PCIs, such as T172298, preferentially target cdks involved in transcription [8]. As potential antivirals, PCIs display several advantages: (i) in contrast to antiviral drugs that target viral proteins, PCIs are active against many different viruses including drug-resistant strains of HIV and HSV; (ii) PCI-resistant mutants of HIV or HSV have not been identified despite intensive efforts [2, 3]; and (iii) the antiviral effects of PCIs and conventional antivirals appear to be additive, as expected from drugs targeting independent pathways [9]. For those diseases that include unrestricted cell division and a cdk-requiring virus (e.g. Kaposi's sarcoma, cervical carcinoma, HIV-associated nephropathy [10]), PCIs would thus target both the etiological agent (i.e., the virus) and the pathogenic mechanisms (i.e., unrestricted cell division). This is nicely illustrated in the recent findings of Nelson et al. [10] who have reported the first study on the efficacy of flavopiridol in a mouse model of HIV-associated nephropathy. In this presentation we will review the antiviral properties of the most extensively characterized PCIs, with special emphasis on the mechanisms of inhibition of viral transcription.

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