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Hydroxyurea Inhibits HIV-1 Replication by Inducing Low dNTP Levels. A Cellular Enzyme as a Target to Inhibit HIV-1.

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Incomplete viral DNA originating from reverse transcription before or during virus budding is encapsidated into mature HIV-1 virions. Here we show that the virion associated DNA contributed to the formation of an early pool of incomplete latent viral DNA in infected primary lymphocytes, suggesting that carrying preformed DNA could be advantageous for HIV-1 latency during infection of quiescent cells. This DNA is completed extremely slowly and inefficiently in quiescent PBL compared to that in stimulated PBL. We demonstrate here that this phenomenon is caused by the existence of lower levels of deoxynucleotides (dNTP) in quiescent compared to activated PBL impairing the HIV-1 reverse transcriptase activity. Hydroxyurea, a widely used drug in human therapy, by inhibiting the cellular enzyme ribonucleotide reductase decreases the levels of dNTP in stimulated PBL and reduces DNA synthesis rate as well as DNA elongation to levels comparable to quiescent PBL. At concentrations commonly used in human therapy, hydroxyurea inhibits HIV-1 replication in primary human PBL and macrophages and acts synergistically in combination with the nucleoside analogs AZT and ddI. Our data therefore indicate that low levels of dNTP may explain why HIV-1 DNA is synthesized slowly and inefficiently in quiescent PBL and suggest that pharmacologic induction of low dNTP levels represents a novel therapeutic approach for inhibition of HIV-1 replication.

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Uveitis In Prototype AIDS Vaccines Using SIV

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Development of adjuvants capable of producing more potent immune responses without adverse side effects is crucial to the development of protein–direct vaccines. In a study conducted at the TRPRC, nine experimental adjuvants were evaluated in combination with inactivated whole SIV. Ocular examination was performed on these animals to identify adverse side effects (if any) of these vaccines following both immunization and challenge with live SIV. No significant intraocular inflammation was detected following any immunization except in groups that received vaccinia–env recombinant preparations. Following SIV–challenge however, uveitis was observed in some animals immunized with one of three adjuvant preparations: Complete Freund's Adjuvant (CFA), initially, with subsequent booster immunizations given in Incomplete Freund's Adjuvant (IFA), threonyl muramyl dipeptide (tMDP) formulated with Incomplete Freund's Adjuvant (IFA), and L310 + detoxified RaLPS. The results in these assessments are as follows:

	Animals with Uveitis	Duration	Intensity
Vaccinia-recomb.	8/16	2 weeks	Mild
CFA	1/8	2 weeks	Mild
tMDP–GDP + IFA	5/8	3-4 weeks	Mild – Moderate
L310 + detoxified RaLPS	1/8	5 weeks	Moderate

Appearance of uveitis correlated temporally with systemic signs of pneumonitis, dyspnea, fever, glomerulosclerosis and skin erythema (redness) following challenge in monkeys immunized with tMDP–GDP + IFA. In each case, the appearance of uveitis was predictive of lack of protective immunity.