

## HIGHLY POTENT *IN VIVO* ACTIVITY OF QD ADMINISTRATION OF 4'-ETHYNYL-2-FLUORO DEOXYADENOSINE IN SIV-INFECTED RHESUS MACAQUES

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4'-Ethynyl-2-fluoro deoxyadenosine (EFdA) is a nucleoside that possesses a 3'-hydroxyl moiety, yet functions as a terminator of HIV DNA synthesis due to a novel mechanism of action not exhibited by any of the current clinically used nucleoside analog inhibitors, hindrance of nucleic acid translocation following incorporation. While EFdA is an exceptionally potent inhibitor of HIV replication in human PBMCs and SIV replication in monkey PBMCs ( $EC_{50} = 50$  pM), the antiviral efficacy of EFdA in non-human primate models for HIV infection was unknown. We therefore carried out a pilot study in two male SIV-infected rhesus macaques, both presenting with end stage SIV-induced AIDS (SAIDS; chronic unresolved diarrhea, loss of >20% body weight, persistent high plasma viral loads, constant dehydration). Both animals had previously been treated with PMPA (20 mg/kg, s.c., QD); only one animal responded to this treatment. Both animals had been off drug treatment for 2 years prior to initiation of EFdA treatment (2 mg/kg, s.c., QD). Animals received regular physical examinations, and blood samples were taken at regular intervals to determine plasma SIV viral loads and liver enzyme panels (to assess possible hepatotoxicity). EFdA treatment resulted in 2-3 log decreases in plasma SIV in both animals within 7 days of treatment; these levels declined to undetectable (5-log reduction) within 2 months of treatment. SAIDS symptoms (diarrhea, dehydration) resolved within 1 month. The animals showed steady weight gain and retained normal liver enzyme levels throughout the course of EFdA treatment (up to 6 months). One animal was sacrificed after 3 months of treatment due to respiratory distress unrelated to drug treatment. SIV RNA was undetectable in most tissues and only low levels (< 100 copies) were noted in a few CD4+ T-cell rich lymph nodes, suggesting that EFdA treatment was able to clear SIV from many tissue reservoirs despite the short drug treatment. Such dramatic clearance was not noted in the second animal as plasma SIV levels rebounded following cessation of EFdA treatment. This pilot study shows that EFdA is safe and very effective in reducing plasma virus load and in resolving SAIDS symptoms. More extensive studies are warranted.

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