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## MECHANISM OF ANTI-HIV ACTIVITY OF D4-NUCLEOSIDE ANALOGUES AGAINST ZIDOVUDINE- AND LAMIVUDINE-RESISTANT HIV-1 MUTANTS: MOLECULAR MODELLING STUDIES

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Frequent drug-resistant mutation of HIV-1 reverse transcriptase (RT) presents a major challenge in the treatment of HIV patients because initially potent drugs lose their efficacy over time. While there is an urgent need for a comprehensive understanding of the molecular mechanism of drug resistance, limited detailed structural information of the mutant RTs has prevented investigation to delineate the mechanism. The work that will be presented includes molecular modelling studies of mutant RTs (zidovudine-resistant: M41L/D67N/K70R/T215Y and lamivudine-resistant: M184V) based on the wild-type RT structure published by Harrison's group ([Science. 1998 Nov 27;282\(5394\):1669-75.](#)) Zidovudine-TP, lamivudine-TP, DXG-TP, D-2'-F-d4C-TP, L-2'-F-d4C-TP, D-2'-F-4'-Sd4C-TP and L-2'-F-4'-Sd4C-TP were docked into the mutant RT so that the differential effects of mutations on different nucleotide analogues could be examined at the atomic level using the energy-minimized 3D-structure of RT-inhibitor complexes. From these studies, the antiviral activity of DXG/DAPD against zidovudine – as well as lamivudine-resistant RTs – could be explained based on the characteristic of a D-dioxolane moiety. The dioxolane moiety did not clash with the Val184 in M184V RT, but allowed stabilizing interaction with the active site residues, such as Tyr115 and Arg72 in zidovudine and lamivudine-resistant RTs. The stable orientations of D- & L-2',3'-unsaturated nucleosides (d4Ns) at the active site of the wild-type RT maintain through the extensive hydrogen bonding by Arg72 as well as the pi-pi interaction between 2',3'-unsaturated bond of the sugar moiety and the aromatic side chain of Tyr115. In lamivudine-resistant mutant RT (M184V), L-d4Ns could not be located at the active site without steric clash with the bulky Val184, which is consistent with the broad cross-resistance of this mutant RT against the unnatural L- nucleosides. In contrast, the M184V did not affect the binding affinity of the natural D-configured d4N such as D-2'-Fd4C-

TP, which may be one of the reasons for the potent antiviral activity of D-2'-F-d4C-TP against the lamivudine-resistant RT. However, the isosteric replacement of 4'-oxygen of D-2'-F-d4CTP to 4'-sulfur provided cross-resistance with M184V RT. In comparison to D-2'-F-d4CTP, the large van der Waals radius of the 4'-sulfur atom as well as longer C-S bond length of D-2'-F-4'-Sd4CTP results in a steric hindrance with Val184, which destabilized the resulting complex.

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