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EFdA, a supremely excellent anti-HIV active nucleoside: Design, synthesis and biological evaluation

Highly Active Anti-Retroviral Therapy (HAART) has made HIV infection from fatal to clinically tractable lifelong infectious disease. However, the emergence of resistant HIV mutants and the adverse effects of drugs are still critical problems to solve. EFdA which could solve these problems was developed by us. I will like discuss a general idea based on the mutation of viruses that it is possible to develop nucleosides which are active to viruses and not toxic to human beings, the working hypotheses for designing nucleoside which could solve the above problems, the efforts for the better syntheses of EFdA and the biological evaluation of EFdA by Dr. H. Mitsuya and other groups and the clinical trials (phase 1 and 1b) reported by Merck Sharp & Dohme. On the basis of the general idea and the working hypotheses, 4'-C-substituted-2'-deoxynucleoside (4'SdN) was designed as the nucleoside which could prevent the emergence of resistant HIV mutant and could be stable in plasma. The method to decrease the toxicity of nucleoside that the additional modification of a toxic nucleoside could decrease the toxicity of the nucleoside will be also discussed. Finally, EFdA was designed and synthesized by our constant efforts on the syntheses and biological evaluation of 4'SdN. The details of the general idea, the working hypotheses, the syntheses of EFdA and the biological evaluation of EFdA will be discussed. The extensive studies on 4'SdN have successfully developed EFdA. EFdA has prevented the emergence of resistant HIV mutants more than ten years and is over 400 times more active than AZT and several orders of magnitude more active than the other clinical drugs and stable in plasma and lowly toxic. The clinical trials by Merck Sharp & Dohme have shown that EFdA is efficiently absorbed by both oral and parenteral administration and converted to 5'-O-triphosphate (EFdA-TP) promptly, EFdA-TP is very stable in human PMMCs and the half life of EFdA-TP is over 100 hours and further, once a week dosing of 10 mg of EFdA is efficacious. Thus, EFdA is a very promising anti-HIV drug which could open a new paradigm in the anti-retroviral therapy.

Biography

Hiroshi Ohrui has received his PhD degree in 1971 from The University of Tokyo, Japan. He has joined RIKEN in 1966, moved to Tohoku University in 1981 and then to Yokohama University of Pharmacy in 2006. His interest covers organic synthesis, chemical biology and chiral discrimination.

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