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EFdA: A very excellent anti-HIV modified nucleosides - from design to the current results of clinical trials

4'-C-Ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) is attracting much attention due to its extremely excellent anti-HIV activity and physiological properties. EFdA prevents the emergence of resistant HIV mutants, is over 400 times more active than AZT and several orders of magnitude more active than the other clinical reverse-transcriptase inhibitor y 2', 3'-dideoxynucleoside drugs, very low toxic, very long acting, and very useful for prophylaxis. EFdA is now under clinical trialsby Merck & Co. as MK-8591. In the beginning, a general idea for the development of anti-viral modified nucleosides is presented, and next, the development of EFdA is discussed and then the current results of the clinical trials reported by Merck will be presented. For the design of the modified nucleoside which could solve the critical problems that the clinical drugs have (emergence of drug-resistant HIV mutants, adverse effect by drugs, necessity to take consirerble amount of drugs), four working hypotheses were proposed . They are (1) the way to prevent the emergence of drug-resistant HIV mutants, (2) the way to decrease the toxicity of modified nucleosides, (3) the way to provide the modified nucleoside with stability to both enzymatic and acidic glycolysis for long acting, and (4) it is possible to develop selectively active to HIV and very low toxic to human based on the difference of the substrate selectivity between HIV and human nucleic acid polymerses (cf; the general idea). 4'-C-substituted-2'-deoxy nucleoside (4'SdN) was designed based on the hypotheses (1 and 3), and the additional modification of 4'SdN was performed based on the hypothesis (2). The details of the all hypotheses will be discussed. To prevent the deamination of adenine by adenosine deaminase, a fluorine atom was introduced at the 2-position of adenine. Finally, EFdA, modified at the two position (2 and 4') of the physiologic 2'-deoxyadenosine and has extremely excellent anti-HIV activity, was successfully developed.

Biography

Hiroshi Ohrui received PhD Degree (1971) from The University of Tokyo. He joined Riken (1966), moved to Tohoku University (1981) and to Yokohama University of Pharmacy (2006). He worked for Dr. J. J. Fox at Sloan-Kettering Institute for Cancer Research (1972-1973) and Dr. J. G. Moffatt at Syntex Research (1973-1974). He received several awards including The Japan Society for Analytical Chemistry Award (2004), and Japan Academy Prize (2010). His research interests cover organic synthesis, chemical biology and chiral discrimination.

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