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Hiroshi Ohrui

Yokohama University of Pharmacy, Japan

EFdA: An extremely excellent anti-HIV nucleoside from design to the current clinical trials results

4'-C-Ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) has attracted much attention due to its extremely excellent anti-HIV activity; prevent the emergence of resistant HIV mutants, over 400 times more active than AZT and several orders of magnitude more active than the other clinical reverse-transcriptase inhibitor 2',3'-dideoxynucleoside drugs, very low toxic, long acting, could be used for prophylaxis, and so on. EFdA is now under clinical investigation as MK-8591 by Merck & Co. General idea for the development of anti-viral nucleoside based on the mutation of viruses and the development of EFdA, especially the design of it, will be presented and discussed. For the design of the modified nucleoside which could solve the problems the clinical drugs have: (1) Emergence of drug-resistant HIV-mutants, (2) Adverse effects by drugs, and (3) Necessary to take plenty amount of drugs. The following working hypotheses to solve the problems were proposed: (1) The way to prevent the emergence of resistant HIV mutants, (2) The way to decrease the toxicity of modified nucleosides, and (3) The way to provide the nucleoside with the stability to both enzymatic and acidic hydrolysis of nucleobase for long acting. 4'-C-substituted-2'-deoxynucleoside was designed to meet the hypotheses (1), (3) and the two-site-modification was conducted to meet the hypothesis (2). The details of the hypotheses and the reason of the 4'-C-substitution will be discussed. To prevent the deamination of adenine base, fluorine atom was introduced at the 2-position of adenine base. Finally, EFdA which is modified at the two position of the physiologic 2'-deoxyadenosine and has extremely excellent anti-HIV properties been successfully developed.

Biography

Hiroshi Ohrui has received his PhD degree (1971) from The University of Tokyo, Japan. He has Joined RIKEN (1966) and moved to Tokyo University (1981) and then to Yokohama University of Pharmacy (2006). He has 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 has received several awards including Inoue Prize for Science (2001), Japan Prize for Agricultural Sciences (2004), The Japan Society for Analytical Chemistry Award (2004) and Japan Academy Prize (2010). His research interests cover organic synthesis, chemical biology and chiral discrimination.

h.ohrui@hamayaku.ac.jp

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