An extremely excellent anti-HIV active modified nucleoside, EFdA-focused on its design

Hiroshi Ohrui
Yokohama University of Pharmacy, Japan

4'-C-Ethynyl-2-fluoro-2'-deoxyadenosine (EFdA) has attracted much attention due to its extremely excellent anti-HIV properties: (1) prevent the emergence of resistant HIV mutants, (2) over 400 times more active than AZT and several orders of magnitude more active than the other clinical reverse-transcriptase inhibitor 2', 3'-dideoxy-nucleoside drugs, (3) very low toxic, (4) long acting, (5) possible use for prophylaxis and so on. EFdA is now under clinical trials as MK-8591 by Merck & Co. For the design of the modified nucleoside which could solve the problems that the clinical drugs have: (1) emergence of drug-resistant HIV mutants, (2) adverse effect by drugs and 3) necessity of taking quite a few number of drugs. I have proposed the following working hypotheses. 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. 4'-C-substituted-2'-deoxy nucleoside was designed to meet the hypotheses 1, 3 and the two-site modification was performed to meet the hypothesis 2. The details of the hypothesis and the reasons of the design of 4'-C-substituted-2'-deoxy nucleoside will be presented. 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 positions (2 and 4') of the physiologic 2'-deoxyadenosine and has extremely excellent anti-HIV properties has been successfully developed.

Biography

Hiroshi Ohrui has received his PhD degree from The University of Tokyo, Japan. He has worked for Dr. J J Fox at Sloan-Kettering Institute for Cancer Research and Dr. J G Moffatt at Syntex Research. He has received several awards including Inoue Prize for Science in 2001, Japan Prize for Agricultural Sciences in 2004, The Japan Society for Analytical Chemistry Award 2004 and Japan Academy Prize in 2010. His research interests cover organic synthesis, chemical biology and chiral discrimination.

choish@snu.ac.kr