Development of extremely excellent anti-HIV active EFdA, focused on the design

4'-C-Ethynl-2'- uoro-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'-dideoxynucleoside drugs 3. very low toxic 4. long acting 5. could be used for prophylaxis, and so on). EFdA is now under clinical investigation as MK-8591 by Merck & Co. In my talk, the development of EFdA, especially the design of it will be presented and discussed. For the design of th modi ed nucleoside which could solve the problems (1. emergence of drug-resistant HIV-mutants. 2. adverse e ects by drugs. 3. necessary to take plenty number of drugs) that the clinical drugs have, I have proposed the following working hypotheses t solve the problems. ey are: (1) the way to prevent the emergence of resistant HIV mutants, (2) the way to decrease the toxicity of modi ed nucleosides, (3) the way to provide the nucleoside with the stability to both enzymatic and acidic hydrolysis of nucleobase. 4'-C-substituted-2'-deoxynucleoside was designed to meet the hypotheses (1), (3) and the 2-site-modi cation wa conducted to meet the hypothesis (2). e details of the hypotheses and the reason of the 4'-C-substitution will be discussed. To prevent the deamination of adenine base, uorine atom was introduced at the 2-position of adenine base. Finally, EFdA