

Novel 4'-Substituted Stavudine Analog with Improved Anti-Human Immunodeficiency Virus Activity and Decreased Cytotoxicity

Ginger E. Dutschman,¹ Susan P. Grill,¹ Elizabeth A. Gullen,¹ Kazuhiro Haraguchi,²
Shingo Takeda,² Hiromichi Tanaka,² Masanori Baba,³ and Yung-Chi Cheng^{1*}

Department of Pharmacology, School of Medicine, Yale University, New Haven, Connecticut 06520,¹ and School of Pharmaceutical Sciences, Showa University, Tokyo 142-8555,² and Center for Chronic Viral Diseases, Division of Antiviral Chemotherapy, Faculty of Medicine, Kagoshima University, Kagoshima 890-8520,³ Japan

Received 28 October 2003/Returned for modification 18 December 2003/Accepted 3 February 2004

The antiviral drug 2',3'-didehydro-3'-deoxythymidine (D4T; also known as stavudine and Zerit), which is used against human immunodeficiency virus (HIV), causes delayed toxicity (peripheral neuropathy) in long-term use. After examining a series of 2',3'-didehydro-3'-deoxy-4'-substituted thymidine (4'-substituted D4T) analogs, 4'-ethynyl D4T was found to have a fivefold-better antiviral effect and to cause less cellular and mitochondrial toxicity than D4T. The antiviral activity of this compound can be reversed by dThd but not by dCyd. The compound acted synergistically with β -L-2',3'-deoxy-3'-thiacytidine (also known as lamivudine) and β -L-2',3'-dideoxy-2',3'-didehydro-5-fluorocytidine (also known as elvucitabine) and additively with 2',3'-dideoxyinosine (also known as didanosine and Videx) and 3'-azido-3'-deoxythymidine (also known as Retrovir and zidovudine) against HIV. 4'-Ethynyl D4T is phosphorylated by purified human thymidine kinase 1 (TK-1) from CEM cells with a faster relative V_{max} and a lower K_m value than D4T. The efficiency of TK-1 in the phosphorylation of 4'-ethynyl D4T is fourfold better than that of D4T. While D4T is broken down by the catabolic enzyme thymidine phosphorylase, the level of breakdown of 4'-ethynyl D4T was below detection. Since 4'-ethynyl D4T has increased anti-HIV activity and decreased toxicity and interacts favorably with other currently used anti-HIV drugs, it should be considered for further development as an anti-HIV drug.
