Keynote Address

Beautiful Biology But Bad Chemistry: Recognizing Chemistry Problems Earlier Rather Than Later

Christopher Lipinski, Ph.D.

Melior Discovery, Waterford CT, USA

doi:10.1016/j.antiviral.2009.02.014

Oral Session 1: Mini-Symposium: Development of Novel Therapies for Hepatitis C Virus (HCV): Continuing the Fight

8

HCV and the Immune Response

Stan Lemon, Ph.D.

University of Texas Medical Branch, Galveston, TX, USA

doi:10.1016/j.antiviral.2009.02.015

9

The Complexities of Hepatitis C Virus Entry

Jane McKeating, Ph.D.

University of Birmingham, United Kingdom

doi:10.1016/j.antiviral.2009.02.016

10

Targeting Hepatitis C Virus NS2—An Unusual Protease with Multiple Functions

Thomas Pietschmann, Ph.D.

TWINCORE-Center for Experimental and Clinical Infection Research, Hannover, Germany

doi:10.1016/j.antiviral.2009.02.017

11

New Methods to Identify and Analyze HCV Helicase Inhibitors

David Frick, Ph.D.

New York Medical College, Valhalla, NY, USA

doi:10.1016/j.antiviral.2009.02.018

12

New Targets within Hepatitis C Virus NS4B

Jeffrey Glenn, Ph.D.

Stanford University School of Medicine, Stanford, CA, USA

doi:10.1016/j.antiviral.2009.02.019

13

The Hepatitis C Virus NS5A: New Functions and New Mysteries

Tim Tellinghuisen, Ph.D.

The Scripps Research Institute, Jupiter, FL, USA

doi:10.1016/j.antiviral.2009.02.020

Oral Session 2: Hepatitis Viruses

16

2′-Deoxy-nucleoside Analogs can be Potent Dual Inhibitors of HCV and HIV Replication with Selectivity against Human Polymerases

Klaus Klumpp[1,*], Guoping Su[1,2], Vincent Leveque[1], Jerome Deval[1], Gabrielle Heilek[1], Sonal Rajyaguru[1], Yu Li[1], Julie Q. Hang[1], Han Ma[1], Nicole Inocencio[1], Genadiy Kalayanov[3], Anna Winqvist[3], David B. Smith[1], Nick Cammack[1], Nils Gunnar Johansson[3], Isabel Najera[1]

[1] *Roche, Palo Alto, USA;* [2] *Rigel, South San Francisco, USA;* [3] *Medivir, Huddinge, Sweden*

Background: HCV polymerase and HIV reverse transcriptase (RT) can both accept modified deoxynucleoside analogs as substrates. Nucleoside analogs may be designed that inhibit both enzymes, while retaining selectivity against human RNA and DNA polymerases. Such compounds may provide specific benefit in HCV/HIV co-infected persons by reducing the overall drug burden in combination therapies.

Methods: Nucleoside analogs were tested for antiviral activity and cytotoxicity using Con1 HCV subgenomic replicon, HXB2 HIV-1, and Dengue virus replication assays. Nucleoside triphosphate analogs were tested as inhibitors of viral and human RNA and DNA polymerases including HCV NS5B, Dengue and West Nile virus NS5, HIV-1 reverse transcriptase, CMV DNA polymerase and human mitochondrial DNA polymerase gamma.

Results: Novel cytidine analogs with superior anti-HIV potency as compared to reference compounds 3TC ($IC_{50} = 2.5 \pm 1.2\ \mu M$), FTC ($IC_{50} = 0.43 \pm 0.17\ \mu M$) and AZT ($IC_{50} = 0.095 \pm 0.028\ \mu M$) were identified. The most potent compound RO-0622 inhibited HCV replicon replication ($IC_{50} = 24 \pm 3.0\ nM$) and was thus ~50-fold more potent than R1479 (4′-azido-cytidine). RO-0622 inhibited HIV-1 replication in MT-4 cells with an antiviral IC_{50} of $0.4 \pm 0.1\ nM$, and was therefore more than 6000-fold more potent than 3TC. RO-9187 also inhibited both HCV ($IC_{50} = 171 \pm 12\ nM$) and HIV-1 replication ($IC_{50} = 49 \pm 27\ nM$). Both compounds were not cytotoxic or cytostatic in HCV replicon cells and protected HIV-1 infected cells from HIV-induced cell death. The corresponding nucleoside triphosphates were competitive inhibitors of HCV and HIV polymerases, but were highly selective against human polymerases as well as other viral polymerases, consistent with low toxicity in cell culture.

Conclusions: Novel nucleosides have been identified that can inhibit both HCV and HIV replication with higher potency as compared to reference compounds 3TC, FTC, AZT or R1479, while retaining selectivity against human and other viral polymerases.

doi:10.1016/j.antiviral.2009.02.021