

Current Topics in Microbiology and Immunology

Volume 389

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The Future of HIV-1 Therapeutics

Resistance Is Futile?

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ISSN 0070-217X ISSN 2196-9965 (electronic)
Current Topics in Microbiology and Immunology
ISBN 978-3-319-18517-0 ISBN 978-3-319-18518-7 (eBook)
DOI 10.1007/978-3-319-18518-7

Library of Congress Control Number: 2015937951

Springer Cham Heidelberg New York Dordrecht London
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Printed on acid-free paper

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Preface



HIV and Antibodies. In this cross-section, HIV is shown at lower right, with viral proteins in red and magenta, and viral RNA in yellow. Blood plasma is shown at the top and left side. Several broadly neutralizing antibodies (*A*), are binding to HIV envelope glycoprotein (*B*). Other viral proteins include matrix (*C*), capsid (*D*), reverse transcriptase (*E*), integrase (*F*), protease (*G*), Vif (*H*), and Tat (*I*)

The development of antiretroviral drugs and the implementation of combination antiretroviral therapy for the treatment of human immunodeficiency virus type 1 (HIV-1) ranks as one of the great success stories of clinical management of an infectious disease. Treatment with highly active retroviral therapy has altered the disease course in millions of individuals from a death due to acquired immunodeficiency syndrome (AIDS) to one of managed care. Since the epidemic was first reported in 1981, approximately 78 million people worldwide have been infected with HIV-1, with an estimated 39 million deaths occurring.¹ Increased access to antiretroviral therapy, combined with a declining incidence of HIV-1 infection, has resulted globally in a significant drop in the number of adults and children dying from HIV-related causes. WHO has estimated that antiretroviral therapy programs have averted ~7.6 million deaths between 1995–2013.²

The number of drugs approved for antiretroviral use since the introduction of zidovudine (AZT) in 1987 has blossomed to include 30 individual drugs and at least 8 fixed-dose combination antiretroviral therapies (See Chapter “[HIV Therapy—The State of ART](#)”). The approved drugs target just four viral proteins, protease, integrase, reverse transcriptase, and gp41, and the host chemokine receptor, CCR5, used by the virus to enter cells. The use of combination antiretroviral therapy with drugs targeting distinct viral pathways reduces the chance of selecting for mutations that confer resistance to any single treatment. Current combination therapies can control HIV-1 for extended periods, allowing life expectancies to approach that of uninfected individuals. However, these therapies will not lead to viral eradication, as the virus can be maintained in reservoirs that are not susceptible to current treatment. Combination therapies are expensive and compliance can be difficult; viral drug resistance does occur and is higher in resource-limited areas. Furthermore, drug-resistant viruses can be transmitted creating further complications for treatment and reducing the chances of effective treatment. Therefore, new antiretrovirals are needed that target different viral components as well as protease, integrase, or reverse transcriptase in a novel fashion.

The development of novel chemistries and methods for small molecule screening has coincided with an increased knowledge of HIV-1 biology and viral protein structures, prompting a renewed effort to identify the next generation of compounds that target old and new viral targets. In this edition of *Current Topics in Immunology and Microbiology*, each author has taken the challenge to discuss what may be new on the horizon for antiretrovirals; this has resulted in a review series that is both timely and informative. A common theme that emerges throughout Chapters “[Nucleocapsid Protein: A Desirable Target for Future Therapies Against HIV-1](#)” to “[The Triple Threat of HIV-1 Protease Inhibitors](#)” is that by focusing on the disruption of multiple discrete viral pathways, we can provide more effective therapy that is less prone to the development of antiretroviral resistance. The understanding of how viral components interact with each other, host cell

¹http://www.who.int/gho/hiv/epidemic_status/deaths_text/en

²http://www.who.int/gho/hiv/epidemic_status/deaths_text/en

components, and small molecule inhibitors, strongly relies on structure-based modeling. The computational challenges of structure-based modeling for providing a molecular understanding of viral components interacting with inhibitors, as well as insights into antiretroviral resistance, is presented in Chapter “[Computational Challenges of Structure-Based Approaches Applied to HIV](#)”. Lastly, for each chapter an illustration is provided for the viral component discussed in an attempt to integrate what is known from structural biology, electron microscopy, and biophysical studies with the goal of providing a view of the macromolecular structure of HIV in its cellular environment. To produce each illustration required an in-depth analysis of the available literature, which is discussed in Chapter “[Illustrations of the HIV Life Cycle](#)”. Together, the assembled reviews in this edition of Current Topics in Microbiology and Immunology chart the horizon of HIV-1 antiretroviral research. We would like to thank the authors for their contributions of timely and insightful reviews and patience throughout the writing of this issue. Special thanks to Andrea Schlitzberger, Ph.D., for her editorial insights and patience.

Bruce E. Torbett
David S. Goodsell
Douglas D. Richman

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