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# *Successful Strategies for the Discovery of Antiviral Drugs*

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# *Preface*

Viruses are obligate parasites that enter and reproduce within the cells of their host, so their life cycle relies upon forming an intimate partnership and dependency. For many viruses, such as influenza and respiratory syncytial virus (RSV), this relationship is temporary in nature and self-limiting. However, some viruses, including human immunodeficiency virus (HIV, >35 million people infected worldwide), hepatitis B virus (HBV, >400 million people infected) and hepatitis C virus (HCV, >150 million people infected), cause persistent infections and the virus never leaves the host. Such a long-term association is detrimental to the wellbeing of infected cells, the functions of the organ they infect and, ultimately, the overall health of the host.

The central hypothesis to medical intervention for the treatment of viral diseases is to prevent the spread of a virus to uninfected cells by blocking viral replication, helping the host to control infection. The approval of the nucleoside analog acyclovir for the treatment of herpes simplex virus (HSV) infection in 1978 was a key event in the history of antiviral drug discovery and development, setting the standard for a selective and effective therapeutic that is now available over-the-counter. Oral antiviral agents of this type offer a practical, convenient and rapid means of intervening with virus replication, and over the last 30 years over 50 drugs have been licensed for marketing. In addition, in 2012 alone there were >100 industry-sponsored Phase 3 trials currently registered at ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

The demand for antiviral agents has been driven by the HIV-1 epidemic, a virus that continues to present a significant challenge, and the large number of worldwide HBV and HCV infections, all of which contribute to an ever-increasing morbidity and mortality in those unfortunate enough to host these infectious agents. Although HIV-1 and HBV infections have proven extremely difficult to cure, the RNA-based life cycle of HCV is currently susceptible to curative intervention with combinations of pegylated interferon- $\alpha$ , ribavirin

and a protease inhibitor. However, recent clinical studies have clearly indicated the potential for combinations of small-molecule, direct-acting antiviral agents that selectively and effectively target viral proteins to effect cures with as little as 12 weeks of therapy. Consequently, there is a growing belief that HCV infection will be the first chronic viral infection to be cured by small molecules. For HIV-1 infection, the launch of Atripla<sup>®</sup>, a combination of the nucleoside phosphonate prodrug tenofovir disoproxil, the nucleoside analog emtricitabine and the non-nucleoside reverse transcriptase inhibitor efavirenz, by the collaborative effort of Gilead Sciences and Bristol-Myers Squibb, represented a watershed in the treatment of this disease by providing a convenient, fixed-dose combination taken once a day that effectively controls viral replication.

The focus of this book is to summarize successful strategies for the discovery and development of antiviral agents into clinically relevant therapeutic agents. The book is organized according to the strategies deployed both to discover and to optimize lead compounds. Section I provides an overview of drug discovery programs that span HCV, RSV, dengue virus and pox viruses and that owe their origin to a robust *in vitro* cell culture system used both to identify lead inhibitors using high-throughput screens and to optimize molecules for potency and selectivity. This kind of chemical genomics screening paradigm has proven to be a highly successful strategy for the discovery of mechanistically interesting antiviral agents, many of which could not be discovered using biochemical assays. By applying selective pressure to viruses grown in cell culture with repeated rounds of replication (passaging) in the presence of increasing concentrations of lead inhibitors, resistant viruses can be isolated and their genomes sequenced for mutations that usually afford insight into the mode of action of a lead inhibitor.

Biochemical screens are an equally important source of leads, a strategy of particular importance in the early days of HCV drug discovery where the enzymatic activities of the NS3 protease and NS5B polymerase could be recapitulated *in vitro* and used to assay compound collections using high-throughput screening methodology. Lead optimization campaigns were subsequently facilitated by structure-based drug design since these proteins were crystallized with inhibitors bound. Section II provides examples of the application of these contemporary technologies that rely upon biochemical screening and structure-based optimization strategies for the discovery of potent and selective antiviral agents for the treatment of HIV-1 and HCV and nicely illustrate the evolution of modern medicinal chemistry technology. Section III includes some of the recent mechanistic approaches that take advantage of host-viral interactions for the treatment of HCV that could be complementary to direct-acting oral antivirals. Finally, the delivery of antiviral agents can present significant challenges and Section IV highlights the development and application of strategies that can be deployed to facilitate oral absorption of nucleosides or the systemic delivery of an entire therapeutic regimen that improves compliance.

The objective of this book is to capture tactical aspects of problem solving in antiviral drug design and development, an approach that not only holds special

appeal for those engaged in the antiviral research, but will also be instructive to the broader medicinal chemistry community.

As we compose this Preface in January 2013, we note the passing in 2012 of two chemists who made seminal contributions to antiviral drug discovery. Professor Antonín Holý, a pioneer of the nucleoside phosphonate chemotype that led to the discovery of cidofovir, adefovir and tenofovir, passed away on 16 July 2012 in his native Prague. Jerome P. Horwitz, who synthesized azidothymidine, the first drug approved to treat HIV-1 infection and whose research led to the development of dideoxycytidine, passed away on 6 September 2012 in West Bloomfield, Michigan, close to his native Detroit. We recognize the critically important contributions that these scientists made to the therapy of HIV-1 infection.

We would like to thank the authors of the chapters in this volume for their hard work, patience, dedication and scholarship in the lengthy process of writing, editing and making last-minute revisions to their contributions.

Manoj C. Desai  
Nicholas A. Meanwell





# Contents

## Section I Phenotypic Screening to Discover Antiviral Agents

<b>Chapter 1</b>	<b>Discovery and Clinical Validation of HCV Inhibitors Targeting the NS5A Protein</b>	<b>3</b>
	<i>Makonon Belema, Nicholas A. Meanwell, John A. Bender, Omar D. Lopez, Piyasena Hewawasam and David R. Langley</i>	
1.1	Introduction	3
1.2	The HCV NS5A Protein	4
1.3	The Discovery of HCV NS5A Replication Complex Inhibitors	6
1.4	Highlights of Recent Literature Disclosures	10
1.5	Clinical Trials with HCV NS5A Replication Complex Inhibitors	14
1.6	Mode of Action Studies with HCV NS5A Replication Complex Inhibitors	19
1.7	Conclusion	22
	References	23
<b>Chapter 2</b>	<b>Respiratory Syncytial Virus Fusion Inhibitors</b>	<b>29</b>
	<i>David Sperandio and Richard Mackman</i>	
2.1	Introduction	29
2.2	Challenges in the Development of RSV Antivirals	31
2.3	Small Molecule RSV Fusion Inhibitor Target Product Profile	34
2.4	RSV Fusion Inhibitors – Biologics	35
2.4.1	Palivizumab (Synagis)	36
2.4.2	Motavizumab (Numax)	36
2.4.3	RSV Nanobody (F-VHHb)	38

2.5	Small Molecule Fusion Inhibitors	38
2.5.1	J&J 2408086 and TMC-353121	38
2.5.2	BMS-433771	40
2.5.3	AstraZeneca WO 2010/103306	46
2.5.4	BTA9881	46
2.5.5	RFI-641	47
2.5.6	VP-14637, MDT-637	48
2.5.7	University of Gothenburg, Sweden	48
2.5.8	RSV Inhibitors Targeting Other RSV Genomic Proteins	49
2.6	Options for the Clinical Development of RSV Fusion Inhibitors	50
2.6.1	Clinical Trials in Immunosuppressed Patients	51
2.6.2	Clinical Studies in COPD or CHF Patients	52
2.6.3	Clinical Studies in Infants	53
2.6.4	RSV Challenge Strain (Memphis 37)	55
2.7	Conclusion and Outlook	56
	References	57

**Chapter 3 Phenotypic Screening to Discover Inhibitors of Dengue Virus** **63**  
*Qing-Yin Wang, Bin Zou, Simon J. Teague and Pei-Yong Shi*

3.1	Introduction	63
3.1.1	Disease Burden of Dengue	63
3.1.2	Antiviral Targets of Dengue Virus	64
3.2	Approaches for Anti-dengue Drug Discovery	65
3.2.1	Overall Antiviral Approaches	65
3.2.2	Cell-based Phenotypic Assays	66
3.3	DENV Inhibitors Identified Through Cell-based Screens	66
3.3.1	Aminothiazole Compound: an Inhibitor Targeting Viral NS4B	66
3.3.2	Benzomorpane Compound: an Inhibitor of Viral Translation	68
3.3.3	Pyrazole Compound: an Inhibitor of Host Pyrimidine Biosynthesis	71
3.4	Discussion	74
3.4.1	Stratification of Inhibitors of Viral and Cellular Targets	74
3.4.2	Rationale for Dengue Antiviral Therapy	75
3.5	Conclusion	76
	References	76

<i>Contents</i>	xi
<b>Chapter 4 Discovery and Development of Antiviral Drugs for Treatment of Pathogenic Human Orthopoxvirus Infections</b>	<b>81</b>
<i>Robert Jordan</i>	
4.1 Introduction	81
4.2 Natural History of Human OPV Infections	83
4.3 Antiviral Discovery and Development	85
4.3.1 Regulatory Path to Developing OPV Therapeutics	85
4.3.2 Animal Models of OPV Infection	85
4.4 Development of OPV Therapeutics	91
4.4.1 Cidofovir	92
4.4.2 CMX001	95
4.4.3 ST-246	99
4.5 Conclusion	104
References	105
<b>Chapter 5 HCV Replication Inhibitors That Interact with NS4B</b>	<b>111</b>
<i>Christopher D. Roberts and Andrew J. Peat</i>	
5.1 Introduction	111
5.2 Identification of NS4B as the Target of Inhibitors Discovered in a Phenotypic HCV Replicon Screen	112
5.3 NS4B Function and Mechanism of Action of NS4B Inhibitors	113
5.4 Lead Optimization of Series	117
5.5 <i>In Vivo</i> Proof of Concept	133
5.6 Challenges Ahead	138
References	141
<b>Section II Biochemical Screening and Structure-based Drug Design to Discover Antiviral Agents</b>	
<b>Chapter 6 HIV Integrase Inhibitors</b>	<b>149</b>
<i>Brian A. Johns, Takashi Kawasuji and Emile J. Velthuisen</i>	
6.1 Introduction	149
6.1.1 HIV Integrase	150
6.2 First-generation HIV Integrase Drugs Raltegravir and Elvitegravir	153
6.3 Discovery and Development of Dolutegravir	158
6.3.1 Differentiation Objectives	158
6.3.2 Design of a Next-generation Scaffold	158
6.3.3 Execution and Delivery of the Tricyclic Carbamoylpyridone	164

6.3.4	Choosing the Optimal Candidate	169
6.3.5	Tricyclic Carbamoylpyridones Deliver 'Next-generation' Virological Profiles	169
6.3.6	Preclinical Pharmacokinetics	171
6.3.7	Choosing a Lead and Back-up	172
6.3.8	Clinical Development of Dolutegravir	173
6.3.9	Long-acting Parenteral INI – S/GSK744	175
6.4	Non-catalytic Site Integrase Inhibitors	176
6.5	Conclusion	180
	References	180
<b>Chapter 7</b>	<b>HCV NS3/4a Protease Inhibitors: Simeprevir (TMC-435350), Vaniprevir (MK-7009) and MK-5172</b>	<b>189</b>
	<i>John A. McCauley, Michael T. Rudd and Nigel J. Liverton</i>	
7.1	Introduction	189
7.2	Discovery of Simeprevir (TMC-435350)	192
7.3	Discovery of Vaniprevir (MK-7009)	203
7.4	Discovery of MK-5172	218
7.5	Conclusion	234
	References	235
<b>Chapter 8</b>	<b>Design and Development of NS5B Polymerase Non-nucleoside Inhibitors for the Treatment of Hepatitis C Virus Infection</b>	<b>248</b>
	<i>Pierre L. Beaulieu</i>	
8.1	Introduction	248
8.2	The NS5B RNA-dependent RNA Polymerase	250
8.3	Non-nucleoside NS5B Polymerase Inhibitors	251
8.3.1	Thumb Pocket 1 Inhibitors	251
8.3.2	Thumb Pocket 2 Inhibitors	264
8.3.3	Palm Site 1 Inhibitors	271
8.3.4	Palm Site 2 Inhibitors	279
8.3.5	Covalent NS5B Inhibitors	280
8.4	Conclusion	282
	Acknowledgements	283
	References	283
<b>Chapter 9</b>	<b>Virus-coded Ion Channels as Antiviral Targets</b>	<b>295</b>
	<i>Stephen Griffin</i>	
9.1	Introduction	295
9.1.1	Discovery and Expansion of the Viroporin Family	296
9.1.2	Characteristics Inherent to Viroporins	297

9.1.3	Experimental Approaches to Identifying and Understanding Viroporin Function	300
9.1.4	The Current Viroporin Inhibitor Chemical Toolbox	302
9.1.5	Non-ion Channel Functions of Viroporins: Confounding Factors in the Study of Virus-coded Ion Channels	308
9.2	Viroporins Encoded by Pathogenic Human RNA Viruses with Known Small-molecule Inhibitors	308
9.2.1	Influenza A Virus M2: Clinical Precedent and Prototype Viroporin	308
9.2.2	Human Immunodeficiency Virus Type 1 (HIV-1) Vpu	318
9.2.3	Hepatitis C Virus p7	323
9.3	Other RNA Virus Viroporins: Prospective Targets for Emerging and Clinically Important Viruses	336
9.3.1	Viroporin Activities in Picornaviruses	336
9.3.2	Coronavirus (CoV) E, 3a and ORF8a Proteins	337
9.3.3	The Small Hydrophobic (SH) Proteins of Paramyxoviridae	338
9.3.4	Alphavirus 6K Proteins	340
9.3.5	Flavivirus M proteins	340
9.3.6	Human T-cell Lymphotropic Virus Type 1 (HTLV-1) p13ii Protein	341
9.3.7	The Rotavirus NSP4 Enterotoxin	341
9.4	Viroporins Encoded by DNA Viruses	342
9.4.1	Viroporins of Polyomaviruses	342
9.4.2	The E5 Protein of Human Papillomavirus 16 (HPV16) is an Oncogenic Viroporin	343
9.5	Viroporins of Animal Viruses	344
9.6	Conclusion and Future Perspectives: How Can Viroporin Inhibitors Fit into Modern Clinical Drug Discovery Scenarios?	345
	References	347

### Section III Host Targets

<b>Chapter 10</b>	<b>TLR-7 Agonists for the Treatment of Viral Hepatitis</b>	<b>365</b>
	<i>Randall L. Halcomb</i>	
10.1	Introduction: TLR-7 and the Antiviral Effects of Interferon- $\alpha$ Induction	365
10.2	Nucleoside Analogs and Prodrugs	367
10.3	Imidazoquinoline Agonists	369
10.4	8-Oxopurine and 8-Oxodeazapurine Agonists	372

10.5	Conclusion and Outlook	378
	References	379
<b>Chapter 11</b>	<b>Optimization of Cyclophilin Inhibitors for Use in Antiviral Therapy</b>	<b>384</b>
	<i>Michael Peel and Andrew Scribner</i>	
11.1	Cyclophilin Distribution, Function and Inhibition by Cyclosporine A	385
11.1.1	Cyclophilins	385
11.1.2	Cyclosporine A	387
11.2	Cyclophilins Involved in Viral Replication	388
11.2.1	Human Immunodeficiency Virus	388
11.2.2	Hepatitis C Virus	389
11.2.3	Dengue, West Nile and Other Flaviviruses	393
11.2.4	Non-flaviviruses	393
11.3	Modification of Cyclosporine to Treat Viral Diseases	395
11.3.1	Factors Affecting Cyclophilin Binding and Selectivity	395
11.3.2	Removing Immunosuppressive Potential	398
11.3.3	Antiviral Structure–Activity Relationships – HIV, HCV	400
11.3.4	ADME Properties of Cyclosporine and Derivatives	403
11.4	New Opportunities for Cyclophilin Inhibitors as Antiviral Agents	405
11.4.1	Non-cyclosporine Cyclophilin Inhibitors	405
11.4.2	Immunomodulation by Cyclophilin Inhibition	407
11.5	Conclusion	408
	References	409
<b>Section IV Delivery of Antiviral Agents</b>		
<b>Chapter 12</b>	<b>Prodrugs in the Treatment of Viral Diseases</b>	<b>421</b>
	<i>Michael J. Sofia</i>	
12.1	Introduction	421
12.2	Prodrugs of Alcohols and Carboxylic Acids	424
12.3	Prodrugs of Phosphates and Phosphonates	428
12.4	Prodrugs to Address Solubility-limiting Absorption	439
12.5	Prodrugs Designed to Exploit Carrier-mediated Mechanisms	442

12.6 Conclusion	444
References	444

### **Chapter 13 Cobicistat and Ritonavir as Pharmacoenhancers for Antiviral Drugs 451**

*Lianhong Xu and Manoj C. Desai*

13.1 Introduction	451
13.2 Antiviral Resistances and HIV Protease Inhibitor Ritonavir	452
13.2.1 Virus and Drug Resistance Mutations	452
13.2.2 HIV and HIV-1 Protease Inhibitor Ritonavir	453
13.2.3 Drug-resistant Mutations and Pharmacokinetic Profiles	454
13.2.4 Combination Therapy and HAART	456
13.3 Ritonavir as a Pharmacoenhancer for HIV Therapy	457
13.4 Mechanism of CYP3A Inhibition of Ritonavir	461
13.5 Discovery of the Pharmacoenhancer Cobicistat	466
13.6 Cobicistat as a Pharmacoenhancer in HIV Therapy	471
13.6.1 Cobicistat Boosting the PK Profile of CYP3A Substrate	471
13.6.2 Cobicistat as a Pharmacoenhancer for Anti-HIV Agents	471
13.7 Future Perspectives	473
13.7.1 Pharmacoenhancers in Antiviral Therapies	473
13.7.2 Novel Pharmacoenhancers	474
13.8 Conclusion	476
References	477

### **Chapter 14 Clinical Benefits of Single-tablet Regimens 482**

*Danielle P. Porter and Bill Guyer*

14.1 Introduction	482
14.2 Adherence	485
14.2.1 Clinical Trials	485
14.2.2 Retrospective and Observational Studies	486
14.3 Persistence	489
14.4 Efficacy	490
14.4.1 Treatment-naïve Studies	491
14.4.2 Switch Studies	492
14.4.3 Cohort Study	494



14.5	Safety	494
	14.5.1 Treatment-naive Studies	495
	14.5.2 Switch Studies	495
14.6	Patient-reported Outcomes	496
14.7	Healthcare Resource Utilization	500
14.8	Ongoing Studies	502
14.9	Pipeline	503
14.10	Conclusion	505
	References	505
	<b>Subject Index</b>	<b>509</b>

**Section I**  
**Phenotypic Screening to Discover Antiviral**  
**Agents**



## CHAPTER 1

# *Discovery and Clinical Validation of HCV Inhibitors Targeting the NS5A Protein*

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## 1.1 Introduction

Significant effort has been invested in elucidating the exact role and function of the NS5A protein in the hepatitis C virus (HCV) replication cycle. Although, unlike the NS3 and NS5B proteins, no enzymatic function has been identified thus far for NS5A, it has become apparent that this protein plays a diverse and critical set of roles both in the replication of the virus and in the mediation of host–virus interactions. Despite its multifunctional role, the lack of a well-characterized function coupled with the limited availability of structural information, compared with the NS3 protease and NS5B polymerase, initially made the NS5A protein a less compelling target for therapeutic intervention. That changed, however, with the validation of NS5A as a clinically relevant target by daclatasvir (**1**), where single doses effected pronounced and rapid declines in viral RNA in HCV-infected subjects (Figure 1.1).<sup>1</sup> Highlights of the