tion of chemical structures, which appear to have been produced by a rather unskilled user of chemical software. Amino acid side chains and modification reagents more often than not are poorly drawn and, despite their fairly large size, illustrations are not always clear or informative enough about the relevance of the transformations under discussion.

In the subsequent chapter, the residue-specific transformations outlined in Chapter 2 are discussed in the light of current proteomic strategies, for example, stable isotope labeling for quantitative proteomics, modification at specific binding sites for activity-based proteomics, or protein labeling with fluorescent dyes prior to fractionation. This reviewer found this chapter to be probably the most useful one in the entire book, even if the above caveats about the quality and instructiveness of the chemical formulas remain.

The following two chapters (4–5) deal with sample preparation and prefractionation, respectively; two aspects usually crucial for the success of any proteomic experiment. As it is, they receive a disparate treatment in the text. The former is discussed at reasonable length, again with chemical modification as a frequent but justified recurring theme. Issues such as cell and tissue extraction, sample stability, or proteolytic inhibition receive adequate coverage with abundant reference to both classical and current literature. In contrast, prefractionation is dealt with in a slighter way. For instance, prefractionation strategies based on affinity capture (e.g. pull-down or depletion experiments), often the bedrock of any proteomics workflow, are only succinctly discussed, arguably because in these approaches the role of chemical modification is less conspicuous.

The last three chapters are dedicated to analytical technologies (Chapter 6), clinical proteomics (Chapter 7), and validation issues (Chapter 8). Chapter 6 covers most current aspects of protein analytical methodology, including mass spectrometry, though again not in substantial detail. Given its superficial treatment of most issues, the chapter will not be particularly helpful to readers not already versed in the matter. Chapter 7 offers a limited but insightful review of some selected topics in the fast-expanding field of clinical proteomics, and concludes with a pessimistic and controversial assessment of the promise of these technologies to deliver clinically relevant results any faster than more traditional biochemical or immunochemical approaches. The last chapter of the book offers a prospect into issues such as assay variability and validation, and their bearing on the long-term goal of proteomics-based personalized medicine.

In summary, this may be a useful book for readers already familiar with the essential aspects of proteomics. In stressing the connection, both historical and current, between classical protein chemical modification and modern proteomics methodologies, Dr. Lundblad is undoubtedly on target, and this is clearly the strongest point of the book.

Prof. Dr. David Andreu
Pompeu Fabra University (Spain)

Entry Inhibitors in HIV Therapy

Edited by *Jacqueline D. Reeves* and *Cynthia A. Derdeyn*.

Birkhäuser, Basel 2007. x + 200 pp., hardcover € 119.00.—ISBN 978-3-7643-7782-3

Human immunodeficiency virus (HIV) infection affects around 40 million people worldwide, and represent the fourth leading cause of mortality. The discovery of a safe and effective HIV vaccine is still a hope, and the focus on this disease treatment remains on anti-HIV agents. The presently available antiretroviral therapy (ART) is able to delay the destruction of the host immune system, to reduce severity and frequency of opportunistic infections, and so, to delay the progression of acquired immune deficiency syndrome (AIDS). Highly active antiretroviral therapy (HAART) is a combination of nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and/or aspartic protease inhibitors (PIs), which were eventually combined with fusion inhibitors (FIs); the introduction of HAART has made it possible to reduce the viral load in plasma, resulting in improved patient health and life span. However this kind of therapy only suppresses, and not eradicates, the virus and multiple-drug therapies like HAART can lead to increased adverse effects and toxicity due to long-term use and drug–drug interactions. Furthermore, the massive viral replication (with more than 10^9 virions produced daily), and the high error rate of the reverse transcriptase, has led to the emergence of drug and multidrug-resistant viral strains and the stringent need of new therapeutic strategies. Ultimately several new approaches have been explored. The emergence of the worldwide AIDS epidemic has fostered much research and great progress in this area of antiviral drugs, and presently more than 32 antiviral drugs are available, possessing a variety of mechanisms of action; most of these drugs are used for the management of HIV infection and AIDS, but are also used for the treatment of other viral diseases such as hepatitis B, influenza, herpes simplex, varicella-zoster and cytomegalovirus infections.

HIV entry and fusion are two steps in the viral life cycle that were shown to be targeted by several classes of antiviral drugs. The discovery of chemokines focused the attention on cellular coreceptors used by the virus for entering cells, and to the various steps of such processes, which are subject to interactions with small molecules. Intense research led to a wide range of effective compounds that are able to inhibit these initial steps of viral replication. All steps in the process of HIV entry into the cell may be targeted by specific compounds, classified in three main classes: (i) attachment inhibitors, (ii) coreceptor-binding inhibitors, and (iii) fusion inhibitors that may be (or have already been) developed as novel types of antiretroviral drugs.

The book edited by Reeves and Derdeyn represents a collection of valuable articles describing in some detail these processes, the various strategies used to target HIV entry into the cells, the compounds in clinical development at the time the chapters were written (presum-

ably late 2006). Its main drawback is that in such a dynamic research field, most of these data are already outdated, for example, both an HIV entry inhibitor (Maraviroc, Selzentry) as well as an HIV integrase inhibitor (Raltegravir) were launched for clinical use in HIV infected patients since this book was published. The clinical role of these agents in the management of the disease has since been established, especially in patients harboring resistance to other classes of antiretroviral drugs (NRTIs, NNRTIs, PIs, FIs, etc).

The first chapter of the book, by Tilton and Doms, discusses in a detailed manner the Env viral protein, which constitutes the molecular determinant for viral attachment and membrane fusion, as well as the biochemical steps of these processes. The HIV entry process is described in an excellent manner but all figures are in black and white and are very small, making them of little use and difficult to understand (this is in fact a general defect of this book). An excellent second chapter, by Vergne (who tragically died in Africa in early 2007 at the age of 31) and Peeters presents the genetic diversity of the Env protein in *Homo sapiens* and *Pan troglodytes*, and its implications for the development of fusion inhibitors, or for the development of drug resistance to such agents.

The next chapters present the inhibitors of the gp120–CD4 interaction, the small-molecule chemokine receptor antagonists acting as HIV entry inhibitors, which interact both with the CXCR4 coreceptors (such as AMD3100, AMD3465, ALX40-4C, T22, T134 and T140), or which are antagonist of the CCR5 coreceptor (TAK-779, TAK-220, E913, AK-602 and NSC among others), together with new types of fusion inhibitors possessing the same mechanism of action as enfuvirtide, based on peptidomimetic or non-peptidomimetic scaffolds. A chapter by Hart and Evans-Strickfaden is dedicated to the possible use of HIV entry inhibitors as microbicides, with the various agents in different stages of clinical development being described in some details, but without chemical structures, which represents in many chapters (but not in all) a second main drawback of this book.. There are then three chapters dedicated to the clinical aspects of this type of antivirals, which are inappropriately placed in the middle of the book, between the compounds/targets described earlier and Enfuvirtide (T20), the first fusion inhibitor to be used clinically as an anti-HIV agent, already for several years.

The following chapter dedicated to Enfuvirtide, written by one of its discoverers (M.L. Greenberg), is the best of the entire book as it tells a story of scientific and economic success for the company and researchers that discovered this antiviral drug. The steps leading to this compound, its mechanism of action and clinical efficacy are very well presented. A final chapter by Gulick presents some of the HIV entry and fusion inhibitors which are currently being investigated in controlled clinical trials, but this reviewer found it too schematic (again structures are missing) as if it was written in a big hurry.

The overall impression of this book is rather disappointing for the reasons enumerated above. With several exceptions of very well-written chapters, most of the information is outdated, the figures are too small and in black and white, many chemical structures are missing, etc.

Prof. Dr. Claudiu T. Supuran
Università degli Studi di Firenze (Italy)
DOI: 10.1002/cmdc.200800220

Leishmania: After the Genome

Edited by *Peter J. Myler* and *Nicolas Fasel.*

Caister Academic Press, Wymondham 2008. xiv + 306 pp., hardcover £150.00.—ISBN 978-1-904455-28-8

Leishmania species cause a variety of diseases manifestations, predominantly in the developing world, ranging from potentially disfiguring cutaneous lesions to fatal visceral infections. This book reviews what is known about the biology of *Leishmania*, comments on how the recent availability of the *Leishmania* genome has enhanced our understanding of the biology of the parasite, and also attempts to look ahead at the possible implications of experimental and genomic data on the development of diagnostics, vaccines and drugs against this parasite. The latter aim is of primary interest to medicinal chemists intrigued by *Leishmania*.

Thirteen review articles are included on a wide variety of topics relating to this parasite, with each chapter representing a well-written, and extensively referenced overview from experts in *Leishmania* research. Several of these reviews will be of interest to medicinal chemists. Those that first come to mind are chapters concerning *Leishmania* metabolism. *The Metabolic Repertoire of Leishmania and Implications for Drug Discovery* by Opperdoes and Michels presents a thorough overview of the major metabolic pathways in the parasite, complete with metabolic charts, while placing an emphasis on the peculiarities of the organism that could be exploitable in terms of drug discovery and development. In addition, this chapter points out the complexity of target identification in *Leishmania*, given that metabolic strategies are poorly understood in the clinically relevant amastigote stage of the parasite, and stresses the need to validate potential targets in the host stage of the organism. Other valuable insights provided by Opperdoes and Michels include discussions of the difficulties of target validation in *Leishmania*, given that RNA interference cannot be used in this parasite, and of the barriers presented to drug delivery by the residence of *Leishmania* in acidic phagosomes within the host macrophage. The topics covered in *Analysis of the Leishmania Metabolome* by McConville et al. overlap those discussed in the chapter by Opperdoes and Michels, but the McConville et al. review is also very well done, and provides detailed information regarding experimental and technical issues encountered in the study of the *Leishmania* metabolome.

Several other chapters should be useful to chemists with an interest in this parasite. *Drug Resistance in* Leishmania by Ouellette et al. provides an excellent overview of the current state of knowledge regarding the mechanisms of action of known antileishmanial drugs

