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 Its main drawback is that in such a dynamic research field, most of these data are already outdated, for example, both an HIV entry inhibitor (Maraviroc, Selzentry) as well as an HIV integrase inhibitor (Raltegravir) were launched for clinical use in HIV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.

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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

(antimonials, pentamidine, amphotericin B, and miltefosine) and laboratory (and in some cases field) derived resistance to these agents. The introductory chapter (*Leishmaniasis: Epidemiological Trends and Diagnosis* by Jhingaran et al.) gives a good discussion of the manifestations of the disease and its geographical distribution, although the inclusion of maps and tables would have been helpful. *Regulation of Gene Expression in* Leishmania *Throughout a Complex Digenetic Lifestyle* by Papadopoulou et al. summarizes insights into gene expression in the parasite gained from the genome project, such as the characteristics of transcription and life stage-specific expression of mRNAs. For those interested in animal models of visceral and cutaneous leishmaniasis, *Host Responses to Infections with* Leishmania by Tacchini-Cottier and Launois provides a brief but useful summary before describing in detail the host immunological responses to *Leishmania* infection. Other reviews discuss topics such as the *Leishmania* genome structure and content, the *Leishmania* proteome, *Leishmania* differentiation, *Leishmania* surface proteins, interactions between the parasite and the Sandfly host, interactions between the parasite and the host macrophage, and the influence of the genome on vaccine development.

This book provides a comprehensive, up-to-date snapshot of the biology of this parasite and is an essential resource for those interested in *Leishmania*, chemist and nonchemist alike. However, does the book succeed in communicating the impact of the availability of *Leishmania* genomic information on the discovery of new antileishmanial drugs? No chapters are included on the identification of new drug candidates based on genomic data, so perhaps the book gives an answer to this question through its silence. The chapter by Myler dealing with the structure and content of the *Leishmania* genome points out that a known function can be assigned to only about 35% of the genes predicted to code for proteins in the *L. major* genome, and a better knowledge of the function of the other genes may help to identify critical drug targets. However, agents that affect multiple targets or nonprotein targets could be equally effective and may be less likely to engender the rapid development of resistance. A balanced approach between genome-driven drug discovery and chemistry-driven strategies aimed at identifying agents with selective activity against live organisms is likely to bear more fruit in the search for novel chemotherapeutics against this parasite, compared with a strategy based solely on genomic approaches.

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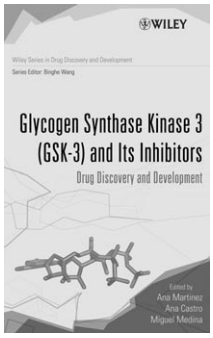
Glycogen Synthase Kinase 3 (GSK-3) and Its Inhibitors

Edited by *Ana Martinez*, *Ana Castro* and *Miguel Medina*.

Wiley-VCH, Weinheim 2006. xxxi + 346 pp., hardcover €89.90.—ISBN 978-0-471-77001-5



The appreciation of GSK-3's multifold roles in developmental signaling, cellular pathway regulation, and etiology of disease has undergone a renaissance since its discovery some 25 years ago. No longer thought of simply as a mediator of insulin signaling, activating glycogen synthase and increasing glycogen deposition; GSK-3 research has revealed a complex tapestry of signaling regulation in which GSK-3 plays numerous roles depending on the developmental stage of an organism, the metabolic state of tissues and cells, and the differential regulation in specific tissues or cell types. GSK-3 regulation occurs through a wide variety of cellular regulatory molecules, such as insulin, Wnt proteins, growth factors, estrogen, acetyl choline among others, and a plethora of substrates. Unraveling the key roles for GSK-3 in developmental processes like stem cell maturation and differentiation, and in disease states such as diabetes, Alzheimer's, neurodegeneration, and cancer is a daunting task whether a seasoned veteran researcher trying to keep informed amidst the hundreds of new GSK-3 papers being published yearly, or someone new to the field who may be interested in a specific therapeutic area. Speaking to audiences ranging from advanced undergraduates and graduate students to pharmaceutical researchers, therapeutic area experts and cellular signaling specialists, this book will provide insight into current GSK-3 research, and understanding through a series of well-written, referenced and indexed review monographs. Well respected expert GSK-3 authors examine the biology, regulation, signaling pathways, physiology, role in human diseases, potential for therapeutic application, and some current small-molecule drug discovery research programs, giving the reader a breadth of knowledge and viewpoint.

The foreword of the book is an introduction to the discovery of GSK-3, and a personal account of the trials and triumphs that led to the isolation and identification of this unique kinase written by Professor Sir Philip Cohen. This intriguing retrospective gives insight into the evolution of GSK-3 research touching on the pivotal innovations and breakthroughs, which exposed GSK-3's multifaceted regulation, even within the insulin pathway, and many of the significant collaborators and researchers who were integrally involved through the quarter century of GSK-3 investigation. One of the original investigators and expert in GSK-3 biology, Professor James R. Woodgett, provides a comprehensive introductory overview to the regulation, structure, biochemical function, selectivity and involvement in glucose metabolism and neuronal biology of GSK-3. This chapter gives a firm grounding in the basics of GSK-3 biology and function, which lays the ground work for more specific and detailed chapters. Topics covered in the subsequent chapters branch out to include embryonic and neuronal development, neuronal cell biology, and the important modulation of Tau phosphorylation at an expert level including primary

