infection. Perhaps inverse agonists of chemokine receptors can eventually be employed as anti-viral drugs.

Everyone will be able to find their own favorite sections in this book. I especially appreciate the efforts made by the editors to include a chapter on linking constitutive GPCR activity to cell physiology and pathophysiology (Chapter 7). For those who are intrigued by the concept of inverse agonism, Chapter 7 provides convincing evidence that constitutive activity may play a special role in regulating our physiology, and that there is indeed therapeutic potential in the development of inverse agonists. Though not a novice in inverse agonism myself, I am indebted to the authors for introducing me to the wide variety of GPCRs that exhibit constitutive activity. The alarmingly large number of constitutively active GPCRs has profoundly changed my own thoughts on the biological significance of the various conformations of the GPCR. Overall, I find "G Protein-Coupled Receptors as Drug Targets" to be extremely informative and generally easy to read and understand. It is an important reference book for researchers (medicinal chemists, physiologists, and pharmacologists) working on the most favorite group of drug targets–the GPCRs.

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DNA Methylation: Approaches, Methods and Applications

Edited by *Manel Esteller*.

CRC Press, Boca Raton 2005. 240 pp., hardcover $ 149.00.—ISBN 0-8493-2050-X

The field of epigenetics and, more particularly DNA methylation, is constantly expanding, and most scientific disciplines are now concerned. The book *DNA Methylation: Approaches, Methods and Applications* presents an extensive overview of the role of DNA methylation in human physiology (genomic imprinting and X inactivation) and pathology (mostly cancer). It highlights the link between the biological role of DNA methylation in gene regulation and the pathogenesis of cancer. A few articles outline that a comprehensive analysis of epigenomes represents the next stage of biomarkers for detection and prognostic evaluation of cancer with subsequent outcomes in terms of treatment by demethylating agents, drugs acting on histone modification and possibly RNA interference against DNA methyltransferases.

The articles dedicated to the techniques of analysis of DNA methylation have been written by leaders in the field. They discuss the current approaches and protocols used to study DNA methylation and also other epigenetic modifications. The techniques are well described in terms of applications and protocols, and the benefits and caveats of each technique are particularly well addressed.

However, I think that the phenomenon of genomic imprinting deserved a full chapter (extension to other imprinting disorders, more illustrations, etc.) and also an emphasis of the imprinting risk of assisted reproductive technology.

It would have probably been easier for the reader to have the techniques of analysis of DNA methylation after bisulfite treatment (treated in two different chapters in the book) developed in only one chapter. The two chapters dedicated to the use of DNA demethylating agents are also sometimes redundant.

In conclusion, this book is interesting for both researchers and clinicians. It is an excellent summary of the subject for scientists starting in the field of epigenetics and it is also a reference book for professionals already familiar with the subject.

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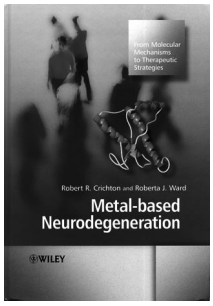
Metal-based Neurodegeneration: From Molecular Mechanisms to Therapeutic Strategies

By *Robert R. Crichton* and *Roberta J. Ward*.

Wiley, Chichester 2006. X+227 pp., hardcover £ 75.00.—ISBN 0-470-02255-8



Advances in health and medical treatments have resulted in dramatically increased life spans. However a consequence of this is that age-related neurodegenerative diseases such as Alzheimer's disease (AD) have become more prevalent. The escalating adverse social and economic costs associated with the increasing prevalence of these debilitating diseases means that effective therapeutic strategies are urgently required. Efficient design of therapeutic strategies requires intimate knowledge of the molecular pathways underlying these diseases.

Elucidating these molecular pathways is a very active area of research, and many different hypotheses have been put forward, among them metal-mediated oxidative stress. This book by Crichton and Ward gives an overview of the neurodegenerative diseases and how metal-mediated oxidative stress contributes to disease pathology. This book is extremely ambitious in scope as it not only attempts to cover the chemistry underpinning metal-mediated oxidative stress but also summarises what is known about a wide range of neurodegenerative diseases and the therapeutic strategies targeting them.

The first two chapters of the book deal with the chemistry and biochemistry of metal ions. In many ways these first two chapters are the most important and the best of the book as they deal with such fundamental processes as how metal ions are stored and transported. The links between tight regulation of metal homeostasis and the down-stream consequences this has for induction of

oxidative stress are clearly stated. For this reviewer, this link between metal homeostasis and oxidative stress is the most important take-home message in the book. Oxidative stress is the result of an imbalance in pro-oxidant/antioxidant homeostasis that leads to the generation of toxic reactive oxygen species. However oxidative stress is not something that occurs spontaneously, as the generation of reactive oxygen species requires the activation of oxygen to take place and this is usually done through an interaction with a redox-active metal ion. These are the interactions that must be inhibited if effective therapeutics targeting "metal-based neurodegeneration" are to be designed.

Subsequent chapters (3–9) describe a series of clinical settings in which metal-mediated oxidative stress appears to be a pivotal part of disease progression. A large number of neurological diseases are covered, ranging from the more common, such as Parkinson's and Alzheimer's diseases, through to many that are less well known. Most of these descriptions are functional recitations of what is in the literature, without giving any particularly novel insights.

The last three chapters deal with therapeutic strategies. The first of these chapters reviews strategies currently in clinical use. Virtually none of these strategies target the metal-mediated processes that are described throughout the book, and, as these strategies do not target the underlying disease process, they are of limited long-term value and we must hope that new, more robust strategies will become available in the near future. One criticism, on p. 177 the authors state "There have been no reports of the use of specific iron chelating compounds in the treatment of AD"; putting aside arguments about what exactly constitutes a specific chelator, desferrioxamine, a high-affinity iron chelator, has been trialled with some promise in AD.[1] Chapter 11 reviews the various animal models that are currently available for studying the various diseases and for evaluating potential therapeutic strategies. It is worth reiterating, as pointed out by Crichton and Ward, that, while very useful information can be gained from studying these mouse models, they are not able to fully replicate the human diseases. In the last chapter the authors speculate on possible future directions that therapeutic strategies might take.

One thing that is missing from the narrative is the sense that the metal-mediated hypotheses articulated in this book, while widely accepted for some diseases, remain highly controversial for others. Although the evidence presented in this book that metal-mediated oxidative stress is driving the pathological processes appears persuasive, much work remains to convince many members of the research community working on these diseases that this is indeed the case. The most compelling way to achieve this will be to develop therapeutic strategies targeting the mechanisms of metal-mediated oxidative stress.

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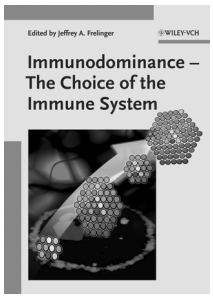
[1] D. R. Crapper McLachlan, A. J. Dalton, T. P. Kruck, M. Y. Bell, W. L. Smith, W. Kalow D. F. Andrews, *Lancet* **1991**, *337*, 1304-–1308.

Immunodominance: The Choice of the Immune System

Edited by *Jeffrey A. Frelinger.*

Wiley-VCH, Weinheim 2005. XXVI + 288 pp., hardcover € 139.00.—ISBN 3-527-31274-9



How can our T cells mount a response to the enormous, diverse world of microorganisms and foreign antigens? Several decades ago this was one of the important questions of immunology. Today we know that the adaptive immune system has a built-in ability to generate diversity. This salient feature endows us theoretically with an ability to generate a response to all possible antigens we may meet. Soon these discoveries raised an even more complex question: If we can generate a response against a large number of antigens, how does the immune response choose between them? Seminal observations would soon make it clear that the immune system—like any other complex system—needs to focus. Although, theoretically, many antigens could be targeted, a hierarchy within the responding T cells shapes the immune response to focus on a few or in some cases perhaps only one epitope. This concept, known as immunodominance, is an intriguing aspect of immune regulation and might not only be an important physiological principle, but could turn out to be essential for understanding a number of important diseases we today consider to be autoimmune diseases.

It is therefore a timely and welcome book that Dr. Jeffrey Frelinger has put together. Being a well-known immunologist within this field himself, Dr. Frelinger has received contributions from a number of prominent leaders, who are driving the research in this interesting area of immunology. The book contains 12 chapters that are divided into four main themes: I) Mechanics of Antigen Processing, II) Proteosome Specificity and Immuno-Proteosomes, III) Effect of the T Cell Repertoire on Dominance, and IV) Effects of Pathogens on the Immune Response.

In the first theme of antigen processing, Miller and Collins recapitulate the essential features of class I MHC antigen processing in a concise and well-referenced chapter, and Drake and Sant discuss class II processing and the establishment of a peptide hierarchy. These chapters provide a nice overview of the fundamental immunology behind antigen processing. The antigen-processing theme is closed by an important chapter written by Sette and Sundaram dealing with speculations on the nature of immunodominance. Peptide–MHC binding, processing, the nature of antigen-presenting cells, T cell repertoire, the immune synapse between the individual T cell, and the antigen-presenting cell all determine the final immunodominant response. One would have welcomed an even more detailed discussion of the significance of immunodominance for vac-

