

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.

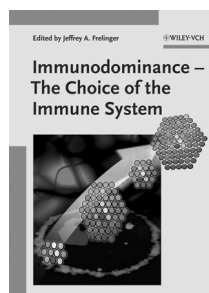
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How can our T cells mount a response to the enormous, diverse world of microorganisms and foreign antigens? Several decades ago this was one of the important questions of immunology. Today we know that the adaptive immune system has a built-in ability 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) Proteasome Specificity and Immuno-Proteasomes, 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-



cine development than the short paragraph at the end of the chapter.

The second theme on proteasomes is covered by Yewdell's nontraditional, but interesting chapter on endogenous antigen processing. In a short but well-written chapter, Yewdell makes an interesting economics approach to the numbers of various reactants in the cell to discuss the mechanisms of peptide generation in the cell. This is the only chapter in the second theme. An additional chapter discussing regulation of immunoproteasomes in greater detail would have fitted in nicely.

The third theme covers the aspects of the T-cell repertoire. Schmitt and Zúñiga-Pflücker take us through the early T-cell development in the thymus and discuss the exciting observations of notch regulation of the cell fate choice between T- and B-cell lineages. The fascinating aspects of CD8 T-cell immunodominance, repertoire, and memory are excellently covered by Gaddis, Fuller, and Zajac. For newcomers to the field of immunodominance, this chapter encompasses some of the stimulating findings about immunodominance and how epitopes can skew the repertoire during primary, memory, and recall responses. Also, the

thought-stimulating concept of heterologous infections is dealt with in the context of immunodominance. A separate chapter devoted to the latter very interesting aspects would have been justified.

The interaction between pathogens and the immune system is the fourth and last theme, to which almost half of the book is dedicated. This seems to be a good choice, since this book is clearly of interest to those working with infection and immunity. This section provides interesting discussions of T-cell hierarchy and immunodominance for infections such as *Listeria monocytogenes* (Porter and Harty), *Mycobacterium tuberculosis* (Lewinsohn and Flynn), respiratory viral infections (Crowe and Woodland), HIV (Takiguchi), viral hepatitis (Maini and Bertolotti), and herpes viruses (Munks and Hill). Despite the completely different approach to the chapters by the individual authors, each of these chapters provides a well-written overview of the subject. Now and then throughout the book, it may be difficult to figure out whether statements are true for both mouse and man. In this regard, the chapters by Lewinsohn and Flynn as well as Munks and Hill should be commended for their clear

division of the text in human and mouse studies.

Overall, *Immunodominance: The Choice of the Immune System* is a timely book in a fast-moving field. It covers the topic well, although some aspects could have deserved a separate chapter. A few minor points: some chapters exclude the title of the papers in the references. Since this book will be read by people not familiar with all the references, the title is helpful in selecting further literature. The book is printed in black and white with the inclusion of a separate section with color plates for seven figures. A consistent use of color figures throughout the book would obviously have improved the overall impression. The broad coverage of the topics may appeal to many readers: first of all scientists working with infections and the immune system, but basic immunologists may also appreciate the significant chapters on pathogens and immunodominance. To serve them all, it would have been nice, though, to have a much more detailed index.

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