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Antibiotics as Anti-Inflammatory and Immunomodulatory Agents

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Editors

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Preface

The antibiotic era began in earnest during World War II with the "miracle of penicillin". Following the introduction of penicillin, the quest was on to discover similar antimicrobial agents. In the late 1940s, erythromycin A was isolated from a soil sample found in the Philippine island of Iloilo, and in 1952 erythromycin was introduced by Eli Lilly Company under the name of Ilosone, as an alternative to penicillin for emerging penicillin-resistance bacteria. It was recognized early on that the gastrointestinal side effects of erythromycin A could be modified by altering the chemical structure of the agent, and in the early 1990s clarithromycin and azithromycin were developed to be more acid-stable and with fewer side effects. Not long after this, it was shown that the macrolide antibiotics had immunomodulatory effects separate from antimicrobial properties.

The "steroid sparing" properties of the 14-member macrolides troleandomycin and oleandomycin, were first described in patients with severe, steroid-dependent asthma. Erythromycin was also found to reduce the need for corticosteroids in patients with asthma and, as described by Rose Jung, Mark H. Gotfried and Larry H. Danziger, in these trials some severe, steroid-dependent asthmatics were able to discontinue systemic corticosteroids with the use of macrolide antibiotics. Although it was speculated that the mechanism of macrolide action for severe asthma was by interfering with corticosteroids metabolism, in the clinical trials the reduction in steroid side effects, dosage, and in some cases discontinuation of steroids suggested a different effect on the underlying disease.

This was exploited in the 1980s in Japan for the treatment of the nearly uniformly fatal airway disease diffuse panbronchiolitis (DPB), as described by Arata Azuma and Shoji Kudoh. Since that time, many investigators in Japan – and now around the world – have studied these immunomodulatory properties not only of macrolide antibiotics but also of other classes of antimicrobials. Studies in the last 5 years have confirmed these effects, not only for the treatment of DPB but for also cystic fibrosis (CF) as discussed by Adam Jaffé and Andrew Bush. With the widespread adoption of macrolide therapy for the treatment of CF there has been an explosion of interest and publications in the field. A literature search conducted in

June 2004 from the PubMed database shows that there have been nearly 300 references to the immunomodulatory or anti-inflammatory properties of antibiotics since 1976.

This book is divided into two sections; the first, on basic research, evaluates the effects of macrolide antibiotics on bacteria other than by ribosomally-mediated bacteriostasis. Specifically the macrolide antibiotics have been shown to influence the expression of virulence factors in gram-negative organisms and decrease the ability of these bacteria to form biofilms as detailed in the chapters by Kazuhiro Tateda, Theodore J Standiford, and Keizo Yamaguchi. A series of six chapters then follow detailing the various anti-inflammatory and immunomodulary effects of these antibiotics. Immunomodulation in this sense refers to the ability to downregulate deleterious hyperimmunity leading to airway damage as opposed to anti-inflammatory properties, which refers to the suppression of all inflammatory responses whether beneficial or not. Thus immunomodulation should not impair the normal host defense but will prevent an acute inflammatory response from becoming chronic and destructive inflammation. Michael Parnham gives a superb overview of the role of inflammation and its resolution with antibiotics. This is then followed by chapters that document the effect of macrolide antibiotics on cell membrane protection and epithelial stabilization (Charles Feldman and Ronald Anderson), neutrophil activation and chemotaxis (Jun-ichi Kadota), reduction of proinflammatory cytokine expression and release (HajimeTakizawa), the oxidative burst (Marie-Thérèse Labro), and immune activation (Jun-ichi Kadota).

Related to these immunomodulatory effects are the effects on mucus secretion. It is well established that mucus secretion is beneficial to the airway preventing bacterial infection, airway desiccation, and aiding particle clearance; however mucus hypersecretion can lead to airflow obstruction and entrap microorganisms as seen in patients with chronic airway inflammation. Many chronic inflammatory airway diseases such as COPD, asthma, sinusitis, DPB, bronchiectasis and CF are associated with hyperinflammation and airway obstruction with secretions. Kiyoshi Takeyama discusses the role of macrolides in mucus production and secretion and Jun Tamaoki reviews the related data on the regulation of ion channels and how this relates to macrolide antibiotics and mucus secretion.

The second part of the book discusses the clinical results using antibiotics as mucoregulatory agents in a variety of diseases. Shoji Kudoh, who was the first to describe the role of macrolides in the treatment of DPB, and Arata Azuma provide a superbly updated overview of DPB including the current Japanese recommendations for the use of macrolides in treating this disease. These guidelines have proven useful for establishing appropriate therapy for Adam Jaffé and Andrew Bush, who discuss not only their landmark studies of azithromycin for the treatment of CF but also the results of recent large-scale studies that have led to wide acceptance of this therapy. This is followed by a chapter by Kazuhiko Takeuchi, Yuichi Majima, and Qutayba Hamid that reviews the use of macrolides in the therapy chronic upper air-

way diseases including sinusitis and nasal polyposis. Rose Jung, Mark H. Gotfried, and Larry H. Danziger then summarize the use of macrolides and the treatment of chronic asthma; in particular for persons with neutrophil-predominant, steroid dependent asthma. The role of immunomodulatory antibiotics in the treatment of lung injury is reviewed by Arata Azuma.

Eiji Kita, Keiichi Mikasa and Kei Kasahara give a superb review of the data suggesting a possible role of immunomodulatory antibiotics that can decrease proinflammatory cytokines for the therapy of nonpulmonary disorders including arthritis, inflammatory bowel disease, and cancer. The final chapter by Markus O. Henke, Axel Dalhoff, and Bruce K. Rubin reviews the immunomodulatory properties of antibiotics other than macrolides with the special emphasis on the quinolones, where data now support the ability of these agents to affect the immune systems.

This is an exciting and a rapidly changing field and we are delighted to have the opportunity to summarize the state of the art as of 2004. Thus it is timely that this book be published summarizing these data and it is appropriate that half of the authors are from Japan. We personally believe it is likely that we will see a more widespread use of these antibiotics for their immunomodulatory properties as well as the development of derivatives of these medications that have no antibacterial properties but that do have more potent and directed immunomodulatory activity. This may permit more precise therapy for preventing biofilm diseases or chronic inflammation while reducing the risk of developing antimicrobial resistance to the macrolide class of antibiotics. The editors would like to thank Michael Parnham, the PIR series editor, for suggesting this book and for agreeing to write the overview chapter. We would also like to thank our editors at Birkhäuser Publishing including Karin Neidhart and Hans Detlef Klüber for their outstanding support. Finally the Editors of this monograph would like to thankfully acknowledge the many students and postdoctoral investigators who have worked with us over the years and enriched both our research laboratories and our lives.

Winston-Salem/Tokyo, July 2004

Bruce K. Rubin
Jun Tamaoki

I. Basic research

Indirect antimicrobial effects