PREFACE

Immunology of Protein and Peptide Therapies

Issues 3, 4, and 5 of *Critical Reviews in Immunology*, Volume 27, are special issues that comprise articles based on papers delivered at the 11th International Symposium of Immunobiology. The conference was held September 21–23, 2006, at Granlibakken Resort and Conference Center, Tahoe City, California. In addition, a few of the abstracts submitted by participants were selected for minisymposia, and some of the authors, whose presentations were judged by the Scientific Council to be of high quality, were invited to submit papers for publication in this volume.

The International Symposium of Immunobiology was established in 1976 by the Institute of Immunobiology, a nonprofit, educational organization devoted to the advancement of the science of immunology. The purpose of the symposium is to bring together, once every two or three years, active investigators at the forefront of contemporary immunology to present their findings and to discuss the significance of those findings in light of current concepts, and to identify important new directions of investigation. The founding of the symposium was stimulated by the achievement of major breakthroughs in the understanding of the immune recognition of proteins and peptides. The founders expected these breakthroughs to lead to the creation of a new generation of protein and peptide reagents that would have enormous potential in biological, therapeutic, and basic applications. This anticipated explosion has in fact occurred, and many benefits of these peptides are now being realized.

To foster the exchange of ideas, participation in the conference was limited to about 150 scientists, selected on a first-come-first-accepted basis. The small-size meeting held in a pleasant venue encouraged lively discussions and was extremely effective in promoting interactions among participants. The lectures are published in this journal so their impact has been felt far beyond the group of actual attendees. The 11th Conference focused on the immunological responses associated with protein and peptide therapies, and it was comprised of five main sessions, namely, peptide immunotherapy, toxins as therapeutic agents, autoimmunity, cytokine and hormone immunotherapy, and cancer immunotherapy.

Part I (Issue 3) deals with selected topics of peptide immunotherapy. In the last three decades the innovative use of synthetic peptides has aided in defining, at a submolecular level, our understanding of antigen presentation and immune recognition, and it has generated a number of diagnostic and therapeutic agents. The studies have also enabled, for some models of autoimmune disease, a delineation of the main events and submolecular interactions that contribute to the associated pathology. The first article describes work on human autoantibodies to surface receptors of cells of the immune system and reviews the T-cell receptor γ/δ chains, the molecules of the immunoglobulin superfamily, and opioid receptors. This is followed by an article describing a therapeutic protein that displayed the capability to effect rapid clearance of bacteria and bacterial toxins. Another topic outlines studies on peptide mimotopes as prototypic templates of broad-spectrum surrogates of carbohydrate antigens and their potential for cancer vaccination. Finally, an approach is described for selective targeting of the binding site of HLA alleles involved in presentation of pathogenic epitopes of an autoantigen. This has the capability of shutting off an ongoing autoimmune response to the autoantigen without effect on the immune function of other HLA alleles and is demonstrated to be quite effective in mouse models in the treatment of autoimmune disease.

Part II (Issue 4) deals with the use of toxins as therapeutic proteins. Some snake and bacterial toxins have been employed successfully in therapy of human neuromuscular disorders. Alpha-Cobratoxin, normally a very toxic small protein in the venom of the snake *Naja naja atra*, has been modified chemically to yield a nontoxic derivative that might have a potential in therapy of multiple sclerosis. The literature leading to the development of this application for cobra toxin is reviewed. Botulinum neurotoxins (BoNTs) act on the nervous system and cause paralysis by blocking the release of acetylcholine from nerve terminals at the neuromuscular junction. Various vaccine designs and approaches for protection against BoNT poisoning are described and their protective efficacy compared. Because of its activity at the neuromuscular junction, BoNT, particularly types A and B, are employed in the treatment of a variety of clinical conditions associated with involuntary muscle spasm and contractions as well as cosmetic and other therapeutic applications. But the benefits are of limited duration because the partial paralysis caused by the toxin is reversible and injections need to be repeated to sustain the benefit. In some patients, the treatment elicits blocking antibody responses against the toxin that reduce or completely prevent the patient's responsiveness to further treatment. These immune responses to BoNT/A are discussed here.

In Part III (Issue 4), selected examples of autoimmune responses and diseases are described. Successful suppression of autoimmune arthritis by an altered peptide ligand of type II collagen is described here. One cause of autoimmunity stems from immune responses to cell molecules and products generated by cell apoptosis. The responses of peripheral CD8 T cells to apoptotic cell proteins and peptides play an important role and are described in this part. Activation-induced cytidine deaminase (AID) encoded by the *aicda* gene is essential for immunoglobulin gene somatic hypermutation and class switch DNA recombination that unfold in general in germinal centers and are central to an effective antibody response maturation. Activated B cell CD40 signaling, which is critical for the germinal center reaction, induces AID expression and is further supplemented by other stimuli, including interleukin-4 from $CD4^+$ T cells or Toll-like receptor (TLR)-activating bacterial and/or viral molecules. This part provides a review of the role of B-cell activation signals, transcription regulation programs and posttranslational modifications in controlling *aicda* expression and AID activity, thereby delineating an integrated model of modulation of SHM and CSR in the germinal center reaction.

Kaposi sarcoma lesions usually found on the skin and/or in the mouth, gastrointestinal tract, and respiratory tract appear typically as palpable or raised red, purple, brown, or black nodules or blotches. They can be very slow growing or extremely fast, and are associated with significant mortality and morbidity. It appears in AIDS patients as an opportunistic infection because of the weakened immune system in these patients. In Part IV (Issue 5), Dr. Robert Yarchoan and his colleagues review their preliminary findings on treatment of AIDS-related Kaposi's sarcoma with interleukin-12 and discuss the rationale for these studies. Activated T cells express OX40 and activated B cells express OX40 ligand (L) (members of the tumor necrosis factor/nerve growth factor family of cytokines) on their cell surfaces. Interaction of OX40 and OX40L causes the activated B cells to proliferate and secrete immunoglobulin. These molecules and their interactions are important in autoimmune pathogenesis and in cancer. Results showing the potential and prospects of targeting OX40 and OX40L for the treatment of autoimmunity and cancer are presented here.

In the final part (Issue 5), examples of cancer immunotherapy are described. These include poxyvirus vaccines, dendritic-tumor cell fusion hybrids, and enhancement of MHC presentation of peptide epitopes derived from tumor antigen.

The Scientific Council of the 11th Conference consisted of the following individuals: president, M. Zouhair Atassi (Baylor College of Medicine); vice president, John J. Marchalonis (University of Arizona, College of Medicine); K. Roger Aoki (Allergan), Garvin S. Bixler (Sanofi Pasteur), Paolo Casali (University of California, Irvine), Peter A. Cohen (Cleveland Clinic), and Leonard A. Smith (U.S. Army Medical Research Institute of Infectious Diseases).

A number of organizations provided generous support for the 11th Conference. The following organizations were sponsors: Allergan, Inc.; Amgen; Neurotoxin Institute; NeoGenix Oncology; NutraPharma; and Solstice.

M. Zouhair Atassi
Baylor College of Medicine
Houston, Texas, USA