

# **THE ANTIGENS**

**Volume VII**

**EDITED BY  
MICHAEL SELA**

# **The Antigens**

**VOLUME VII**

## Contributors

RON N. APTE

JAY A. BERZOFSKY

IRUN R. COHEN

HUGH O. McDEVITT

EDNA MOZES

YEHUDA SHOENFELD

PAUL TRAVERS

# The Antigens

VOLUME VII

EDITED BY

**MICHAEL SELA**

*Department of Chemical Immunology*

*The Weizmann Institute of Science*

*Rehovot, Israel*



ACADEMIC PRESS, INC.

Harcourt Brace Jovanovich, Publishers

San Diego New York Berkeley Boston

London Sydney Tokyo Toronto

COPYRIGHT © 1987 BY ACADEMIC PRESS, INC.  
ALL RIGHTS RESERVED.  
NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR  
TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC  
OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR  
ANY INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT  
PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS, INC.  
1250 Sixth Avenue, San Diego, California 92101

*United Kingdom Edition published by*  
ACADEMIC PRESS INC. (LONDON) LTD.  
24-28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data  
(Revised for vol. 7)

The Antigens.

Includes bibliographies and indexes.

1. Antigens—Collected works. 2. Immunochemistry—  
Collected works. 3. Immune response—Collected works.

I. Sela, Michael. II. Arnheim, Norman.

QR186.5.S44 599'.0292 73-799

ISBN 0-12-635507-X (v. 7: alk. paper)

PRINTED IN THE UNITED STATES OF AMERICA

87 88 89 90 9 8 7 6 5 4 3 2 1

Contents

List of Contributors . . . . . vii

Preface . . . . . ix

Contents of Other Volumes . . . . . xi

Chapter 1     *Ir* Genes: Antigen-Specific Genetic Regulation  
                  of the Immune Response

*Jay A. Berzofsky*

I. Introduction/Definitions . . . . . 1

II. Developing Concepts . . . . . 3

III. The Role of Genetic Restriction of Cell Interactions in *Ir* Gene  
      Function . . . . . 11

IV. Levels of Imposition of Genetic Restriction; Role of the Thymic  
      Environment; Studies in Chimeras . . . . . 24

V. Ia Antigens as *Ir* Gene Products . . . . . 35

VI. Non-MHC-Linked *Ir* Genes . . . . . 48

VII. The Role of Suppressor Cells in *Ir* Gene Control . . . . . 51

VIII. The T Cell Repertoire Model . . . . . 59

IX. The Antigen Presentation Model . . . . . 68

X. T Cell Influences on Antibody Specificity . . . . . 98

XI. Epilogue . . . . . 105

      References . . . . . 113

Chapter 2     Molecular Genetics of Class II (Ia) Antigens

*Paul Travers and Hugh O. McDevitt*

I. Introduction . . . . . 147

II. Immunogenetics . . . . . 148

III. Genomic Organization of the *I* Region . . . . . 154

IV. Correlation of Immunogenetic and Molecular Genetic Maps . . . . . 159

V. Gene Organization . . . . . 166

VI. Polymorphism of Class II Antigens . . . . . 171

VII. Correlation between Structure and Function of Class II Antigens . . . . .	188
VIII. Regulation of Ia Expression . . . . .	194
IX. Conclusion . . . . .	197
References . . . . .	199

### Chapter 3      Antigen-Specific T Cell Clones and T Cell Factors

*Edna Mozes and Ron N. Apte*

I. Introduction . . . . .	213
II. Functional T Cell Hybridomas and Their Soluble Products . . . . .	215
III. Antigen-Specific Virus-Transformed Functional T Cell Lines . . . . .	236
IV. T Cell Continuous Lines and Clones . . . . .	240
V. The T Cell Receptor . . . . .	276
VI. Concluding Remarks . . . . .	284
References . . . . .	289

### Chapter 4      Infection and Autoimmunity

*Yehuda Shoenfeld and Irun R. Cohen*

I. Introduction . . . . .	307
II. Molecular Mimicry between Microbial and Host Antigens . . . . .	310
III. Autoantibodies Produced by Patients with Infections . . . . .	313
IV. Altered Self . . . . .	315
V. Polyclonal Activation . . . . .	315
VI. The Role of Infection in the Expression of HLA Class II Antigens in Self Tissues . . . . .	317
VII. The Anti-Idiotypic Network . . . . .	317
VIII. Specific Therapy of Autoimmune Disease . . . . .	320
References . . . . .	322
<i>Index</i> . . . . .	327

## List of Contributors

*Numbers in parentheses indicate the pages on which the authors' contributions begin.*

RON N. APTE (213), Department of Microbiology and Immunology,  
Faculty of Health Sciences, Ben-Gurion University of the Negev,  
Beer-Sheva 84105, Israel

JAY A. BERZOFSKY (1), Metabolism Branch, National Cancer Institute,  
National Institutes of Health, Bethesda, Maryland 20892

IRUN R. COHEN (307), Department of Cell Biology, The Weizmann  
Institute of Science, Rehovot 76100, Israel

HUGH O. McDEVITT (147), Department of Medical Microbiology,  
Stanford University School of Medicine, Stanford, California  
94305

EDNA MOZES (213), Department of Chemical Immunology, The Weiz-  
mann Institute of Science, Rehovot 76100, Israel

YEHUDA SHOENFELD (307), Research Unit of Autoimmune Diseases  
and Department of Medicine 'D,' Soroka Medical Center, Fac-  
ulty of Health Sciences, Ben-Gurion University of the Negev,  
Beer-Sheva 84105, Israel

PAUL TRAVERS (147), Department of Medical Microbiology, Stanford  
University School of Medicine, Stanford, California 94305



This page intentionally left blank

## Preface

This is the seventh volume of a comprehensive treatise that covers all aspects of antigens and related areas of immunology, focusing its attention on the chemistry and biology of antigens as well as on their immunological roles and expression. Each chapter covers a particular subject, including both historical background and recent developments. The ultimate purpose of the treatise is to present an integrated picture that will lead to a better understanding of manifold immunological phenomena and of the nature of the immune response.

This volume contains four chapters, the first three of which are devoted to different aspects of the genetic control of the immune response, a most important field of research which has been triggered largely by the availability of synthetic antigens. Investigations in this field are crucial for our present-day understanding of both immunology and genetics. In the first chapter, the author discusses the determinant-specific genetic regulation of the immune response and the genes that control it. The second chapter deals with the molecular genetics of the antigens these genes control, first denoted Ia ("immune response associated") and now called class II antigens. In the third chapter the antigen-specific T cell clones and the specific factors derived from them are discussed. These three chapters present an integrated picture of a fascinating field in which enormous progress has been made in recent years, although some crucial questions are still to be answered.

The fourth and last chapter deals with an interesting approach, linking infection with autoimmunity. The authors also discuss the role of infection in the expression of class II antigens mentioned above. In addition to exploring processes responsible for the induction of autoimmune diseases, the authors suggest a specific therapy for them.

It is a pleasure to acknowledge the whole-hearted cooperation of the staff of Academic Press in the preparation of this treatise.

*MICHAEL SELA*

This page intentionally left blank

## Contents of Other Volumes

### Volume I

Nucleic Acid Antigens

*B. David Stollar*

Immunochemistry of Enzymes

*Ruth Arnon*

Structure of Immunoglobulins

*Joseph A. Gally*

Immunoglobulin Allotypes

*Rose Mage, Rose Lieberman, Michael Potter,  
and William D. Terry*

The Evolution of Proteins

*Norman Arnheim*

Phylogeny of Immunoglobulins

*R. T. Kubo, B. Zimmerman, and H. M. Grey*

Chemistry and Biology of Immunoglobulin E

*Kimishige Ishizaka*

AUTHOR INDEX—SUBJECT INDEX

### Volume II

Protein Antigens: The Molecular Bases of Antigenicity and Immunogenicity

*Michael J. Crumpton*

**Blood Group Antigens**

*Sen-itiroh Hakomori and Akira Kobata*

**Low Molecular Weight Antigens**

*A. L. de Weck*

**The Application of Antibody to the Measurement of Substances of Physiological and Pharmacological Interest**

*Edgar Haber and Knud Poulsen*

**Idiotypy of Antibodies**

*Jacques Oudin*

**Immunoglobulin A**

*J. F. Heremans*

**AUTHOR INDEX—SUBJECT INDEX****Volume III****Microbial Polysaccharides**

*Klaus Jann and Otto Westphal*

**Antigenic Determinants and Antibody Combining Sites**

*Joel W. Goodman*

**Lymphocytic Receptors for Antigens**

*G. L. Ada and P. L. Ey*

**Allergens and the Genetics of Allergy**

*David G. Marsh*

**A Biologic and Chemical Profile of Histocompatibility Antigens**

*S. Ferrone, M. A. Pellegrino, and R. A. Reisfeld*

**Antigens of the Mycoplasmatales and Chlamydiae**

*George E. Kenny*

**Virus Infections and the Immune Responses They Elicit**

*William H. Burns and Anthony C. Allison*

**AUTHOR INDEX—SUBJECT INDEX**

**Volume IV**

Immune Reactions of Lipids and Lipid Model Membranes

*Carl R. Alving*

Immunology of the Antibiotics

*Janet M. Dewdney*

Protective Antigens of Bacteria

*E. J. Steele, C. R. Jenkin, and D. Rowley*

Antigens of Pathogenic Fungi

*S. B. Salvin and Ruth Neta*

Antigenic Competition

*Michael J. Taussig*

Adjuvants

*Felix Borek*

Lectins: Their Chemistry and Application to Immunology

*Halina Lis and Nathan Sharon*

AUTHOR INDEX—SUBJECT INDEX

**Volume V**

Tumor Antigens

*Karl Erik Hellström and Joseph P. Brown*

Antigens of Helminths

*Pierre Pery and Gérard Luffau*

Cytotoxic Lymphocytes

*Peter Perlmann and Jean-Charles Cerottini*

Complement

*Peter J. Lachmann*

AUTHOR INDEX—SUBJECT INDEX

**Volume VI**

Dynamic Aspects of Antibody Function

*Israel Pecht*

Parasite Antigens and Their Immunogenicity in Infected Hosts

*Graham F. Mitchell and Robin F. Anders*

Immunological Tolerance

*B. Cinader*

AUTHOR INDEX—SUBJECT INDEX

# **The Antigens**

**VOLUME VII**



This page intentionally left blank

# *Ir* Genes: Antigen-Specific Genetic Regulation of the Immune Response

JAY A. BERZOFSKY

I.	Introduction/Definitions . . . . .	1
II.	Developing Concepts . . . . .	3
	A. Discovery and Antigen Specificity . . . . .	3
	B. Early Evidence for T Cell versus B Cell Involvement in <i>Ir</i> Gene Expression . . . . .	4
	C. MHC Linkage of <i>Ir</i> Genes and the Discovery of Ia Antigens . . . . .	9
III.	The Role of Genetic Restriction of Cell Interactions in <i>Ir</i> Gene Function . . . . .	11
	A. The Emerging Concept of Genetic Restriction of T Cell Interaction with Other Cells . . . . .	11
	B. The Role of T Cell Genetic Restriction in <i>Ir</i> Gene Function . . . . .	18
IV.	Levels of Imposition of Genetic Restriction; Role of the Thymic Environment; Studies in Chimeras . . . . .	24
V.	Ia Antigens as <i>Ir</i> Gene Products . . . . .	35
VI.	Non-MHC-Linked <i>Ir</i> Genes . . . . .	48
VII.	The Role of Suppressor Cells in <i>Ir</i> Gene Control . . . . .	51
VIII.	The T Cell Repertoire Model . . . . .	59
IX.	The Antigen Presentation Model . . . . .	68
	A. Epitope Specificity of <i>Ir</i> Genes . . . . .	68
	B. Determinant Selection. . . . .	72
	C. Antigen Processing . . . . .	75
	D. Attempts to Demonstrate Antigen Binding to Ia . . . . .	83
	E. Ia Influence on Single T Cell Clones . . . . .	89
	F. Separable Sites on Antigen for Interaction with T Cell and Ia . . . . .	92
X.	T Cell Influences on Antibody Specificity . . . . .	98
XI.	Epilogue . . . . .	105
	References . . . . .	113

## I. Introduction/Definitions

Immune-response (*Ir*) genes are defined as genes which regulate the ability of an individual to produce an immune response, cellular or humoral, against a specific antigen. Specificity is central to this