

ROITT'S

ESSENTIAL IMMUNOLOGY

Ivan Roitt

NINTH EDITION



b

Blackwell
Science

DOCKET
A L A R M

Find authenticated court documents without watermarks at docketalarm.com.

© 1971, 1974, 1977, 1980, 1984, 1988,
1991, 1994, 1997 by Blackwell Science Ltd
Editorial Offices:
Osney Mead, Oxford OX2 0EL
25 John Street, London WC1N 2BL
23 Ainslie Place, Edinburgh EH3 6AJ
350 Main Street, Malden
MA 02148 5018, USA
54 University Street, Carlton
Victoria 3053, Australia

Other Editorial Offices:

Blackwell Wissenschafts-Verlag GmbH
Kurfürstendamm 57
10707 Berlin, Germany
Zehetnergasse 6
A-1140 Wien
Austria

All rights reserved. No part of
this publication may be reproduced,
stored in a retrieval system, or
transmitted, in any form or by any
means, electronic, mechanical,
photocopying, recording or otherwise,
except as permitted by the UK
Copyright, Designs and Patents Act
1988, without the prior permission
of the copyright owner.

Set by Excel Typesetters Co., Hong Kong
Printed and bound in Italy
by Rotolito Lombarda S.p.A., Milan

The Blackwell Science logo is a
trade mark of Blackwell Science Ltd,
registered at the United Kingdom
Trade Marks Registry

First published 1971
Reprinted 1972 (twice), 1973 (twice)
Second edition 1974, Reprinted 1975
Third edition 1977, Reprinted 1978, 1979
Fourth edition 1980, Reprinted 1982, 1983
Fifth edition 1984
Sixth edition 1988, Reprinted 1988
Reprinted with corrections 1989
Seventh edition 1991
Eighth edition 1994, Reprinted 1996
Ninth edition 1997
Spanish editions 1972, 1975, 1978, 1982,
1988, 1989, 1993
Italian editions 1973, 1975, 1979, 1986,
1988, 1990, 1993, 1995
Portuguese editions 1973, 1979, 1983
French editions 1975, 1979, 1990
Dutch editions 1975, 1978, 1982
Japanese editions 1976, 1978, 1982, 1986, 1988
German editions 1977, 1984, 1988, 1993
Polish edition 1977
Greek editions 1978, 1989, 1992
Turkish edition 1979
Slovak edition 1981
Indonesian editions 1985, 1991
Russian edition 1988
Korean edition 1991
ELBS editions 1977, 1982, 1988, Reprinted 1991
Chinese (Taiwan) editions 1991, 1994

DISTRIBUTORS

Marston Book Services Ltd
PO Box 269
Abingdon
Oxon OX14 4YN
(Orders: Tel: 01235 465500
Fax: 01235 465555)

USA

Blackwell Science, Inc.
Commerce Place
350 Main Street
Malden, MA 02148 5018
(Orders: Tel: 800 759 6102
617 388 8250
Fax: 617 388 8255)

Canada

Copp Clark Professional
200 Adelaide St West, 3rd Floor
Toronto, Ontario M5H 1W7
(Orders: Tel: 416 597-1616
800 815-9417
Fax: 416 597-1617)

Australia

Blackwell Science Pty Ltd
54 University Street
Carlton, Victoria 3053
(Orders: Tel: 3 9347 0300
Fax: 3 9347 5001)

Catalogue records for this title
are available from the British Library
and the Library of Congress

ISBN 0-86542-729-1

CONTENTS

PREFACE	xiii	Target cells are told to commit suicide	19
ACKNOWLEDGEMENTS	xiv	Eosinophils	20
ABBREVIATIONS	xv	SUMMARY	20
USER GUIDE	xix		
 PART 1 • THE BASIS OF IMMUNOLOGY			
1 • Innate immunity, 3			
EXTERNAL BARRIERS AGAINST INFECTION	3		
PHAGOCYtic CELLS KILL MICROORGANISMS	6		
Polymorphs and macrophages are dedicated 'professional' phagocytes	6		
The polymorphonuclear neutrophil	6		
The macrophage	6		
Microbes are engulfed by phagocytosis	6		
There is an array of killing mechanisms	8		
Killing by reactive oxygen intermediates	8		
Killing by reactive nitrogen intermediates	9		
Killing by preformed antimicrobials	10		
COMPLEMENT FACILITATES PHAGOCYTOSIS	11		
Complement and its activation	11		
C3 undergoes slow spontaneous cleavage	11		
C3b levels are normally tightly controlled	11		
C3 convertase is stabilized on microbial surfaces	11		
The post-C3 pathway generates a membrane attack complex	12		
Complement has a range of defensive biological functions	12		
1 C3b adheres to complement receptors	12		
2 Biologically active fragments are released	12		
3 The terminal complex can induce membrane lesions	14		
COMPLEMENT CAN MEDIATE AN ACUTE INFLAMMATORY REACTION	14		
The mast cell plays a central role	14		
Macrophages can also do it	15		
HUMORAL MECHANISMS PROVIDE A SECOND DEFENSIVE STRATEGY	16		
Acute phase proteins increase in response to infection	16		
Interferons inhibit viral replication	18		
EXTRACELLULAR KILLING	18		
Natural killer (NK) cells	18		
		2 • Specific acquired immunity, 22	
		THE NEED FOR SPECIFIC IMMUNE MECHANISMS	22
		ANTIBODY – THE SPECIFIC ADAPTOR	22
		Antibody initiates a new complement pathway ('classical')	23
		Complexed antibody activates phagocytic cells	25
		CELLULAR BASIS OF ANTIBODY PRODUCTION	25
		Antibodies are made by lymphocytes	25
		Antigen selects the lymphocytes which make antibody	26
		The need for clonal expansion means humoral immunity must be acquired	26
		ACQUIRED MEMORY	28
		Secondary antibody responses are better	28
		ACQUIRED IMMUNITY HAS ANTIGEN SPECIFICITY	30
		Discrimination between different antigens	30
		Discrimination between self and nonself	32
		VACCINATION DEPENDS ON ACQUIRED MEMORY	32
		CELL-MEDIATED IMMUNITY PROTECTS AGAINST INTRACELLULAR ORGANISMS	33
		Cytokine-producing T-cells help macrophages to kill intracellular parasites	33
		Virally infected cells can be killed by cytotoxic T-cells and ADCC	33
		IMMUNOPATHOLOGY	35
		SUMMARY	35
		FURTHER READING	37
		General reading	37
		Reference work	37
		Historical	38
		In-depth series for the advanced reader	38
		Current information	38
		Multiple choice questions	38
		Electronic publications (linked to 'Rollit's Essential Immunology')	39
		Major journals	39

PART 2 · THE RECOGNITION OF ANTIGEN**3 · Antibodies, 43**

THE BASIC STRUCTURE IS A FOUR-PEPTIDE UNIT	43
AMINO ACID SEQUENCES REVEAL VARIATIONS IN IMMUNOGLOBULIN STRUCTURE	45
IMMUNOGLOBULIN GENES	45
Immunoglobulins are encoded by multiple gene segments	45
A special mechanism effects VDJ recombination	46
STRUCTURAL VARIANTS OF THE BASIC IMMUNOGLOBULIN MOLECULE	47
Isotypes	47
Allotypes	47
Idiotypes	50
IMMUNOGLOBULINS ARE FOLDED INTO GLOBULAR DOMAINS WHICH SUBSERVE DIFFERENT FUNCTIONS	50
Immunoglobulin domains have a characteristic structure	50
The variable domain binds antigen	51
Constant region domains determine secondary biological function	51
IMMUNOGLOBULIN CLASSES AND SUBCLASSES	51
Immunoglobulin G has major but varied roles in extracellular defenses	53
Activation of the classical complement pathway	53
The diversity of Fc γ receptors	54
Nonprecipitating 'univalent' antibodies	57
Immunoglobulin A guards the mucosal surfaces	57
Immunoglobulin M provides a defense against bacteremia	58
Immunoglobulin D is a cell surface receptor	59
Immunoglobulin E triggers inflammatory reactions	59
Immunoglobulins are further subdivided into subclasses	60
SUMMARY	61
FURTHER READING	62

4 · Membrane receptors for antigen, 63

THE B-CELL SURFACE RECEPTOR FOR ANTIGEN	63
The B-cell inserts a transmembrane Immunoglobulin into its surface	63
The surface Immunoglobulin is complexed with associated membrane proteins	64
THE T-CELL SURFACE RECEPTOR FOR ANTIGEN	65
The receptor for antigen is a transmembrane heterodimer	65
There are two classes of T-cell receptors	65
The encoding of T-cell receptors is similar to that of Immunoglobulins	66
The CD3 complex is an integral part of the T-cell receptor	67
THE GENERATION OF DIVERSITY FOR ANTIGEN RECOGNITION	68
Intrachain amplification of diversity	69
Random VDJ combination increases diversity geometrically	69
Playing with the junctions	69
Interchain amplification	70
Somatic hypermutation	70
THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)	71
Class I and class II molecules are membrane-bound heterodimers	71
MHC class I	71
MHC class II	71

Complement genes contribute to the remaining class III region of the MHC	72
Gene map of the MHC	72
The genes of the MHC display remarkable polymorphism	75
Nomenclature	75
Inheritance of the MHC	77
The tissue distribution of MHC molecules	77
MHC functions	77
SUMMARY	78
FURTHER READING	79

5 · The primary interaction with antigen, 80

WHAT IS AN ANTIGEN?	80
Of epitopes and antigen determinants	81
Identification of B-cell epitopes	81
ANTIGENS AND ANTIBODIES INTERACT BY SPATIAL COMPLEMENTARITY NOT BY COVALENT BONDING	83
Variation in hapten structure shows importance of shape	83
Spatial complementarity of epitope and paratope can be demonstrated	83
Antigen-antibody bonds are readily reversible	84
THE FORCES BINDING ANTIGEN TO ANTIBODY BECOME LARGE AS INTERMOLECULAR DISTANCES BECOME SMALL	86
1 Electrostatic	86
2 Hydrogen bonding	87
3 Hydrophobic	87
4 Van der Waals	87
AFFINITY MEASURES STRENGTH OF BINDING OF ANTIGEN AND ANTIBODY	88
The avidity of antiserum for antigen — the bonus effect of multivalency	88
THE SPECIFICITY OF ANTIGEN RECOGNITION BY ANTIBODY IS NOT ABSOLUTE	90
WHAT THE T-CELL SEES	91
Haplotype restriction reveals the need for MHC participation	91
T-cells recognize a linear peptide sequence from the antigen	91
PROCESSING OF INTRACELLULAR ANTIGEN FOR PRESENTATION BY CLASS I MHC	92
PROCESSING OF ANTIGEN FOR CLASS II MHC PRESENTATION FOLLOWS A DIFFERENT PATHWAY	93
THE NATURE OF THE 'GROOVY' PEPTIDE	96
Binding to MHC class I	96
Binding to MHC class II	97
THE $\alpha\beta$ T-CELL RECEPTOR FORMS A TERNARY COMPLEX WITH MHC AND ANTIGENIC PEPTIDE	98
Topology of the ternary complex	99
T-CELLS WITH A DIFFERENT OUTLOOK	99
Non-classical class I molecules can also present antigen	99
MHC class I-like molecules	99
The family of CD1 non-MHC class I-like molecules can present exotic antigens	99
$\gamma\delta$ TCRs have some features of antibody	100
SUPERANTIGENS STIMULATE WHOLE FAMILIES OF LYMPHOCYTE RECEPTORS	100
Bacterial toxins represent one major group of T-cell superantigens	100
Endogenous mouse mammary tumor viruses (MMTV) act as superantigens	100
Microbes can also provide B-cell superantigens	101

THE RECOGNITION OF DIFFERENT FORMS OF ANTIGEN BY B- AND T-CELLS IS ADVANTAGEOUS TO THE HOST	101
SUMMARY	102
FURTHER READING	103

PART 3 • TECHNOLOGY

6 • Immunochemical techniques, 107

ESTIMATION OF ANTIBODY	107
Antigen-antibody interactions in solution	107
What does serum 'antibody content' mean?	107
The classical precipitin reaction	109
Nonprecipitating antibodies can be detected by nephelometry	109
Complexes formed by nonprecipitating antibodies can be precipitated	110
Enhancement of precipitation by countercurrent immunoelectrophoresis	110
Measurement of antibody affinity	110
Agglutination of antigen-coated particles	111
Immunoassay for antibody using solid-phase antigen	112
The principle	112
A wide variety of labels is available	113
ELISA (enzyme-linked immunosorbent assay)	113
Other labels	113
Surface plasmon resonance	114
IDENTIFICATION AND MEASUREMENT OF ANTIGEN	114
Precipitation reaction can be carried out in gels	114
Characterization of antigens by electrophoresis and immunofixation	114
Quantification by single radial immunodiffusion (SRID)	115
The nephelometric assay for antigen	115
Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) for analysis of immunoprecipitates and immunoblotting	118
The immunoassay of antigens	117
Immunoassay on multiple microspots	118
Epitope mapping	118
T-cell epitopes	118
B-cell epitopes	119
DETECTION OF IMMUNE COMPLEX FORMATION	120
MAKING ANTIBODIES TO ORDER	120
The monoclonal antibody revolution	120
First in rodents	120
Catalytic antibodies	121
Human monoclonals can be made	123
Engineering antibodies	124
Fields of antibodies	125
Drugs can be based on the CDRs of minibodies	125
PURIFICATION OF ANTIGENS AND ANTIBODIES BY AFFINITY CHROMATOGRAPHY	126
NEUTRALIZATION OF BIOLOGICAL ACTIVITY	127
To detect antibody	127
Using antibody as an inhibitor	127
SUMMARY	128
FURTHER READING	129

7 • Cellular techniques, 130

ISOLATION OF LEUKOCYTE SUBPOPULATIONS	130
--	-----

Bulk techniques	130
Separation based on physical parameters	130
Separation exploiting biological parameters	131
Selection by antibody coating	131
Cell selection by the FACS	131
Enrichment of antigen-specific populations	131

IMMUNOHISTOCHEMISTRY — LOCALIZATION

OF ANTIGENS IN CELLS AND TISSUES	133
Immunofluorescence techniques	133
Direct test with labeled antibody	134
Indirect test for antibody	134
High resolution with the confocal microscope	135
Flow cytometry	135
The detection and isolation of rare cells	137
Other labeled antibody methods	139
Localization in tissues of a gene product	139
ASSESSMENT OF FUNCTIONAL ACTIVITY	140
The activity of phagocytic cells	140
Lymphocyte responsiveness	140
Limiting dilution analysis	140
Enumeration of antibody-forming cells	140
The immunofluorescence sandwich test	140
Plaque techniques	141
Analysis of functional activity by cellular reconstitution	142
Radiation chimeras	142
Mice with severe combined immunodeficiency (SCID)	142
Cellular interactions <i>in vitro</i>	142
Probing function with antibodies	143
GENETIC ENGINEERING OF CELLS	144
Insertion and modification of genes in mammalian cells	144
Introducing new genes into animals	144
Establishing 'designer mice' bearing new genes	144
Transgenes introduced into embryonic stem cells	144
Gene therapy in humans	145
SUMMARY	147
FURTHER READING	148

PART 4 • THE ACQUIRED IMMUNE RESPONSE

8 • The anatomy of the immune response, 151

THE SURFACE MARKERS OF CELLS IN THE IMMUNE SYSTEM	151
THE NEED FOR ORGANIZED LYMPHOID TISSUE	151
LYMPHOCYTES TRAFFIC BETWEEN LYMPHOID TISSUES	153
Lymphocytes home to their specific tissues	153
Transmigration occurs in three stages	153
Step 1: Tethering and rolling	153
Step 2: β_2 Integrin activation and cell flattening	154
Step 3: Transmigration into the tissue (diapedesis)	154
A closer look at the interacting receptors and their ligands	156
ENCAPSULATED LYMPH NODES	156
B-cell areas	156
T-cell areas	157
SPLEEN	158
MUCOSAL-ASSOCIATED LYMPHOID TISSUE (MALT)	161
Intestinal lymphocytes	162
BONE MARROW CAN BE A MAJOR SITE OF ANTIBODY SYNTHESIS	162

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.