Monoclonal Antibodies in Cancer

Contemporary Biomedicine

Monoclonal Antibodies in Cancer

Edited by **Stewart Sell** and **Ralph A. Reisfeld**, 1985

Calcium and Contractility: Smooth Muscle

Edited by **A. K. Grover** and **E. E. Daniel**, 1984

Carcinogenesis and Mutagenesis Testing

Edited by **J. F. Douglas**, 1984

The Human Teratomas: *Experimental and Clinical Biology*

Edited by **Ivan Damjanov**, **Barbara B. Knowles**, and
Davor Solter, 1983

Human Cancer Markers

Edited by **Stewart Sell** and **Britta Wahren**, 1982

Cancer Markers: *Diagnostic and Developmental Significance*

Edited by **Stewart Sell**, 1980

MONOCLONAL ANTIBODIES IN CANCER

Edited by

STEWART SELL

*University of Texas Health Science Center,
Houston, Texas*

and

RALPH A. REISFELD

*Scripps Clinic and Research Foundation,
La Jolla, California*

Humana Press • Clifton, New Jersey

Library of Congress Cataloging in Publication Data

Main entry under title:

Monoclonal antibodies in cancer.

(Contemporary biomedicine)

Includes bibliographies and index.

1. Tumor antigens—Analysis. 2. Antibodies,
Monoclonal. 3. Cancer—Diagnosis. I. Sell, Stewart,
1935-. II. Reisfeld, Ralph A. III. Series.

[DNLM: 1. Antibodies, Monoclonal—immunology.
2. Antigens, Neoplasm—immunology. 3. Neoplasms—
immunology. QW 575 M75105]

RC268.3.M67 1985 616.99'4079 85-4735

ISBN-13: 978-1-4612-9598-3 e-ISBN-13: 978-1-4612-5176-7

DOI: 10.1007/978-1-4612-5176-7

© 1985 The Humana Press Inc.

Softcover reprint of the hardcover 1st edition 1985

Crescent Manor
PO Box 2148
Clifton, NJ 07015

All rights reserved

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the Publisher.

CONTENTS

<i>Preface</i>	xvii
----------------------	------

CHAPTER 1

Monoclonal Antibody Defined Antigens on Animal Tumors

Michael R. Price and Robert W. Baldwin

1. Introduction	1
2. Antigen Expression on Chemically Induced Tumors	2
2.1. Murine Tumors.....	2
2.2. Rat Tumors.....	4
2.3. Guinea Pig Tumors	6
3. Use of Monoclonal Antibodies in Tumor Localization and Therapy	7
3.1. In Vivo Localization of Monoclonal Antibodies in Experimental Tumors.....	7
3.2. Serotherapy Using Antitumor Monoclonal Antibodies.....	9
3.3. Therapy Using Antitumor Monoclonal Antibodies Conjugated to Cytotoxic Agents	10
4. Conclusion	13
References	14

CHAPTER 2

Monoclonal Carcinoembryonic Antigen Antibodies

**Gustavo Reynoso, Margaret Keane, and
Mary Ann Reynoso**

1. Introduction	19
2. The Development of Monoclonal CEA Immunoassays	22
2.1. General Concepts of Monoclonal Antibody Methodology.....	22
2.2. Experimental and Clinical Experience with Monoclonal CEA Antibodies.....	24
3. Monoclonal Antibodies in the Immunohistological Evaluation of CEA	29
4. Monoclonal Anti-CEA Antibodies in Tumor Imaging	31
5. Immunotherapy with Monoclonal CEA Antibodies	35
6. Summary	36
References	38

CHAPTER 3

Monoclonal Antibodies to Alphafetoprotein and
Regulation of AFP Gene Expression

Stewart Sell

1. Introduction	41
2. Monoclonal Antibodies to AFP	42
2.1. ELISA Using Monoclonal Antibodies.....	42
2.2. Immune Localization Using Anti-AFP	44
2.3. Radioimmunescentigraphy	44
2.4. Immunotherapy.....	46
3. Control of AFP Gene Expression.....	49
3.1. AFP and Albumin Gene Expression During Development.....	49
3.2. AFP and Albumin Gene Structure.....	58
3.3. AFP and Albumin Gene Expression and Methylation.....	59
4. Summary	59
References	60

CHAPTER 4

Human Chorionic Gonadotropin Detection with
Monoclonal Antibodies**Paul H. Ehrlich, Zeinab A. Moustafa,
Alexander Krichevsky, and Ricardo Mesa-Tejada**

1. Introduction: hCG Chemistry and Immunochemistry with Antisera	65
2. Description of Monoclonal Antibodies to hCG.....	67
2.1. Affinity, Isotype, Subclass, and Cross-Reactivity of Antibodies.....	67
2.2. Topological Mapping of Monoclonal Antibodies: Relative Orientation of Epitopes	67
2.3. Biological Effects of Monoclonal Antibodies Against hCG.....	71
2.4. Special Properties of Monoclonal Antibodies to hCG: Synergistic Effects	73
3. Immunoassays with Monoclonal Antibodies to hCG	77
3.1. Description of Commercial Immunoassays for hCG Employing Monoclonal Antibodies.....	80
3.2. Research Immunoassays for hCG	81
4. In Vivo Immunodetection of Tumors.....	82
5. Immunocytochemistry with Monoclonal Antibodies to hCG	85
6. Summary	90
References	92

CHAPTER 5

Products of the Major Histocompatibility Complex on
Tumor Cells**Gerald N. Callahan**

1. Introduction	97
2. Variable Expression of MHC Antigens by Tumor Cells ...	100
2.1. Inducible MHC Antigens on Murine Tumor Cells	101
2.2. Inducible MHC Antigens on Human Tumors.....	106
2.3. Implications for Human Tumor Immunology.....	106

3. Abnormal Expression of MHC Antigens by Tumor Cells ..	107
3.1. Abnormal Expression of MHC Antigens on Murine Tumor Cells	107
3.2. Abnormal Expression of MHC Antigens on Human Tumor Cells	114
4. Conclusions	116
References	117

CHAPTER 6

Monoclonal Antibodies: Probes for the Study of Malignant T Cells

**Elizabeth A. Harden, Thomas J. Palker, and
Barton F. Haynes**

1. Introduction	121
2. Monoclonal Antibodies as Probes for the Study of Malignant T Cells	123
3. Normal T-Cell Maturation as Defined by Monoclonal Antibodies	123
4. Phenotypic Analysis of Malignant T Cells in Defined Clinical Syndromes	126
4.1. T-Cell Acute Lymphoblastic Leukemia	126
4.2. T-Cell Lymphoblastic Lymphoma	129
4.3. T-Cell Prolymphocytic Leukemia	129
4.4. Cutaneous T-Cell Lymphoma	130
4.5. T-Cell Chronic Lymphocytic Leukemia	131
4.6. IgG Fc Receptor Bearing (T _G) Lymphoproliferative Disease	131
4.7. Hairy Cell Leukemia	132
4.8. HTLV-Associated Japanese, Caribbean, and American Adult T-Cell Leukemia/Lymphoma (ATL)	133
4.9. Diffuse Lymphomas	136
4.10. T-Cell "Premalignant" Proliferative Disease	137
4.11. Thymoma	138
5. Summary and Conclusions	138
References	140

CHAPTER 7

Antigenic Markers on Normal and Malignant B Cells

Stephen Baird

1. Introduction	147
2. Antigenic Markers on Normal B Cells	148
3. Antigenic Markers on Malignant B Cells	155
Bibliography for Further Reading	166

CHAPTER 8

Nonlymphoblastic Leukemia-Associated Antigens Identified
by Monoclonal Antibodies**Robert G. Andrews and Irwin D. Bernstein**

1. Introduction	167
2. Myeloid-Associated Antigens Expressed by Normal Hematopoietic Cells and Cell Lines.....	170
2.1. Monoclonal Antibodies to Antigens Expressed Primarily on Granulocytes	170
2.2. Monoclonal Antibodies to Antigens Primarily Expressed by Monocytes	175
2.3. Monoclonal Antibodies to Antigens Associated with Granulocytes and Monocytes.....	178
2.4. Monoclonal Antibodies to Antigens Primarily Expressed on Immature Granulocytes and Monocytes.....	179
2.5. Antibodies Against Erythroid and Megakaryocytic Lineage-Associated Antigens.....	182
2.6. Myeloid-Associated Antigens Expressed by Hematopoietic Progenitors.....	182
2.7. Expression of Myeloid-Associated Antigens During Ontogeny and Phylogeny	184
2.8. Myeloid-Associated Antigens on Human Myeloid Cell Lines	184
3. Expression of Myeloid-Associated Antigens by Myeloid Leukemias	185
3.1. Diagnosis of Acute Nonlymphoblastic Leukemia Using Monoclonal Antibodies: Discrimination from ALL.....	185

3.2. Subsets of Acute Nonlymphoblastic Leukemia Defined by Monoclonal Antibodies.....	188
3.3. Prognostic Implications of Cell Surface Phenotype ..	189
4. Monoclonal Antibodies as Probes of Leukemic Stem Cell Phenotype and Differentiation	190
5. Therapy of Myeloid Leukemias Using Antibodies to Leukemia-Associated Antigens.....	191
6. Conclusions	193
References	194

CHAPTER 9

Monoclonal Antibodies as Probes for the Molecular Structure and Biological Function of Melanoma-Associated Antigens

Ralph A. Reisfeld

1. Introduction	205
2. Immunological Characterization of Monoclonal Antibodies	207
3. Immunochemical and Molecular Profiles of Human Melanoma-Associated Antigens	210
3.1. Glycoproteins	210
3.2. Glycolipids	214
4. Biosynthesis and Structure of Melanoma-Associated Antigens.....	218
5. Function of Melanoma Antigens Defined by Monoclonal Antibodies	220
5.1. In Vitro Studies	220
5.2. In Vivo Studies.....	223
6. Conclusions	224
References	225

CHAPTER 10

Lung Cancer Markers as Detected by Monoclonal Antibodies

James L. Mulshine, Frank Cuttitta, and John D. Minna

1. Introduction	229
2. Methods	230

3. Characterization Studies	231
4. Monoclonal Antibodies to Small-Cell Lung Cancer	233
4.1. Analysis of Antigen Expression in Small-Cell Lung Cancer	238
5. Monoclonal Antibodies to Nonsmall-Cell Lung Cancer	239
6. Monoclonal Antibodies to Defined Proteins of Lung Cancer	240
7. Imaging Lung Cancer with Monoclonal Antibodies	241
8. Monoclonal Antibodies with Therapeutic Applications	241
8.1. In Small-Cell Lung Cancer Variants	241
8.2. In Small-Cell Lung Cancer	242
9. Summary	243
References	244

CHAPTER 11

Human Breast Cancer Markers Defined by
Monoclonal Antibodies

**J. Schlom, J. Greiner, P. Horan Hand, D. Colcher,
G. Inghirami, M. Weeks, S. Pestka, P. B. Fisher,
P. Noguchi, and D. Kufe**

1. Introduction	247
2. Generation of Monoclonal Antibodies	248
3. Mammary Carcinoma Tissue as Immunogen for the Preparation of Monoclonal Antibodies to Carcinoembryonic Antigen (CEA)	254
4. Identification and Purification of Mammary Tumor- Associated Antigens	255
5. Antigenic Modulation and Evolution Within Human Mammary Carcinoma Cell Populations	257
6. Differential Reactivity of a Monoclonal Antibody (DF3) with Human Malignant Vs Benign Breast Tumors	262
7. Radiolocalization of Human Mammary Tumor Transplants in Athymic Mice by a Monoclonal Antibody	267
8. The Use of Recombinant Interferon to Enhance Detection of Human Carcinoma Antigens by Monoclonal Antibodies	270
References	275

CHAPTER 12

Antigens of Normal and Malignant Human Exocrine
Pancreatic Cells**Michael A. Hollingsworth and Richard S. Metzgar**

1. Introduction	279
2. Human Pancreatic Cell Antigens Defined by Polyclonal Antibodies	281
2.1. Polyclonal Antibodies Elicited to Normal Adult Pancreas or to Pancreatic Secretions.....	281
2.2. Polyclonal Antibodies Elicited to Fetal Pancreas	285
2.3. Polyclonal Antibodies Elicited to Pancreatic Tumors	287
3. Pancreatic Antigens Defined by Monoclonal Antibodies ...	290
3.1. Monoclonal Antibodies Elicited to Normal Pancreatic Cell Antigens	290
3.2. Monoclonal Antibodies Reactive with Pancreatic Tumor-Associated Antigens.....	291
4. General Discussion	302
References	307

CHAPTER 13

Monoclonal Antibodies to Human Prostate
Cancer-Related Antigens**T. Ming Chu**

1. Introduction	309
2. Cell Surface Antigens of Established Prostate Tumor Lines.....	310
3. Prostate Membrane-Associated Antigens.....	314
4. Prostate Antigen	315
5. Prostatic Acid Phosphatase	317
6. Summary	320
References	322

CHAPTER 14

Monoclonal Antibodies to Renal Cancer Markers

Neil H. Bander and Carlos Cordon-Cardo

1. Introduction	325
2. Mab S ₄	326

3. Mab S ₂₂	327
4. Mab S ₂₃	328
5. Mab S ₆	329
6. Use as Markers of Proximal Tubular Cells	330
7. Ability to Discriminate Renal from Nonrenal Cancers	330
8. Subclassification of Renal Cancer	330
8.1. gp/20nr	330
8.2. Subclassification of gp120nr ⁺ Renal Cancers	335
9. Correlation of Antigenic Phenotypes and Clinical Parameters	335
10. Summary	337
References	338

CHAPTER 15

Immunochemistry of Human Teratocarcinoma Stem Cells

Peter W. Andrews and Ivan Damjanov

1. Introduction	339
2. Stem Cells of Human Teratocarcinomas	340
2.1. Human Embryonal Carcinoma Cells	341
2.2. Surface Markers of Human EC Cells	342
2.3. Intermediate Filaments	351
3. Markers of Differentiation	352
3.1. The Nature of Differentiation	353
3.2. The Disappearance of EC Cell Markers	354
3.3. The Appearance of New Cell Markers	355
4. Conclusions	360
References	361

CHAPTER 16

Use of Monoclonal Antibodies in
Neurobiology and Neurooncology**Carol J. Wikstrand and Darell D. Bigner**

1. Introduction	365
2. Markers of Central and Peripheral Nervous System (PNS) Tumors Defined by Mabs	366
2.1. Biochemically Defined Markers	367
2.2. Shared Nervous System–Lymphoid Cell Markers ...	375
2.3. Shared Neuroectodermal–Oncofetal Markers	377
2.4. Putative Tumor-Restricted Markers	379

2.5. Markers of Interest Defined in Animal Model Systems	379
3. Current and Prospective Use of Marker-Mab Systems	382
3.1. The Problem of Antibody Localization and Delivery	382
3.2. The Problem of Antigenic Heterogeneity	386
3.3. Current Use of Single Marker-Mab Systems	388
3.4. The Use of Mab Panels	390
4. Summary and Prospects	391
References	393

CHAPTER 17

Human Monoclonal Antibodies: Humoral Immune Response in Patients with Cancer

Alan N. Houghton and Richard J. Cote

1. Introduction	399
1.1. Serological Evidence of Tumor Immunity in Humans	400
1.2. Clinical Evidence of Tumor Immunity in Humans ..	401
1.3. In Vivo Applications of Human Monoclonal Antibodies	402
2. Approaches to the Generation of Human Monoclonal Antibodies	403
2.1. Immortalization of B Lymphocytes by Epstein-Barr Virus	403
2.2. Strategies Using the Hybridoma Technology	405
3. Further Experimental Strategies	411
3.1. The EBV-Hybridoma Approach	412
3.2. Growth of Nontransformed B Cells in Culture	413
3.3. Preselection of B Cells In Vitro: Systems for In Vitro Stimulation by Antigen	413
3.4. Fusion Partners and Fusion Conditions	414
3.5. Immunoglobulin Genes	415
4. Human Monoclonal Antibodies Derived from Lymphocytes of Patients with Cancer	416
5. Conclusions	418
References	419
Index	423

CONTRIBUTORS

- PETER W. ANDREWS · *Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania*
- ROBERT G. ANDREWS · *Fred Hutchinson Cancer Research Center, Seattle, Washington*
- STEPHEN BAIRD · *University of California, San Diego, California*
- ROBERT W. BALDWIN · *University of Nottingham, Nottingham, Great Britain*
- NEIL H. BANDER · *New York Hospital-Cornell Medical Center, New York, New York*
- IRWIN D. BERNSTEIN · *University of Washington School of Medicine, Seattle, Washington*
- DARELL D. BIGNER · *Duke University Medical Center, Durham, North Carolina*
- GERALD N. CALLAHAN · *Colorado State University, Fort Collins, Colorado*
- T. MING CHU · *Roswell Park Memorial Institute, Buffalo, New York*
- D. COLCHER · *National Institutes of Health, Bethesda, Maryland*
- CARLOS CORDON-CARDO · *Memorial Sloan-Kettering Cancer Center, New York, New York*
- RICHARD J. COTE · *Memorial Sloan-Kettering Cancer Center, New York, New York*
- FRANK CUTTITTA · *National Institutes of Health, Bethesda, Maryland*
- IVAN DAMJANOV · *Hahnemann University School of Medicine, Philadelphia, Pennsylvania*
- PAUL H. EHRLICH · *Columbia University, New York, New York*
- P. B. FISHER · *Columbia University, New York, New York*
- J. GREINER · *National Institutes of Health, Bethesda, Maryland*
- ELIZABETH A. HARDEN · *Duke University, Durham, North Carolina*

- BARTON F. HAYNES · *Duke University, Durham, North Carolina*
A. HOLLINGSWORTH · *Duke University, Durham, North Carolina*
P. HORAN HAND · *National Institutes of Health, Bethesda, Maryland*
ALAN N. HOUGHTON · *Memorial Sloan-Kettering Cancer Center, New York, New York*
G. INGHIRAMI · *National Institutes of Health, Bethesda, Maryland*
MARGARET KEANE · *Yale University, New Haven, Connecticut*
ALEXANDER KRICHEVSKY · *Columbia University, New York, New York*
D. KUFÉ · *Dana Farber Institute, Boston, Massachusetts*
RICHARD MESA-TEJADA · *Columbia University, New York, New York*
RICHARD S. METZGAR · *Duke University, Durham, North Carolina*
JOHN D. MINNA · *National Institutes of Health, Bethesda, Maryland*
ZEINAB A. MOUSTAFA · *Columbia University, New York, New York*
JAMES L. MULSHINE · *National Institutes of Health, Bethesda, Maryland*
P. NOGUCHI · *National Center for Drugs and Biologics, Food and Drug Administration, Bethesda, Maryland*
THOMAS J. PALKER · *Duke University, Durham, North Carolina*
S. PESTKA · *La Roche Institute of Molecular Biology, Nutley, New Jersey*
MICHAEL R. PRICE · *University of Nottingham, Nottingham, Great Britain*
RALPH A. REISFELD · *Scripps Clinic and Research Foundation, La Jolla, California*
GUSTAVO REYNOSO · *Norwalk Hospital, Norwalk, Connecticut*
MARY ANN REYNOSO · *Norwalk Hospital, Norwalk, Connecticut*
J. SCHLOM · *National Institutes of Health, Bethesda, Maryland*
STEWART SELL · *University of Texas Health Science Center, Houston, Texas*
M. WEEKS · *National Institutes of Health, Bethesda, Maryland*
CAROL J. WIKSTRAND · *Duke University, Durham, North Carolina*

Preface

This represents the third volume in a series on cancer markers published by the Humana Press. The first volume, published in 1980, stressed the relationship of development and cancer as reflected in the production of markers by cancer that are also produced by normal cells during fetal development. The concept that cancer represents a problem of differentiation was introduced by Barry Pierce in describing differentiation of teratocarcinomas. Highlighted were lymphocyte markers, alphafetoprotein, carcinoembryonic antigen, ectopic hormones, enzymes and isozymes, pregnancy proteins, and fibronectin.

The second volume, published in 1982 and coedited with Britta Wahren, focused on the diagnostic use of oncological markers in human cancers, which were systematically treated on an organ by organ basis. At that time, the application of monoclonal antibodies to the identification of cancer markers was still in a very preliminary stage. A general introduction to monoclonal antibodies to human tumor antigens was given there by William Raschke, and other authors included coverage of those markers then detectable by monoclonal antibodies in their chapters.

Since the appearance of the second volume there has been an exponential increase in the number of papers published in which monoclonal antibodies have been used to identify cancer markers. This justifies, in part, the award of the 1984 Nobel Prize in which Köhler and Milstein shared. In less than 10 years, the technique of cell hybridization described by Kohler and Milstein [*Nature* **256**, 495 (1975)] has been modified, adapted, transformed, and applied not only to the identification of cancer markers, but also to the identification of microbial and normal tissue molecules, as well as to the provision of highly specific tools for the unraveling of many biological and pathological processes. In view of the decisive impact made by monoclonal antibodies on biological research, it came as no surprise that Köhler and Milstein shared the 1984 Nobel Prize in medicine.

In this third volume, the editors have attempted to update the vast amount of new information that is rapidly accumulating because of the widespread application of monoclonal antibodies in the study, diagnosis,

treatment, and prevention of cancer. The book begins with a brief review of the use of monoclonal antibodies in animals, and continues with the human system on which monoclonal antibodies have possibly made their greatest impact to date, that is, melanoma antigen. In this chapter the molecular characterization of melanoma markers made possible by monoclonal antibodies is presented by coeditor, Ralph Reisfeld, and the theme recurs with variations in subsequent chapters. In addition, the application of monoclonal antibodies to diagnosis is emphasized and the present status of the use of monoclonal antibodies in cancer therapy, now carried out in many laboratories, is presented.

A short history of cancer markers is given in the accompanying table. We feel that the main impact of monoclonal antibodies on cancer and cancer markers is still emerging, and many cancer markers of the future remain still to be discovered. In addition, monoclonal antibodies may also be used to understand the basic biology of cancer and carcinogenesis. As an example, our definition of cancer markers must now also include chromosomal changes that are currently being identified at new levels by ever more sophisticated methods. In the future, by probing for "oncogenes" or oncogene products, even more precise cancer markers should be found. In fact, monoclonal antibodies may prove to be an effective tool to identify oncogene products not yet identifiable.

Stewart Sell
Houston, Texas

Ralph Reisfeld
La Jolla, California

A Short History of Cancer Markers

Year	Author	Markers
1846	H. Bence-Jones	Bence-Jones protein
1928	W. H. Brown	Ectopic hormone syndrome
1930	B. Zondek	HCG
1932	H. Cushing	ACTH
1933	Gutmann and Gutmann	Prostatic acid phosphatase
1949	K. Oh-Uti	Deletion of blood group antigens
1959	C. Markert	Isozymes
1960	P. Newell	Philadelphia chromosome
1963	G. I. Abelev	Alphafetoprotein
1965	Gold and Freeman	Carcinoembryonic antigen
1969	Heubner and Todaro	Oncogenes
1975	Kohler and Milstein	Monoclonal antibodies
1980	Cooper, Weinberg, Bishop, etc.	Oncogene probes and transfection
1981	J. Yunis	Fragile sites