PERSPECTIVES ON GENES AND THE MOLECULAR BIOLOGY OF CANCER

Editors

Donald L. Robberson
Grady F. Saunders

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The University of Texas
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Perspectives on Genes and the Molecular Biology of Cancer

Edited by

Donald L. Robberson, Ph.D.
Department of Molecular Biology
The University of Texas
M. D. Anderson Hospital and
Tumor Institute at Houston
Houston, Texas

Grady F. Saunders, Ph.D.
Department of Biochemistry
The University of Texas
M. D. Anderson Hospital and
Tumor Institute at Houston
Houston, Texas

Raven Press ■ New York

Preface

The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston's Thirty-Fifth Annual Symposium on Fundamental Cancer Research focused on the molecular biology of cancer. From an understanding of the cellular metabolism involved in growth control, we can expect to find new ways to deal with cancer cells. In developing this understanding of the biology of human cancer, the ability to isolate specific DNA fragments through recombinant DNA cloning procedures and then to transfer and study these particular genes experimentally in higher eukaryotic cells and organisms represents profound and revolutionary genetic techniques. Rapid advances in recombinant DNA research and DNA sequence analysis have indeed led to a clearer perspective on genes and the molecular biology of cancer.

The papers presented at the symposium explored a number of systems that are yielding new and exciting information on the molecular biology of cancer. The meeting began with the Ernst W. Bertner Memorial Award lecture by Donald D. Brown, which described developmental control of eukaryotic genes, and the keynote address by Philip Leder, which concerned a new image for the mammalian genome. Thus, the stage was set early in the meeting for the presentation of recent findings indicating, for example, that many genes are interrupted by intervening sequences; that genomic DNA can be highly unstable, often moving about in much the same manner as transposable elements of prokaryotes; and that some genes are "processed" from an RNA transcript, with genetic information returned to the genome at a new location.

This fluidity of genetic information has implications for our understanding of the molecular basis of cancer, since genome rearrangements could lead to the activation of cellular transforming genes. That transforming genes, or proto-oncogenes, already exist within the genome of normal cells can be demonstrated by the presence of DNA sequences, as well as RNA transcripts, that can be isolated from normal human cells and shown to hybridize to the tranforming genes of animal tumor viruses. Furthermore, cloned fragments of DNA have been isolated from two different human bladder carcinoma cell lines that have the ability to transform cells of a particular cultured mouse cell line, NIH 3T3. Differences are detected in the vicinity of the transforming genes but are likely to be reflections of restriction enzyme fragment length polymorphism arising from variable numbers of short repeated sequences present in the regions flanking these genes in both normal and transformed cells. Thus far, three distinct transforming genes have been isolated from human cell lines derived from different tissues. A distinct transforming gene also has been isolated from a lung carcinoma cell line, and we can anticipate that transforming genes from other tumor cell lines will be isolated in the near future.

Since transcription of the transforming gene occurs in the bladder carcinoma cell lines but not in normal tissue, or at least only at extremely low levels, it is clear

that a key point in understanding the molecular biology of cancer lies in understanding the transcriptional activation of the transforming gene. This new or increased transcription of the cellular transforming gene is probably not a reflection of gene amplification but rather is the result of turning the gene on by mutation, such as the insertion of DNA sequences or rearrangement of sequences at a site that regulates transcription. The situation does, however, appear more complicated since alteration of the promoter or insertion of a promoter for the transcription could occur in an unexpected position, possibly far away on either side of the genes. Here, especially, studies of DNA tumor virus transcription can lead to a detailed understanding of how gene expression is regulated at the transcriptional level, knowledge that appears to be necessary to understanding the molecular biology of cancer. The finding of distinct transforming genes from different tumor lines also implies the existence of different gene products that regulate cell growth, any one of which when expressed ultimately can lead to cell division. Thus, these different genes are likely to be involved in regulating DNA replication.

It is fascinating to consider the evidence that viral transforming genes have been derived by reverse transcription of a cellular messenger RNA. There are now a number of examples of such "processed" genes that lack the intervening sequences (introns) of the "parental" gene and, in some cases, actually contain a sequence representing the poly(A) tail of the progenitor messenger RNA. Processed genes represent a new pathway for the generation of genetic material that can not only move between chromosomes, but may also move between species. One example of this was a cluster of histone genes that had crossed species barriers. Thus, the genetic processes involved in cancer may share a heritage with molecular mechanisms that mediate discontinuous evolutionary advances.

Until recently, facile manipulation of the eukaryotic genome has not been possible in the manner that has been so revealing for the bacterial geneticist. With the elegant techniques of site-specific mutagenesis and development of appropriate vectors through recombinant DNA techniques, the study of eukaryotic genetics has reached an exciting stage, which allows specific *in vitro* alteration of genetic elements at the nucleotide level and subsequent assay of their *in vivo* consequences. Although most of these procedures are applicable now only in yeast, there is enormous promise that these approaches will soon be available for mammalian cells. We have arrived at a stage in genetic engineering at which we are now able to transfer specific genes into single cells or embryos and then study the expression of these genes in dividing and differentiating tissues.

Finally, we have seen the development of powerful methods of DNA sequence determination that complement the precision of recombinant DNA cloning. These techniques have revealed new approaches to analyzing carcinogen and mutagen modification of DNA structure, to mention only one area. Knowledge of the DNA sequences for different families of eukaryotic genes, including those that code for globin, collagen, interferon, ovalbumin, immunoglobulins, and growth hormone, as well as families of repeated sequences, has provided insight into genome organization and has facilitated the discovery of pseudogenes.

The complete nucleotide sequences for several mammalian mitochondrial DNAs have demonstrated the unexpected novelty of codon usage and have emphasized the extraordinarily compacted and punctuated expression of this cytoplasmic genome in comparison with nuclear genes. These combined findings have shown us the magnificent complexity and diversity by which gene expression may be regulated in normal and malignant cells. Our perspective on the molecular biology of the cancer cell continues to change as we understand the relevant processes in ever-increasing detail, and we anticipate that the decade of the eighties will provide even more insight into differences between normal and malignant cell growth.

Editors' Foreword

"Perspectives on Genes and the Molecular Biology of Cancer" was the topic of the 35th Annual Symposium on Fundamental Cancer Research, held in Houston March 2–5, 1982. Interest in this topic was great because of the recent breakthroughs in molecular biology and the application of these advances to the understanding of human cancer. The symposium was attended by 1067 scientists representing 32 states and 14 foreign countries. This was also our first annual symposium to include a poster session, which was very successful, and we thank those who contributed.

As cochairpersons, we acknowledge our appreciation to the many individuals who provided guidance and advice in all matters pertaining to this symposium and this volume. The Symposium Organizing Committee members from The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston were: Ralph B. Arlinghaus, Emanuel J. Murgola, William K. Plunkett, Jr, and T. Elton Stubblefield. The External Advisory Committee was composed of Richard Axel, David Baltimore, Paul Berg, Pierre Chambon, Philip Leder, Beatrice Mintz, Bert O'Malley, and Charles Weissmann.

Special thanks and appreciation are given to Frances Goff and her staff for the many functions that they expertly and carefully planned and conducted. We welcome Jeff Rasco from Conference Services and thank him for his assistance throughout the symposium. We also express our gratitude to New England Biolabs, Accurate Chemicals, Amicon, Bethesda Research Laboratories, ISCO, P-L Biochemicals, Raytheon Data Systems, and Schleicher and Schuell for providing funds for the hospitality rooms in which speakers and guests could meet and discuss mutual interests. We are especially grateful to the National Cancer Institute and the Texas Division of the American Cancer Society for their continued support. We also very much appreciate the support of the Mike Hogg Foundation, and we thank The University of Texas Graduate School of Biomedical Sciences at Houston for its assistance. The Department of Scientific Publications and the Department of Public Information and Education aided invaluably in all matters pertaining to the information, announcements, and publications of the symposium. Marianne W. Doran of the Department of Scientific Publications edited and compiled the manuscripts into the monograph presented here, and we express our thanks for a job well done.

Donald L. Robberson
Grady F. Saunders

Contributors

James A. Barbosa
Department of Human Genetics
Yale University
New Haven, Connecticut 06511

David Barker
Department of Cellular, Viral, and Molecular Biology and Howard Hughes Medical Institute
University of Utah Medical School
Salt Lake City, Utah 84132

Hugo A. Barrera-Saldana
Department of Biochemistry
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston and The University of Texas Graduate School of Biomedical Sciences at Houston
Houston, Texas 77030

John D. Baxter
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics
University of California
San Francisco, California 94143

Max L. Birnstiel
Institut für Molekularbiologie II
University of Zurich
Hönggerberg
Zürich, Switzerland

Andrew Biro
Department of Human Genetics
Yale University
New Haven, Connecticut 06511

J. Michael Bishop
Department of Microbiology and Immunology
University of California
San Francisco, California 94143

Donald G. Blair
Laboratory of Molecular Oncology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Bonnie Blomberg
Center for Cancer Research
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

David Botstein
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Douglas E. Brash
Sidney Farber Cancer Institute
Laboratory of Biochemical Pharmacology
Department of Pathology
Harvard Medical School
Boston, Massachusetts 02115

Debbie L. Brock
Department of Molecular Biology
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

Donald D. Brown
Department of Embryology
Carnegie Institution of Washington
Baltimore, Maryland 21210

Meinrad Busslinger
Institut für Molekularbiologie II
University of Zürich
Hönggerberg
Zürich, Switzerland

Bruno Calabretta
Department of Biochemistry
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

Antony Carr
Transcription Laboratory
Imperial Cancer Research Fund Laboratories
London WC2A 3PX, England

Guy Cathala
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics
University of California
San Francisco, California 94143

Webster Cavenee
Department of Cellular, Viral, and Molecular Biology and Howard Hughes Medical Institute
University of Utah Medical School
Salt Lake City, Utah 84132

Irvin Chen
McArdle Laboratory
University of Wisconsin—Madison
Madison, Wisconsin 53706

Elena M. Ciejek
Department of Cell Biology
Baylor College of Medicine
Houston, Texas 77030

David A. Clayton
Department of Pathology
Stanford University School of Medicine
Stanford, California 94305

Alison Cowie
Transcription Laboratory
Imperial Cancer Research Fund Laboratories
London WC2A 3PX, England

Nigel Crawford
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

François Cuzin
Centre de Biochimie du Centre Nationale du Research Scientifique
Nice, France

Benoit de Crombrugghe
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

James E. Darnell, Jr.
Rockefeller University
New York, New York 10021

Barbara Dowds
Department of Chemistry
University of California, Davis
Davis, California 95616

Norman L. Eberhardt
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics
University of California
San Francisco, California 94143

Jennifer Favaloro
Transcription Laboratory
Imperial Cancer Research Fund Laboratories
London WC2A 3PX, England

Andrew Fire
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Sterling H. Fly, Jr.
The University of Texas System
Austin, Texas 78701

Gary M. Fox
Department of Chemistry
University of California, Davis
Davis, California 95616

William A. Franklin
Sidney Farber Cancer Institute
Laboratory of Biochemical Pharmacology
Department of Pathology
Harvard Medical School
Boston, Massachusetts 02115

David G. Gardner
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics
University of California
San Francisco, California 94143

Nicholas Glaichenhaus
Centre de Biochimie du Centre Nationale du Research Scientifique
Nice, France

Arthur Gutierrez-Hartmann
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics
University of California
San Francisco, California 94143

William A. Haseltine
Sidney Farber Cancer Institute
Laboratory of Biochemical Pharmacology
Department of Pathology
Harvard Medical School
Boston, Massachusetts 02115

P. Hieter
Laboratory of Molecular Genetics
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20205

G. Hollis
Laboratory of Molecular Genetics
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20205

Michael E. Kamarck
Department of Biology
Yale University
New Haven, Connecticut 06511

Robert Kamen
Transcription Laboratory
Imperial Cancer Research Fund Laboratories
London WC2A 3PX, England

Michael Karin
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics University of California
San Francisco, California 94143

Vincent J. Kidd
Department of Biochemistry
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston and The University of Texas Graduate School of Biomedical Sciences at Houston
Houston, Texas 77030

I. R. Kirsch
Laboratory of Molecular Genetics
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20205

Thymios P. Lambrou
Department of Biochemistry
The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

Nancy C. Lan
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics
University of California
San Francisco, California 94143

Robin Leach
Department of Cellular, Viral, and Molecular Biology and Howard Hughes Medical Institute
University of Utah Medical School
Salt Lake City, Utah 84132

A. Leder
Laboratory of Molecular Genetics
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20205

Philip Leder
Department of Genetics
Harvard Medical School
Boston, Massachusetts 02115

Leslie Leinwand
Department of Microbiology
Albert Einstein College of Medicine
New York, New York 10461

Charles A. LeMaistre
The University of Texas System Cancer Center
Houston, Texas 77030

Judith A. Lippke
Sidney Farber Cancer Institute
Laboratory of Biochemical Pharmacology
Department of Pathology
Harvard Medical School
Boston, Massachusetts 02115

Kwok Ming Lo
Sidney Farber Cancer Institute
Laboratory of Biochemical Pharmacology
Department of Pathology
Harvard Medical School
Boston, Massachusetts 02115

Dan Loewensteiner
Department of Chemistry
University of California, Davis
Davis, California 95616

Paul Luciw
Department of Microbiology and Immunology
University of California
San Francisco, California 94143

Melissa McCoy
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Catherine McKeon
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Synthia H. Mellon
The Howard Hughes Medical Institute Laboratories, the Metabolic Research Unit, and the Departments of Medicine and Biochemistry and Biophysics
University of California
San Francisco, California 94143

Beatrice Mintz
Institute for Cancer Research
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

Charles B. Mullins
The University of Texas System
Austin, Texas 78701

Mark Murray
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

M. Nau
Laboratory of Molecular Genetics
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20205

Jeffrey L. Nordstrom
Department of Cell Biology
Baylor College of Medicine
Houston, Texas 77030

Roel Nusse
Department of Microbiology and Immunology
University of California
San Francisco, California 94143

Hiroaki Ohkubo
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Bert W. O'Malley
Department of Cell Biology
Baylor College of Medicine
Houston, Texas 77030

Ira Pastan
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

K. Eric Paulson
Department of Biochemistry
University of California, Davis
Davis, California 95616

Gregory S. Payne
Department of Microbiology and Immunology
University of California
San Francisco, California 94143

Carolyn A. Peterson
Department of Molecular Biology
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

Minoo Rassoulzadegan
Centre de Biochimie du Centre Nationale du Research Scientifique
Nice, France

J. Ravetch
Laboratory of Molecular Genetics
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20205

Donald L. Robberson
Department of Molecular Biology
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

Urs Rohrer
Institut für Molekularbiologie II
University of Zürich
Hönggerberg
Zürich, Switzerland

Mark Rose
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Frank H. Ruddle
Departments of Human Genetics and Biology
Yale University
New Haven, Connecticut 06511

Sandro Rusconi
Institut für Molekularbiologie II
University of Zürich
Hönggerberg
Zürich, Switzerland

Mark Samuels
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Grady F. Saunders
Department of Biochemistry
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston and The University of Texas Graduate School of Biomedical Sciences at Houston
Houston, Texas 77030

Carl W. Schmid
Department of Chemistry
University of California, Davis
Davis, California 95616

Phillip A. Sharp
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Che-Kun J. Shen
Department of Genetics
University of California, Davis
Davis, California 95616

Chiaho Shih
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

David Shortle
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

T. Somasundaram
Department of Biochemistry
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

Elton Stubblefield
Department of Biochemistry
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

Douglas P. Tapper
Department of Pathology
Stanford University School of Medicine
Stanford, California 94305

Howard M. Temin
McArdle Laboratory
University of Wisconsin—Madison
Madison, Wisconsin 53706

Susumu Tonegawa
Center for Cancer Research
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

John J. Toole
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Richard Treisman
Transcription Laboratory
Imperial Cancer Research Fund Laboratories
London WC2A 3PX, England

Ming-Jer Tsai
Department of Cell Biology
Baylor College of Medicine
Houston, Texas 77030

George F. Vande Woude
Laboratory of Molecular Oncology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Richard A. Van Etten
Department of Pathology
Stanford University School of Medicine
Stanford, California 94305

Harold E. Varmus
Department of Microbiology and Immunology
University of California
San Francisco, California 94143

Mark W. Walberg
Department of Pathology
Stanford University School of Medicine
Stanford, California 94305

Shinichi Watanabe
McArdle Laboratory
University of Wisconsin—Madison
Madison, Wisconsin 53706

Robert A. Weinberg
Center for Cancer Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Sherman W. Weissman
Department of Human Genetics
Yale University
New Haven, Connecticut 06511

David Westaway
Department of Microbiology and Immunology
University of California
San Francisco, California 94143

Ray White
Department of Cellular, Viral, and Molecular Biology and Howard Hughes Medical Institute
University of Utah Medical School
Salt Lake City, Utah 84132

Kirk Wilhelmson
McArdle Laboratory
University of Wisconsin—Madison
Madison, Wisconsin 53706

T. Gordon Wood
Laboratory of Molecular Oncology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Yoshihiko Yamada
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Nancy Yen
Department of Biochemistry
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston
Houston, Texas 77030

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Introductory Remarks

Charles A. LeMaistre

President, The University of Texas System Cancer Center, Houston, Texas 77030

Good evening. It is indeed a pleasure to welcome you to the 35th Annual Symposium on Fundamental Cancer Research. The University of Texas System Cancer Center takes pride in hosting its research symposium each year. This year's meeting on "Perspectives on Genes and the Molecular Biology of Cancer" promises to be an especially pertinent one.

All of us here tonight recognize gene splicing as one of the most exciting achievements in the history of contemporary science. Even the proverbial man-on-the-street realizes that scientists at last have a tool that can generate a tremendous amount of benefit—from giving us the ability to produce large amounts of pure pharmaceuticals like insulin and interferon to helping us study the way cells grow and divide at the DNA level.

It is indeed satisfying to realize that recombinant DNA technology has generated such enthusiasm, even in those who are limited in their knowledge of science. As molecular biologists, you especially have been able to see how this ability to clone and propagate specific DNA fragments has enabled analysis of the structure and function of animal genes.

In 1977, when the UT Cancer Center last held a symposium on a similar topic, the recombinant DNA technology was only beginning to be utilized for mammalian cells. At that time, procedures were just being developed for the rapid sequencing of long sections of DNA molecules. Since that 1977 meeting on "Cell Differentiation and Neoplasia," an enormous amount of information has been gained about the structure, organization, and expression of genes in higher organisms. That knowledge has progressed to the point that, at this year's symposium, we are no longer meeting to discuss the "hows" of recombinant DNA technology, but "what" and "how much" has been and can be accomplished with its use.

One of the most surprising recent findings is that the animal genome is not fixed, but can be reorganized during development. Dr. Philip Leder, our keynote speaker this evening, will explore that subject in further depth. Another area to be discussed at this symposium concerns the exciting area of gene transfer. It is eye-opening to realize that molecular biologists now have the ability to show that a gene can alter a cell—and to prove that fact by transferring a gene from one species to another and propagating it through generations. In addition, a session will focus on the