Transgenic Animals

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Department of Meat and Animal Science

Clarence P. Hazeltine
Center for Population Research
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

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To Dr. Frank Ruddle

In 1976, he outlined, with a pencil on a yellow pad, many experiments that would become possible if animals could be transformed by changing their complement of genetic information. The possibilities were awesome then and their realization has opened vistas beyond our wildest imagination.

CONTRIBUTORS

Jan W. Abramczuk
Laboratory of Oral Medicine
National Institute of Dental Research
National Institutes of Health
Bethesda, Maryland

A.G. Amador
Department of Physiology
School of Medicine
Southern Illinois University
Carbondale, Illinois

P. Bain
Department of Physiology
School of Medicine
Southern Illinois University
Carbondale, Illinois

A. Bartke
Department of Physiology
School of Medicine
Southern Illinois University
Carbondale, Illinois

Karen A. Biery
Granada Genetics, Inc.
Texas A&M University Research Park
College Station, Texas

Leonard Bogarad
Department of Biology
Yale University
New Haven, Connecticut

Kenneth R. Bondioli
Granada Genetics, Inc.
Texas A&M University Research Park
College Station, Texas

Jan L. Breslow
Laboratory of Biochemical Genetics and Metabolism
The Rockefeller University
New York, New York

Guerard W. Byrne
Department of Biology
Yale University
New Haven, Connecticut

Sally A. Camper
Human Genetics
University of Michigan Medical School
Ann Arbor, Michigan

V. Chandrashekar
Department of Physiology
School of Medicine
Southern Illinois University
Carbondale, Illinois

Howard Chen
Merck Sharpe & Dohme Research Laboratories
Rahway, New Jersey

Thomas T. Chen
Center of Marine Biotechnology
University of Maryland
Baltimore, Maryland

Frank Costantini
Department of Genetics and Development
College of Physicians and Surgeons
Columbia University
New York, New York

Lyman B. Crittenden
USDA-ARS Regional Poultry Research Laboratory
East Lansing, Michigan

Chella S. David
Department of Immunology
Mayo Clinic
Rochester, Minnesota

Franko J. De Mayo
Department of Cell Biology
Baylor College of Medicine
Houston, Texas

Eva Derman
Department of Developmental and Structural Biology
The Public Research Institute of the City of New York, Inc.
New York, New York

Thomas C. Doetschman
College of Medicine
University of Cincinnati
Cincinnati, Ohio

Joseph P. Dougherty
Department of Molecular Genetics and Microbiology
University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School
Piscataway, New Jersey

Rex A. Dunham
Department of Fisheries and Allied Aquacultures
Auburn University
Auburn, Alabama

Timothy J. Dyer
Department of Zoological and Biomedical Sciences
Ohio University
Athens, Ohio

Rachel Ehrlich
Experimental Immunology Branch
National Cancer Institute, National Institutes of Health
Bethesda, Maryland

Anthony J. Faras
Department of Microbiology
Institute for Human Genetics
University of Minnesota
St. Paul, Minnesota

Neal L. First
Department of Meat and Animal Science
University of Wisconsin
Madison, Wisconsin

William I. Frels
Agricultural Research Center
USDA
Beltsville, Maryland

Hanan Galski
The Institute of Life Sciences
Department of Zoology
The Hebrew University of Jerusalem
Jerusalem, Israel

Lucia Irene Gonzalez-Villasenor
Department of Biology
Johns Hopkins University
Baltimore, Maryland

Jon W. Gordon
Department of Geriatrics and Adult Development, and
Department of Obstetrics, Gynecology and Reproductive Science
Mt. Sinai School of Medicine
New York, New York

Michael M. Gottesman
Laboratory of Molecular Biology
National Cancer Institute, National Institutes of Health
Bethesda, Maryland

Kevin S. Guise
Department of Animal Science
University of Minnesota
St. Paul, Minnesota

Perry B. Hackett, Jr.
Department of Genetics and Cell Biology
Institute for Human Genetics
University of Minnesota
St. Paul, Minnesota

Florence P. Haseltine
Center for Population Research
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Jan Heideman
University of Wisconsin
Biotechnology Center
Madison, Wisconsin

Lothar Hennighausen
Laboratory of Biochemistry and Metabolism
NIDDK, National Institutes of Health
Bethesda, Maryland

Keith G. Hill
Granada Genetics, Inc.
Texas A&M University Research Park
College Station, Texas

Rosemarie Hunziker
Molecular Biology Section, Laboratory of Immunology
NIAID, National Institutes of Health
Bethesda, Maryland

Luis M. Isola
Polly Annenberg Levy Division of Hematology, Department of Medicine
Mt. Sinai School of Medicine
New York, New York

Yasushi Ito
Laboratory of Biochemical Genetics and Metabolism
The Rockefeller University
New York, New York

Karen B. Jones
Granada Genetics, Inc.
Texas A&M University Research Park
College Station, Texas

Claudia Kappen
Department of Biology
Yale University
New Haven, Connecticut

Anne A.R. Kapuscinski
Department of Fisheries and Wildlife
University of Minnesota
St. Paul, Minnesota

Evelyn M. Karson
Laboratory of Molecular Hematology
NHLBI, National Institutes of Health
Bethesda, Maryland

David L. Kooyman
Department of Zoological and Biomedical Sciences
Ohio University
Athens, Ohio

John J. Kopchick
Department of Zoology
Edison Animal Biotechnology Center
Ohio University
Athens, Ohio

John M. Leonard
Laboratory of Molecular Microbiology
NIAID, National Institutes of Health
Bethesda, Maryland

F. Leung
Merck Sharpe & Dohme Research Laboratories
Rahway, New Jersey

Roger Little
Department of Immunology
Mayo Clinic
Rochester, Minnesota

F. Macken
Hubbard Farms
Walpole, New Hampshire

David H. Margulies
Molecular Biology Section, Laboratory of Immunology
NIAID, National Institutes of Health
Bethesda, Maryland

Javier Martin
Department of Immunology
Mayo Clinic
Rochester, Minnesota

Malcolm A. Martin
Laboratory of Molecular Microbiology
NIAID, National Institutes of Health
Bethesda, Maryland

A. Mayerhofer
Department of Physiology
School of Medicine
Southern Illinois University
Carbondale, Illinois

Glenn T. Merlino
Laboratory of Molecular Biology
National Cancer Institute, National Institutes of Health
Bethesda, Maryland

Ed Mills
Hubbard Farms
Walpole, New Hampshire

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

Ira Pastan
Laboratory of Molecular Biology
National Cancer Institute, National Institutes of Health
Bethesda, Maryland

David S. Pezen
Laboratory of Molecular Microbiology
NIAID, National Institutes of Health, and
Howard Hughes Medical Institute
Bethesda, Maryland

Carl A. Pinkert
DNX, Inc.
Athens, Ohio

Christoph W. Pittius
Laboratory of Biochemistry and Metabolism
NIDDK, National Institutes of Health
Bethesda, Maryland

Dennis A. Powers
Hopkins Marine Station
Stanford University
Pacific Grove, California

Lisa J. Raines
Industrial Biotechnology Association
Washington, D.C.

Caird E. Rexroad, Jr.
Reproduction Laboratory
Livestock and Poultry Sciences Institute
Beltsville Agricultural Research Center
Beltsville, Maryland

Charles Rosenblum
Merck Sharpe & Dohme Research Laboratories
Rahway, New Jersey

Frank H. Ruddle
Department of Biology
Yale University
New Haven, Connecticut

Donald W. Salter
Department of Microbiology and Public Health
Michigan State University
East Lansing, Michigan

Lakshmanan Sankaran
Laboratory of Biochemistry and Metabolism
NIDDK, National Institutes of Health
Bethesda, Maryland

Suresh Savarirayan
Department of Immunology
Mayo Clinic
Rochester, Minnesota

Klaus Schughart
Department of Biology
Yale University
New Haven, Connecticut

Kate Shahan
Department of Developmental and Structural Biology
The Public Health Research Institute of the City of New York, Inc.
New York, New York

Moshe Shani
Institute of Animal Science
Agricultural Research Organization
The Volcani Center
Bet Dagan, Israel

J.G.M. Shire
Department of Biology
University of Essex
Colchester, England

Dinah S. Singer
Experimental Immunology Branch
National Cancer Institute, National Institutes of Health
Bethesda, Maryland

Jim Smith
Hubbard Farms
Walpole, New Hampshire

H. Jin Son
Molecular Neurobiology
Burke Rehabilitation Center
White Plains, New York

R.W. Steger
Department of Physiology
School of Medicine
Southern Illinois University
Carbondale, Illinois

K. Tang
Department of Physiology
School of Medicine
Southern Illinois University
Carbondale, Illinois

Joyce Taylor
Merck Sharpe & Dohme Research Laboratories
Rahway, New Jersey

Howard M. Temin
Department of Oncology
McArdle Laboratory
University of Wisconsin
Madison, Wisconsin

Kirk Thomas
Biology Department
University of Utah
Salt Lake City, Utah

Shirley M. Tilghman
Department of Biology
Princeton University
Princeton, New Jersey

Manuel Utset
Department of Biology
Yale University
New Haven, Connecticut

T.E. Wagner
Edison Animal Biotechnology Center
Ohio University
Athens, Ohio

Annemarie Walsh
Laboratory of Biochemical Genetics and Metabolism
The Rockefeller University
New York, New York

Christoph Westphal
Laboratory of Biochemistry and Metabolism
NIDDK, National Institutes of Health
Bethesda, Maryland

Bing-Yuan Wei
Department of Immunology
Mayo Clinic
Rochester, Minnesota

J.S. Yun
Edison Animal Biotechnology Center
Ohio University
Athens, Ohio

Peijun Zhang
Hopkins Marine Station
Stanford University
Pacific Grove, California

PREFACE

A workshop on transgenic technology was held at the Center for Population Research, National Institutes of Health, Bethesda, MD, in December 1988. The Center for Population Research of the National Institute of Child Health and Human Development fosters programs aimed at promoting research in reproductive biology and medicine that will generate technological advances and lead to the improved reproductive health of the human population. The purpose of the workshop was to provide a forum at which scientists could discuss the many newly recognized applications of transgenic technology and the use of transgenics to enhance our understanding of the control of physiological functions, which are so important to our everyday health.

Transgenic animals are those with a foreign gene introduced into their genome. Such animals were given this designation by Gordon and his colleagues in 1980 (*Proc. Natl. Acad. Sci. USA*, 77, 7380–7384) when they reported the birth of the first mouse with a new gene that had been introduced into its genome by microinjection of that gene into the pronuclei of the early mouse embryo. This technology has subsequently been utilized to produce more than 400 strains of transgenic mice, as well as transgenic amphibians, rats, rabbits, sheep, goats, swine, cattle, poultry, and fish.

The production of transgenic mice was the culmination of previous advances in the areas of recombinant DNA and micromanipulation of mammalian cells. The techniques and their development are described by Dr. Gordon in Chapter 1. Much of the workshop was then devoted to the vast number of possible applications of such techniques.

As discussed in subsequent chapters, transgenic mice have provided a powerful model for the examination of the regulation of gene expression and for investigations into the genetic regulation of cellular and physiological functions. Transgenic mice have provided models for genetic diseases and have helped in the design of strategies for therapy. Other models have been generated for resistance to animal disease and novel or improved products or productivity of domestic animals. Gene transfer into fish, domestic animals, and birds suggests that it may be possible to increase the rate and efficiency of animal growth as well as to enhance disease resistance and to produce new or improved products.

The microinjection method commonly used to produce transgenics is still very inefficient. More efficient or versatile methods are being developed. The most promising techniques involve the use of replication-defective viral vectors for the efficient transfer of genes into cells or embryos and the use of the embryonic stem-cell transfer technique, which consists of the transfection, microinjection, or infection of genes into a nontransformed replicating line of embryonic stem cells. Stem cells enriched after selection for expression of a reporter gene are then incorporated into the germline of a blastocyst-stage embryo as chimeras, with the subsequent birth of mice derived from the stem-cell line. Such gene transfer, mediated by stem cells, when combined with recombination of homologous DNA sequences with native gene sequences, as described in Chapters 4 and 9, has opened new frontiers for site-specific gene transfer, gene deletion, and targeted gene therapy.

Great advances are occurring in our understanding both of promoter-enhancer sequences involved in the intrinsic control of gene expression and in the control of gene expression by external transcription-regulatory proteins, as discussed in Chapters 1 through 4. The introduction of foreign genes into animals has allowed scientists to test theories of genetic regulation and expression in vivo. Major questions about gene regulation, locations of chromosomal material, and the importance of *trans*-acting signals have been studied using this system, and other questions of basic developmental relevance have been posed. Fooling the animal into turning on stage-specific genes whose products have reporter molecules attached has permitted scientists to look more closely at the mechanisms that regulate physiological processes (see Chapters 3, 12, and 26). Three major factors influence the expression of genes in developing eukaryotes: *cis*-acting elements in or around the gene; *trans*-acting factors, which interact with genes in open chromosomal domains and stimulate transcription; and the location of the specific gene within the host genome. Because these same factors must op-

erate in the regulation of transferred genes, analysis of the expression of foreign genes in transgenic mice has revealed the relative importance of these factors in determining developmental timing, efficiency, and tissue distribution of gene expression.

Ultimately, the generation of transgenics that are useful in medicine, agriculture, or biology requires the ability to target gene expression to a specific tissue and to control the timing and level of expression of specific genes. It is becoming possible to manipulate such factors in several tissues of the body, such as the mammary gland, skeletal muscle, eye lens, liver, hemopoietic tissue, etc., as discussed in Chapters 4 through 11.

The possibility of somatic-cell correction of genetic defects and new medical therapies is clearly of salient importance (see Chapters 16 through 18). The targeting of specific tissues for gene expression is also important in agriculture: for example, the production of new or improved products in milk, improvement of the tenderness and reduction in the fat content of meat, or changing the growth patterns of animals, as discussed in Chapters 12, 19, 20, 22, 24, and 25.

Resistance to disease is important to humans and animals. The importance of the major histocompatibility genes in such resistance and strategies for enhancing resistance, by the addition of genes of the MHC complex or by interfering with the recognition of pathogens in birds and animals, are discussed in Chapters 11, 13, 14, 15, and 23.

No matter how useful transgenic animals are to scientists in their quest for a complete understanding of biology and nature, the potential release of transgenics into the natural environment for agricultural, animal conservation, or medical purposes is of public concern. The environmental, public safety, and patent aspects of transgenics are presented in Chapters 16 and 27.

Our understanding of cellular and molecular biology and its application to the whole animal through "transgenics" has grown rapidly throughout the 1980s. Applications of the results described in this volume will proliferate rapidly at an ever increasing rate during the 1990s, and the word "transgenic" will no longer require definition.

We would like to thank Dr. Ann Korner and Ms. Marge Perikles for their help in editing, typing, and assembling the manuscripts.

Neal L. First
Florence P. Haseltine

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