

MOLECULAR CELL GENETICS

Edited by

Michael M. Gottesman

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National Institutes of Health

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CONTRIBUTORS

IRENE ABRAHAM

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

GERALD M. ADAIR

Science Park—Research Division
University of Texas System Cancer
Center
Smithville, Texas

IRENE L. ANDRULIS

Department of Medical Genetics
The Hospital for Sick Children
Toronto, Ontario, Canada

FERNANDO CABRAL

Division of Endocrinology
University of Texas Medical
School
Houston, Texas

LAWRENCE CHASIN

Department of Biological Sciences
Columbia University
New York, New York

JUNG CHOI

Department of Genetics
University of California, Berkeley
Berkeley, California

ERNEST H.Y. CHU

Department of Human Genetics
University of Michigan Medical
School
Ann Arbor, Michigan

L. SCOTT CRAM

Los Alamos National Laboratory
Los Alamos, New Mexico

PAUL J. DOHERTY

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

RAYMOND G. FENWICK

Department of Biochemistry
Dalhousie University
Halifax, Nova Scotia Canada

MICHAEL M. GOTTESMAN

Laboratory of Molecular Biology

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

STEPHEN G. GRANT
Genetics Department and
Research Institute
The Hospital for Sick Children
Toronto, Ontario, Canada

BRUCE H. HOWARD
Laboratory of Molecular Biology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

C. JAMES INGLES
Best Institute
University of Toronto
Toronto, Ontario, Canada

RAMAN M. KOTHARI
Sarabhai Research Center
Baroda, India

VICTOR LING
Ontario Cancer Institute
Toronto, Ontario, Canada

MENASHE MARCUS
Department of Genetics
Hebrew University
Jerusalem, Israel

MARY McCORMICK
Laboratory of Molecular Biology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

DAVID PATTERSON
Department of Biophysics and
Genetics
Eleanor Roosevelt Institute for
Cancer Research
University of Colorado Medical
Center
Denver, Colorado

THEODORE PUCK
Department of Biophysics and
Genetics
Director, Eleanor Roosevelt
Institute for Cancer Research
University of Colorado Medical
Center
Denver, Colorado

CHARLES W. ROTH
Unité d'Immunoparasitologie
Institut Pasteur
Paris, France

RUTH SAGER
Dana Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

IMMO E. SCHEFFLER
Department of Biology
University of California, San Diego
LaJolla, California

MATTHEW J. SCHIBLER
Division of Endocrinology
University of Texas Medical
School
Houston, Texas

JERRY W. SHAY
Department of Cell Biology
University of Texas Health
Sciences Center at Dallas
Dallas, Texas

MICHAEL J. SICILIANO
Department of Genetics
M.D. Anderson Hospital
University of Texas
Texas Medical Center
Houston, Texas

LOUIS SIMINOVITCH
Department of Medical Genetics
University of Toronto
Hospital for Sick Children
Toronto, Ontario, Canada

ANNE E. SIMON
Department of Biology
Indiana University
Bloomington, Indiana

RAYMOND L. STALLINGS
Genetics Group LS-3 MS 886
Los Alamos National Laboratories
Los Alamos, New Mexico

PAMELA STANLEY
Department of Cell Biology
Albert Einstein College of
Medicine
Bronx, New York

CAROLYN STEGLICH
Department of Microbiology
East Carolina School of Medicine
Greenville, North Carolina

MILTON W. TAYLOR
Department of Biology
Indiana University
Bloomington, Indiana

LAWRENCE H. THOMPSON
Biomedical and Environmental
Sciences Division

Lawrence Livermore National
Laboratory
Livermore, California

JOHN J. WASMUTH
Department of Biological
Chemistry
University of California
Irvine, California

CAROLYN D. WHITFIELD
Department of Biochemistry
Howard University College
of Medicine
Washington, D.C.

RONALD G. WORTON
Department of Medical Genetics
University of Toronto
Hospital for Sick Children
Toronto, Ontario, Canada

GEORGE YERGANIAN
Cytogen/Research and
Development, Inc.
West Roxbury, Massachusetts

PREFACE

Molecular cell genetics is the synthesis of somatic cell genetics with molecular biology. This volume focuses on the major role that Chinese hamster cell lines have had in the development of this new biological discipline. For more than two decades, Chinese hamster cells have provided model systems for the study of genetic alterations in cultured mammalian cells. For the somatic cell geneticist, Chinese hamster cells serve the same function that *Escherichia coli* serve for the molecular biologist. Genetic studies using Chinese hamster cells have provided important insights and a logical, more rigorous structure to the study of the function of various metabolic pathways in all mammalian cells. More recently, dramatic developments in recombinant DNA technology have added molecular detail to our understanding of the mechanisms of somatic cell genetic alterations.

This volume will examine a wide variety of genetic systems developed in Chinese hamster cells. Each of the authors addresses the rationale for development of these systems, the details of mutant isolation and analysis, the major conclusions derived from these genetic studies, and, where possible, the molecular basis for the expression of mutant phenotypes. Comparison is made with genetic analysis developed in non-Chinese hamster cell systems, so that the reader has an overview of the state of knowledge for each genetic locus.

The first section of the book contains several personal perspectives on the historical development and characterization of cultured Chinese hamster cells by the scientists who developed these cell lines. The em-

phasis here is on the Chinese hamster cell lines (CHO, V79, and CHEF) that have been the mainstays of somatic cell genetics. The second section focuses on more technical aspects of genetic manipulation involving somatic cells including somatic cell hybridization techniques, chromosome isolation, cDNA cloning and expression, and DNA and vector-mediated gene transfer. The final section explores a wide variety of genetic systems in detail and demonstrates how Chinese hamster cell genetics can be used to study practically any problem in cell biology. The genetic loci discussed in detail here are those that have been most thoroughly analyzed as of this date. Other systems, still in the development stage, are either mentioned in the text or appear in Appendix II, which contains a list of major classes of Chinese hamster cell mutants isolated to date. Appendix I describes the lineage of currently available Chinese hamster cell lines that are referred to throughout the book.

This book is intended as a resource for the practicing somatic cell geneticist and for the cell biologist with an interest in the manner in which genetics can be used to elucidate biological problems. The content is presented in a style that should be easily accessible to an advanced undergraduate, graduate student, or post-doctoral fellow. It is anticipated that *Molecular Cell Genetics* will also be useful as a text of somatic cell genetics for use in the classroom.

MICHAEL M. GOTTESMAN

Bethesda, Maryland
January 1985

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SECTION 1

**THE DEVELOPMENT
AND CHARACTERIZATION
OF CHINESE HAMSTER
CELL LINES**

CHAPTER 1

THE BIOLOGY AND GENETICS OF THE CHINESE HAMSTER

George Yerganian

Cytogen Research and Development, Inc.
West Roxbury, Massachusetts
and Harvard School of Public Health
Department of Population Sciences
Boston, Massachusetts

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I. INTRODUCTION

The Chinese hamster (CH), *Cricetulus griseus*, is undoubtedly the least common rodent in the laboratory today. Its limited numbers contrast with the extensive use of cell lines derived from the CH for somatic cell genetics, mutational and gene transfer studies, and short-term genetic

toxicity (gen-tox) assays. In anticipation of this trend, our laboratory initiated whole animal studies with the intent of establishing additional cultured cell types to accommodate the needs of various *in vitro* applications. In the future, "second-generation" cell lines derived from current inbred strains will be used to extend genetic analysis of cultured cells to include differentiated functions of tissues.

Some 65 years have passed since the CH was first used as a laboratory specimen. Just three decades ago, reviews of the sparse literature centered around the problem of domestication. Shortly thereafter, the early descriptions of chromosomal features and the success in establishing cell lines led to the rapid technical adaptations encompassed by this volume. In this introductory chapter, coverage of the biology and genetics of the CH will be limited to representative examples of observations relevant to the establishment of new cell lines.

II. BRIEF HISTORY

A. 1919–1948

Introductions of hamster species to the laboratory date back to 1919 when Hsieh first reported the substitution of wild specimens of CH in place of mice for typing pneumococci and applying serum for complement fixation. During the 1920s, independent activities of British and American investigators led to implicating the CH as the rodent vector for the transmission of kala azar or leishmaniasis. In turn, the epidemiological aspects of leishmaniasis spurred interest in the Near East, thereby leading to trapping of the endemic Syrian and Armenian hamsters (Yerganian, 1972).

While earlier field workers in China had to compensate for civil strife and, later, the war with Japan, the rise of the People's Republic of China (PRC) was accompanied by the CH ascending to the political scene. The shipment of the ancestors of today's CH to the United States in December, 1948, was followed by the imprisonment of Dr. C.H. Hu of the Department of Pathology at the Peking Union Medical College. Also, Dr. Robert Briggs Watson was sentenced to be hanged *in absentia* for events that took place during his heroic dash from The Rockefeller Foundation Laboratory in Nanking to Shanghai to meet the last PanAm flight to the United States before the fall of the "Bamboo Curtain." The PRC's Germ Warfare Commission's condemnation of Drs. Hu and Watson was based on the assumption that the animals were to be bred in the United States, infected with cholera and plague, and parachuted into Manchuria. These accusations were the forerunners of misjudgements that plagued the CH until recently.