

EYE, RETINA, AND VISUAL SYSTEM OF THE MOUSE

Edited by Leo M. Chalupa and Robert W. Williams

THE MIT PRESS
CAMBRIDGE, MASSACHUSETTS
LONDON, ENGLAND

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This book was set in Baskerville by SNP Best-set Typesetter Ltd., Hong Kong.

Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

Eye, retina, and visual system of the mouse / Leo M. Chalupa and Robert W. Williams, editors.

p. cm.

Includes bibliographical references and index.

ISBN 978-0-262-03381-7 (hardcover : alk. paper)

1. Mice—Sense organs. 2. Eye. 3. Visual pathways.

I. Chalupa, Leo M. II. Williams, Robert W., 1952–

QL737.R6E94 2008

573.8'819353—dc22

2007047445

10 9 8 7 6 5 4 3 2 1

PREFACE

The publication of this volume on the mouse eye and visual system seems overdue, given the burst of studies that have appeared on this topic in recent years. As the chapters in this volume illustrate, mouse models have already contributed to a wide range of scientific breakthroughs for a significant number of ocular and neurological diseases. They have also allowed us to address fundamental issues that could not be pursued using other experimental models.

As is often the case, technical rather than conceptual advances have induced or driven the move to the mouse. The major factor has been the comparatively recent ability to produce mice with precisely defined changes in gene sequence—so-called transgenic and knockout mice. As a result of this powerful technology, genes can now be turned on or off in specific cell types at specific stages of development. Of equal importance, mouse genes can now be swapped for their human equivalents. This advance should ultimately permit us to humanize cells and tissues as complex as the retina, which will allow us to test new therapies in a controlled experimental context.

Although the power of mouse models is now taken for granted, it is worth noting that until fairly recently, study of the mouse visual system was a backwater of vision research. Size matters, and the large eyes of rabbits, cats, and cows were much more tractable for biochemical, histological, and functional studies. However, a small and dedicated cadre of radiation biologists and geneticists began to exploit mice for vision research, collecting and analyzing the stream of spontaneous and induced mutations at the Jackson Laboratory, at Oak Ridge National Laboratory, at the MRC Harwell, at the German Research Center for Environmental Health (GSF, Munich), and at universities and mouse breeding and research centers. Richard Sidman, Jin Kinoshita, Matthew LaVail, Ursula Dräger, and others helped to build the mouse resource infrastructure that we now take for granted, mapping and characterizing some of the first retinal degeneration, cataract, and pigmentation mutations that disturbed visual system function.

The main activity in vision research following the catalytic studies of David Hubel and Torsten Wiesel in the 1960s and 1970s centered on fundamental problems in visual neurophysiology, development, plasticity, and pathology. Cats and macaques were the dominant species used in this program of discovery. These models are still making major contributions to our understanding of mechanisms of vision and visual system development. Because of its small size, experimental fragility, and low acuity, the mouse was generally regarded as a compromised model for this kind of systems neuroscience. Those scientists interested in development typically followed the lead of Roger Sperry and colleagues and turned to cold-blooded vertebrates, particularly fishes and frogs. The sudden introduction of transgenic and knockout technology by Rudolph Jaenisch, Mario Capecchi, Martin Evans, and Oliver Smithies radically restructured experimental possibilities. What once seemed risky or even foolish—for example, functional studies of mouse retinal ganglion cells and visual cortex—now seemed well warranted if only the experimental methods could be miniaturized to deal with an eye with an axial length of 2 mm and a brain with a total mass of 450 mg. It soon became obvious just how informative

it would be to exploit this species to modify gene sequences and to test effects on development, function, plasticity, and disease progression.

This book can be considered a compendium of results from the first wave of studies. We hope that it will answer the question of just how useful mouse models can be as part of the exchange between experimental and clinical research. Study of these mouse models has already demonstrated real translational prowess. However, it is just a beginning, since large gaps in our knowledge remain to be filled, some of which, no doubt, are still blissfully outside our awareness.

We owe thanks to many colleagues. First, we are grateful to Drs. Patsy Nishina and Maureen McCall, as well as the National Eye Institute of the National Institutes of Health and the Jackson Laboratory, for having organized and supported meetings and workshops in 2004 and 2006 on the laboratory mouse in vision research. These meetings helped motivate the assembly of this book. We also thank the staff at MIT Press. For several decades, MIT Press has helped promote vision research by publishing wide-ranging texts on vision from engineering, computational, biological, psychological, and theoretical points of view. In particular, we are grateful to Barbara Murphy and Meagan Stacey for their expert assistance in bringing this project to fruition. Finally, we thank the authors whose work is included herein, for their contributions to this volume and for the sacrifices they made to meet the deadlines necessary to bring this project to a successful conclusion.