

# Springer Handbook of Auditory Research

Volume 75

## Series Editors

Arthur N. Popper, Ph.D., University of Maryland  
Richard R. Fay, Ph.D., Loyola University Chicago

## Editorial Board

Karen Avraham, Ph.D., Tel Aviv University, Israel  
Andrew Bass, Ph.D., Cornell University  
Lisa Cunningham, Ph.D., National Institutes of Health  
Bernd Fritzsche, Ph.D., University of Iowa  
Andrew Groves, Ph.D., Baylor University  
Ronna Hertzano, M.D., Ph.D., School of Medicine, University of Maryland  
Colleen Le Prell, Ph.D., University of Texas, Dallas  
Ruth Litovsky, Ph.D., University of Wisconsin  
Paul Manis, Ph.D., University of North Carolina  
Geoffrey Manley, Ph.D., University of Oldenburg, Germany  
Brian Moore, Ph.D., Cambridge University, UK  
Andrea Simmons, Ph.D., Brown University  
William Yost, Ph.D., Arizona State University

## **The ASA Press**

ASA Press, which represents a collaboration between the Acoustical Society of America and Springer Nature, is dedicated to encouraging the publication of important new books as well as the distribution of classic titles in acoustics. These titles, published under a dual ASA Press/Springer imprint, are intended to reflect the full range of research in acoustics. ASA Press titles can include all types of books that Springer publishes, and may appear in any appropriate Springer book series.

### *Editorial Board*

Mark F. Hamilton, University of Texas at Austin

Timothy F. Duda, Woods Hole Oceanographic Institution

Gary Elko, mh Acoustics

Robin Glosemeyer Petrone, Threshold Acoustics

William M. Hartmann (Ex Officio), Michigan State University

Darlene R. Ketten, Boston University

James F. Lynch (Ex Officio), Woods Hole Oceanographic Institution

Philip L. Marston, Washington State University

Andrew Norris, Rutgers University

Arthur N. Popper (Ex Officio), University of Maryland

Christine H. Shadle, Haskins Laboratories

G. Christopher Stecker, Boys Town National Research Hospital

Ning Xiang (Chair), Rensselaer Polytechnic Institute



Mark E. Warchol • Jennifer S. Stone  
Allison B. Coffin • Arthur N. Popper  
Richard R. Fay  
Editors

# Hair Cell Regeneration



*Editors*

Mark E. Warchol  
Department of Otolaryngology  
Washington University School of Medicine  
St. Louis, MO, USA

Allison B. Coffin  
Department of Integrative Physiology  
and Neuroscience  
Washington State University  
Vancouver, WA, USA

Richard R. Fay  
Department of Psychology  
Loyola University Chicago  
Chicago, IL, USA

Jennifer S. Stone  
Department of Otolaryngology/Head and  
Neck Surgery  
Virginia Merrill Bloedel Hearing  
Research Center  
University of Washington School of  
Medicine  
Seattle, WA, USA

Arthur N. Popper  
Department of Biology  
University of Maryland  
College Park, MD, USA

ISSN 0947-2657

ISSN 2197-1897 (electronic)

Springer Handbook of Auditory Research

ISBN 978-3-031-20660-3

ISBN 978-3-031-20661-0 (eBook)

<https://doi.org/10.1007/978-3-031-20661-0>

© Springer Nature Switzerland AG 2023

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG

The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

# The Acoustical Society of America

On 27 December 1928, a group of scientists and engineers met at Bell Telephone Laboratories in New York City to discuss organizing a society dedicated to the field of acoustics. Plans developed rapidly, and the Acoustical Society of America (ASA) held its first meeting on 10–11 May 1929 with a charter membership of about 450. Today, ASA has a worldwide membership of about 7000.

The scope of this new society incorporated a broad range of technical areas that continues to be reflected in ASA's present-day endeavors. Today, ASA serves the interests of its members and the acoustics community in all branches of acoustics, both theoretical and applied. To achieve this goal, ASA has established Technical Committees charged with keeping abreast of the developments and needs of membership in specialized fields, as well as identifying new ones as they develop.

The Technical Committees include acoustical oceanography, animal bioacoustics, architectural acoustics, biomedical acoustics, engineering acoustics, musical acoustics, noise, physical acoustics, psychological and physiological acoustics, signal processing in acoustics, speech communication, structural acoustics and vibration, and underwater acoustics. This diversity is one of the society's unique and strongest assets since it so strongly fosters and encourages cross-disciplinary learning, collaboration, and interactions.

ASA publications and meetings incorporate the diversity of these Technical Committees. In particular, publications play a major role in the society. *The Journal of the Acoustical Society of America* (JASA) includes contributed papers and patent reviews. *JASA Express Letters* (JASA-EL) and *Proceedings of Meetings on Acoustics* (POMA) are online, open-access publications, offering rapid publication. *Acoustics Today*, published quarterly, is a popular open-access magazine. Other key features of ASA's publishing program include books, reprints of classic acoustics texts, and videos. ASA's biannual meetings offer opportunities for attendees to share information, with strong support throughout the career continuum, from students to retirees. Meetings incorporate many opportunities for professional and social interactions, and attendees find the personal contacts a rewarding experience. These experiences result in building a robust network of fellow scientists and engineers, many of whom become lifelong friends and colleagues.

From the society's inception, members recognized the importance of developing acoustical standards with a focus on terminology, measurement procedures, and criteria for determining the effects of noise and vibration. The ASA Standards Program serves as the Secretariat for four American National Standards Institute Committees and provides administrative support for several international standards committees.

Throughout its history to present day, ASA's strength resides in attracting the interest and commitment of scholars devoted to promoting the knowledge and practical applications of acoustics. The unselfish activity of these individuals in the development of the society is largely responsible for ASA's growth and present stature.

# Series Preface



## Springer Handbook of Auditory Research

The following preface is the one that we published in volume 1 of the Springer Handbook of Auditory Research back in 1992. As anyone reading the original preface, or the many users of the series, will note, we have far exceeded our original expectation of eight volumes. Indeed, with books published to date and those in the pipeline, we are now set for 7 volumes in SHAR. Once volume 77 is completed, we are turning the series over to new Series Editors who will carry on with additional volumes.

We are very proud that there seems to be consensus, at least among our friends and colleagues, that SHAR has become an important and influential part of the auditory literature. While we have worked hard to develop and maintain the quality and value of SHAR, the real value of the books is very much because of the numerous authors who have given their time to write outstanding chapters and to our many co-editors who have provided the intellectual leadership to the individual volumes. We have worked with a remarkable and wonderful group of people, many of whom have become great personal friends of both of us. We also continue to work with a spectacular group of editors at Springer. Indeed, several of our past editors have moved on in the publishing world to become senior executives.

But the truth is that the series would and could not be possible without the support of our families, and we want to take this opportunity to dedicate all of our SHAR books to them. Our wives, Catherine Fay and Helen Popper, and our children, Michelle Popper Levit, Melissa Popper Levinsohn, Christian Fay, and Amanda Fay Sierra, have been immensely patient as we developed and worked on this series. We thank them and state, without doubt, that this series could not have happened without them. We also dedicate the future of SHAR to our next generation of (potential) auditory researchers – our grandchildren – Ethan and Sophie Levinsohn, Emma Levit, Nathaniel, Evan, and Stella Fay, and Sebastian Sierra.

# Preface 1992

The Springer Handbook of Auditory Research presents a series of comprehensive and synthetic reviews of the fundamental topics in modern auditory research. The volumes are aimed at all individuals with interests in hearing research including advanced graduate students, post-doctoral researchers, and clinical investigators. The volumes are intended to introduce new investigators to important aspects of hearing science and to help established investigators to better understand the fundamental theories and data in fields of hearing that they may not normally follow closely.

Each volume presents a particular topic comprehensively, and each serves as a synthetic overview and guide to the literature. As such, the chapters present neither exhaustive data reviews nor original research that has not yet appeared in peer-reviewed journals. The volumes focus on topics that have developed a solid data and conceptual foundation rather than on those for which a literature is only beginning to develop. New research areas will be covered on a timely basis in the series as they begin to mature.

Each volume in the series consists of a few substantial chapters on a particular topic. In some cases, the topics will be ones of traditional interest for which there is a substantial body of data and theory, such as auditory neuroanatomy (Vol. 1) and neurophysiology (Vol. 2). Other volumes in the series deal with topics that have begun to mature more recently, such as development, plasticity, and computational models of neural processing. In many cases, the series editors are joined by a co-editor having special expertise in the topic of the volume.

*SHAR logo by Mark B. Weinberg, Potomac, Maryland, used with permission*

Richard R. Fay\*, Chicago, IL, USA  
Arthur N. Popper, College Park, MD, USA

---

\*Deceased

# Volume Preface

The chapters in this volume review current knowledge of the mechanisms that underly the generation of hair cells in the mature ear and discuss how such new hair cells might reestablish functional connections with the brain. Although older findings are discussed, our emphasis is on work conducted since about 2005 because much exciting work has taken place since chapters in earlier volumes of the *Springer Handbook of Auditory Research*.

Chapter 2, by Madeleine Hewitt, David W. Raible, and Jennifer S. Stone, gives an overview of hair cell regeneration in non-mammalian vertebrates (primarily fishes and birds). They review the evidence that first led scientists to conclude that hair cells can be replaced after damage, and they detail the cellular processes by which supporting cells can give rise to new hair cells. This is followed by Chap. 3, where Mark A. Rudolf and Jeffrey T. Corwin focus on the basic biophysical and mechanical properties of supporting cells during regeneration. Together, Chaps. 2 and 3 build a foundation of understanding for the remarkable capacity for hair cell regeneration shared by nonmammalian vertebrates and establish the context for the next three chapters, which focus on the mammalian ear.

In Chap. 4, Andrew Forge and Ruth Taylor give an overview of hair cell regeneration in the mammalian inner ear. The authors provide a brief review of the development and structure of the mammalian vestibular and auditory sensory epithelia as well as review the phenomenology of natural regeneration in the mature mammalian vestibular organs, how it occurs through phenotypic conversion of supporting cells, and its limitations.

One frequently proposed strategy for inducing regeneration in the mature cochlea is to reactivate the signaling pathways that produce hair cells during embryonic development. In Chap. 5, Melissa M. McGovern and Andrew K. Groves describe the molecular mechanisms that govern organ of Corti development, resulting in the establishment of correct cell phenotypes, numbers, and patterning. The authors then explain how insights gleaned from development have shaped studies of auditory hair cell regeneration.

Another approach to inducing repair in the mammalian inner ear involves the reactivation or surgical introduction of stem cells. Such efforts are reviewed by

Amanda Janesick, Stefan Heller, and Eri Hashino in Chap. 6. The chapter describes current strategies for generating inner ear cell types from pluripotent stem cells in vitro as well as somatic stem and progenitor cells that are present in the ears of non-mammalian vertebrates, in the adult mammalian vestibular organs, and in the cochleae of neonatal rodents.

In Chap. 7, Steven H. Green, Sepand Bafti, Benjamin M. Gansemer, A. Eliot Shearer, Muhammad Taifur Rahman, Mark E. Warchol, and Marlan R. Hansen summarize the causes of spiral ganglion neuron death and review several approaches to their possible regeneration.

Finally, in Chap. 8, Brandon C. Cox, John V. Brigande, and Bradley J. Walters focus on some newer approaches to the biological restoration of hearing. They provide a detailed overview of such methodology and potential applications to otic regeneration.

This volume conveys many of the critical advances in our understanding of hair cell regeneration that have occurred since the 2005 SHAR volumes. We have framed these advances in the context of our shared goal of defining ways to stimulate regeneration, and recovery of hearing and balance function, in humans. In addition, this volume discusses many of the cutting-edge approaches that are being applied, or soon will be applied, to hasten progress toward this goal.

Mark E. Warchol, St. Louis, MO, USA  
Jennifer S. Stone, Seattle, WA, USA  
Allison B. Coffin, Vancouver, WA, USA  
Richard R. Fay, Chicago, IL, USA  
Arthur N. Popper, College Park, MD, USA

# Contents

<b>1</b>	<b>Sensory Regeneration in the Inner Ear: History, Strategies, and Prospects</b> . . . . .	<b>1</b>
	Mark E. Warchol and Jennifer S. Stone	
<b>2</b>	<b>Nonmammalian Hair Cell Regeneration: Cellular Mechanisms of Morphological and Functional Recovery</b> . . . . .	<b>11</b>
	Madeleine N. Hewitt, David W. Raible, and Jennifer S. Stone	
<b>3</b>	<b>Cell Junctions and the Mechanics of Hair Cell Regeneration</b> . . . . .	<b>41</b>
	Mark A. Rudolf and Jeffrey T. Corwin	
<b>4</b>	<b>Mammalian Hair Cell Regeneration</b> . . . . .	<b>73</b>
	Ruth Taylor and Andrew Forge	
<b>5</b>	<b>Specification and Plasticity of Mammalian Cochlear Hair Cell Progenitors</b> . . . . .	<b>105</b>
	Melissa M. McGovern and Andrew K. Groves	
<b>6</b>	<b>Inner Ear Cells from Stem Cells: A Path Towards Inner Ear Cell Regeneration</b> . . . . .	<b>135</b>
	Amanda Janesick, Eri Hashino, and Stefan Heller	
<b>7</b>	<b>Spiral Ganglion Neuron Regeneration in the Cochlea: Regeneration of Synapses, Axons, and Cells</b> . . . . .	<b>163</b>
	Steven H. Green, Sepand Bafti, Benjamin M. Gansemer, A. Eliot Shearer, Muhammad Taifur Rahman, Mark E. Warchol, and Marlan R. Hansen	
<b>8</b>	<b>Genetic and Epigenetic Strategies for Promoting Hair Cell Regeneration in the Mature Mammalian Inner Ear</b> . . . . .	<b>195</b>
	Brandon C. Cox, John V. Brigande, and Bradley J. Walters	

# Contributors

**Sepand Bafti** Nortis Inc., Woodinville, WA, USA

**John V. Brigande** Oregon Hearing Research Center, Oregon Health & Science University, Portland, OR, USA

**Jeffrey T. Corwin** Department of Neuroscience, University of Virginia School of Medicine, Charlottesville, VA, USA

Department of Cell Biology, University of Virginia School of Medicine, Charlottesville, VA, USA

**Brandon C. Cox** Southern Illinois University School of Medicine, Springfield, IL, USA

**Andrew Forge** UCL Ear Institute, London, UK

**Benjamin M. Gansemer** Department of Biology, University of Iowa, Iowa City, IA, USA

**Steven H. Green** Department of Biology, University of Iowa, Iowa City, IA, USA

**Andrew K. Groves** Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA

Department of Human and Molecular Genetics, Baylor College of Medicine, Houston, TX, USA

**Marlan R. Hansen** Department of Otolaryngology – Head & Neck Surgery, University of Iowa, Iowa City, IA, USA

**Eri Hashino** Department of Otolaryngology – Head & Neck Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

**Stefan Heller** Department of Otolaryngology – Head & Neck Surgery, Stanford University School of Medicine, Stanford, CA, USA

Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA

**Madeleine N. Hewitt** Molecular and Cellular Biology Graduate Program, University of Washington School of Medicine, Seattle, WA, USA

Department of Biological Structure, University of Washington School of Medicine, Seattle, WA, USA

Department of Otolaryngology/Head and Neck Surgery, University of Washington School of Medicine, Seattle, WA, USA

**Amanda Janesick** Department of Otolaryngology–Head & Neck Surgery, Stanford University School of Medicine, Stanford, CA, USA

Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA

**Melissa M. McGovern** Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA

**Muhammad Taifur Rahman** Department of Biology, University of Iowa, Iowa City, IA, USA

**David W. Raible** Molecular and Cellular Biology Graduate Program, University of Washington School of Medicine, Seattle, WA, USA

Department of Biological Structure, University of Washington School of Medicine, Seattle, WA, USA

Department of Otolaryngology/Head and Neck Surgery, University of Washington School of Medicine, Seattle, WA, USA

**Mark A. Rudolf** Department of Neuroscience, University of Virginia School of Medicine, Charlottesville, VA, USA

Department of Cell Biology, University of Virginia School of Medicine, Charlottesville, VA, USA

**A. Eliot Shearer** Department of Otolaryngology, Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA

**Jennifer S. Stone** Department of Otolaryngology/Head and Neck Surgery, Virginia Merrill Bloedel Hearing Research Center, University of Washington School of Medicine, Seattle, WA, USA

**Ruth Taylor** UCL Ear Institute, London, UK

**Bradley J. Walters** University of Mississippi Medical Center, Jackson, MS, USA

**Mark E. Warchol** Department of Otolaryngology, Washington University School of Medicine, St. Louis, MO, USA