Springer Handbook of Auditory Research

Colleen G. Le Prell
Edward Lobarinas
Arthur N. Popper
Richard R. Fay *Editors*

Translational Research in Audiology, Neurotology, and the Hearing Sciences

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Springer Handbook of Auditory Research

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Translational Research in Audiology, Neurotology, and the Hearing Sciences

With 24 Illustrations

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Editors
Colleen G. Le Prell
Callier Center for Communication Disorders
University of Texas at Dallas
Dallas, TX
USA

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

Edward Lobarinas
Callier Center for Communication Disorders
University of Texas at Dallas
Dallas, TX
USA

Richard R. Fay
Marine Biological Laboratory
Woods Hole, MA
USA

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Acoustical Society of America

The mission of the **Acoustical Society of America** (www.acousticalsociety.org) is to increase and diffuse the knowledge of acoustics and promote its practical applications. The ASA is recognized as the world's premier international scientific society in acoustics, and counts among its more than 7,000 members, professionals in the fields of bioacoustics, engineering, architecture, speech, music, oceanography, signal processing, sound and vibration, and noise control.

Since its first meeting in 1929, The Acoustical Society of America has enjoyed a healthy growth in membership and in stature. The present membership of approximately 7,500 includes leaders in acoustics in the United States of America and other countries. The Society has attracted members from various fields related to sound including engineering, physics, oceanography, life sciences, noise and noise control, architectural acoustics; psychological and physiological acoustics; applied acoustics; music and musical instruments; speech communication; ultrasonics, radiation, and scattering; mechanical vibrations and shock; underwater sound; aeroacoustics; macrosonics; acoustical signal processing; bioacoustics; and many more topics.

To assure adequate attention to these separate fields and to new ones that may develop, the Society establishes technical committees and technical groups charged with keeping abreast of developments and needs of the membership in their specialized fields. This diversity and the opportunity it provides for interchange of knowledge and points of view has become one of the strengths of the Society.

The Society's publishing program has historically included the *Journal of the Acoustical Society of America*, the magazine *Acoustics Today*, a newsletter, and various books authored by its members across the many topical areas of acoustics. In addition, ASA members are involved in the development of acoustical standards concerned with terminology, measurement procedures, and criteria for determining the effects of noise and vibration.

This book is dedicated to the memory of Bertrand Moore, PhD (1944–2015). Dr. Moore joined the University of Texas at Dallas (UTD) in 1980 as a scholar and clinician. He was appointed dean in 1989. In this role, his steadfast commitment and support for faculty, students, and translational research in the behavioral and brain sciences was unwavering. Dr. Moore was a strong advocate for translational research in hearing science, with the long-term goal of integrating academics, research, and patient care to advance the fields of audiology and speech-language pathology. His advocacy allowed the establishment of the Callier Prize, an award that recognizes individuals, worldwide, for their contributions to the diagnosis and treatment of communication disorders as well as establishment of multiple endowed chair positions and breaking ground for a major expansion of the clinical and research facilities. Dr. Moore believed in and supported the translational activities described in this volume and was an advocate for faculty in all areas of the scientific spectrum. He will be greatly missed.

Series Preface

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 more than 50 volumes in SHAR, and we are still open to new and exciting ideas for additional books.

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 coeditors 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. To our delight, this includes the current president of Springer US, Dr. William Curtis.

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 the SHAR books, past and future, 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; and Nathaniel, Evan, and Stella Fay.

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, postdoctoral 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 coeditor having special expertise in the topic of the volume.

Richard R. Fay, Woods Hole, MA, USA
Arthur N. Popper, College Park, MD, USA

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Volume Preface

Each volume in the Springer Handbook of Auditory Research (SHAR) series provides comprehensive and up-to-date conceptual reviews on specific topics closely related to the sense of hearing. Whereas previous SHAR volumes have focused primarily on either basic science or applied science, this volume provides both an overview and examples of the translational research process, which is defined as the specific activities that allow basic scientific data to be "translated" first into clinical investigation and then into healthcare application. Thus, the authors of each chapter were charged with describing the challenges and joys of translational research and the process whereby one moves from basic scientific inquiry all the way to clinical delivery. The topics in this book were selected with the goal of emphasizing the critical importance of these translational activities to new advances in hearing healthcare based on evidence-based practice (EBP), a principle defined by clinical practices that reflect approaches derived from compelling scientific evidence of efficacy.

Chapter 1 by Le Prell and Lobarinas provides an overview of the volume and puts the contents into the broad perspective of translational science. This is followed in Chap. 2 by Le Prell, who discusses the entire scientific continuum from basic science to clinical trials to the epidemiological assessment of public health with careful attention to potential obstacles in the translational process that may be encountered at each of these stages. Next, in Chap. 3, Kraus and Anderson discuss the challenges of treatment and diagnosis of central auditory processing disorder (CAPD), a clinical disorder for which there are no widely accepted diagnostic criteria or treatment options.

Chapter 4 by Montgomery, Bauer, and Lobarinas then describes sudden hearing loss (SHL), a clinical disorder for which there *are* well-accepted diagnostic criteria and treatment options. Within the translational research spectrum, this chapter highlights the discrepancy among existing practice guidelines, evidence for these guidelines, and public health needs for SHL, a significant clinical problem with limited treatment options. Specifically, there are now multiple systematic reviews and meta-analyses that draw into question the extent and reliability of steroid

treatment, the most widely accepted and used therapeutic intervention. This chapter provides an overview of the challenges associated with establishing etiology, formal assessment, and treatment of SHL. In Chap. 5, Lynch, Kil, and Le Prell describe the myriad of issues related to preclinical development of a drug, with the primary emphasis of the chapter being the issues that emerge with the transition to clinical testing. Chapter 6 by Campbell and Fox continues the theme of new drug development, discussing the challenges of translation of otoprotective drugs from testing in animal models to assessment in humans.

Chapter 7 by Allman, Schormans, Typlt, and Lobarinas transitions from prevention of hearing loss to treatment of tinnitus, a condition often comorbid with hearing loss. Next, in Chap. 8, Staecker, Klickstein, and Brough describe the development of molecular therapeutics for treating profound hearing loss via regeneration of sensory cells in the cochlea. In Chap. 9, Tan, Xia, and Richter discuss the potential for alternative cochlear implant designs that take advantage of new stimulation technologies. The authors specifically review and consider three novel strategies for neural stimulation, including optogenetics, optoacoustics, and infrared neural stimulation.

Although this volume focuses on translational auditory neuroscience, much of the basic and applied science in the previous volumes provides background to these chapters. As a complement to the previous SHAR volumes on the human auditory cortex and cochlear implants, the first case study in the current volume delves into central auditory processing (Chap. 3) and builds on the themes raised in *Neural Correlates of Auditory Cognition* (Vol. 45, 2012, edited by Cohen, Popper, and Fay). The second case study in this volume focuses on sudden hearing loss (Chap. 4) and updates previous discussion of autoimmune inner ear disease as provided in *Auditory Trauma, Protection, and Repair* (Vol. 31, 2008, edited by Schacht, Popper, and Fay).

Similarly, the problem of noise-induced hearing loss was discussed in detail in *Noise-Induced Hearing Loss* (Vol. 40, 2012, edited by Le Prell, Henderson, Fay, and Popper). In the current volume, the process by which a therapeutic intervention would transition from the laboratory, through the regulatory bodies, to clinical trials and ultimately into routine clinical care is presented as a third in-depth case study (Chap. 5). The next case study in this volume (Chap. 6) focuses on ototoxicity, a topic considered in *Auditory Trauma, Protection, and Repair* (Vol. 31, 2008, edited by Schacht, Popper, and Fay). In this new volume, the current state of available therapies to alleviate tinnitus is discussed in the context of translating these interventions into clinical practice in the fifth case study (Chap. 7). The earlier edition, *Tinnitus* (Vol. 44, 2012, edited by Eggermont, Zeng, Popper, and Fay), provided a thorough overview of the proposed underlying mechanisms of tinnitus.

In the next case study (Chap. 8), readers are given a glimpse into the future with specific examples of promising molecular therapies for hearing loss, an update to the information reviewed in *Development of the Inner Ear* (Vol. 26, 2005, edited by Kelley, Wu, Popper, and Fay) and the more recent *Hair Cell Regeneration, Repair, and Protection* (Vol. 33, 2008, edited by Salvi, Popper, and Fay). Finally, novel and emerging cochlear implant technologies progressing through the translation process

are discussed (Chap. 9). This final case study builds on the discussion of current technology in *Cochlear Implants: Auditory Prostheses and Electric Hearing* (Vol. 20, 2004, edited by Zeng, Popper, and Fay) as well as in *Auditory Prostheses* (Vol. 39, 2011, edited by Zeng, Popper, and Fay).

Fundamental to the issue of translational research is selection of the most appropriate animal models. Multiple chapters draw on the important preceding work across mammals as described in *Comparative Hearing: Mammals* (Vol. 4, 1994, edited by Fay and Popper). Another critical element in translational research is the selection of the most appropriate human functional metrics. This new volume builds on the work discussed in both *Clinical Aspects of Hearing* (Vol. 7, 1996, edited by Van De Water, Popper, and Fay) and *Human Psychophysics* (Vol. 3, 1993, edited by Yost, Popper, and Fay).

Collectively, the chapters in this volume build on and frame previous important topics in hearing science in the context of the scrutiny and high bar of the translational process and the critical steps involved in moving from the bench to the bedside.

Colleen G. Le Prell, Dallas, TX, USA
Edward Lobarinas, Dallas, TX, USA
Arthur N. Popper, College Park, MD, USA
Richard R. Fay, Woods Hole, MA, USA

Contents

Contributors

Brian L. Allman Department of Anatomy and Cell Biology, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

Samira Anderson Department of Hearing and Speech Sciences, University of Maryland, College Park, MD, USA

Carol A. Bauer Division of Otolaryngology, Southern Illinois University School of Medicine, Springfield, IL, USA

Douglas E. Brough GenVec Inc., Gaithersburg, MD, USA

Kathleen C.M. Campbell Department of Medical Microbiology, Immunology, and Cell Biology, Southern Illinois University School of Medicine, Springfield, IL, USA

Daniel J. Fox Department of Medical Microbiology, Immunology, and Cell Biology, Southern Illinois University School of Medicine, Springfield, IL, USA

Jonathan Kil Sound Pharmaceuticals, Inc., Seattle, WA, USA

Lloyd Klickstein Novartis Institutes for Biomedical Research, Cambridge, MA, USA

Nina Kraus Departments of Communication Sciences, Neurobiology and Physiology, and Otolaryngology, Northwestern University, Evanston, IL, USA

Colleen G. Le Prell Callier Center for Communication Disorders, University of Texas at Dallas, Dallas, TX, USA

Edward Lobarinas Callier Center for Communication Disorders, University of Texas at Dallas, Dallas, TX, USA

Eric D. Lynch Sound Pharmaceuticals, Inc., Seattle, WA, USA

Scott C. Montgomery Division of Otolaryngology, Southern Illinois University School of Medicine, Springfield, IL, USA

Claus-Peter Richter Department of Otolaryngology, Northwestern University, Chicago, IL, USA; Department of Biomedical Engineering, Northwestern University, Evanston, IL, USA; Department of Communication Sciences and Disorders, The Hugh Knowles Center, Northwestern University, Evanston, IL, USA

Ashley L. Schormans Department of Anatomy and Cell Biology, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

Hinrich Staecker Department of Otolaryngology–Head and Neck Surgery, University of Kansas School of Medicine, Kansas City, KS, USA

Xiaodong Tan Department of Otolaryngology, Northwestern University, Chicago, IL, USA

Marei Typlt Department of Anatomy and Cell Biology, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada

Nan Xia Key Laboratory of Biorheological Science and Technology, Bioengineering College, Chongqing University, Chongqing, China; Department of Otolaryngology, Northwestern University, Chicago, IL, USA

Chapter 1
Perspectives on Auditory Translational Research

Colleen G. Le Prell and Edward Lobarinas

Abstract Translational research encompasses a spectrum beginning with basic scientific inquiry, extending into applied assessment in clinical trial evaluations, and ultimately extending to clinical application and assessment of the impact on public health. Translational research occurs at the boundaries between each of these steps, with specific activities required to move from basic science into clinical testing (translation 1, T1), from clinical testing into clinical best practice guidelines (translation 2, T2), from guidelines into healthcare practice (translation 3, T3), and from clinical practice into public health benefit (translation 4, T4). This volume on translational research introduces scientists and clinicians to this process via specific examples across current "hot topics" in auditory research. Among the topics are examples from central auditory processing disorder, sudden hearing loss, noise-induced hearing loss, tinnitus, cisplatin-induced hearing loss, molecular therapies for hair cell regeneration, and next-generation novel cochlear implant devices relying on optical stimulation. A brief review of each chapter is included here. Across the chapters, readers will appreciate the current state of the science, a review of current clinical practices, and emerging evidence-based interventions with the overarching goal of providing interested parties with a reference highlighting the process, challenges, and rewards of translational research.

Keywords Advances in hearing · Auditory disorders best practices · Clinical research · Evidence-based practice · Translational research

C.G. Le Prell (✉) · E. Lobarinas
Callier Center for Communication Disorders, University of Texas at Dallas,
1966 Inwood Road, Dallas, TX 75235, USA
e-mail: colleen.leprell@utdallas.edu

E. Lobarinas
e-mail: edward.lobarinas@utdallas.edu

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1.1 Introduction to the Volume

Each individual volume within the Springer Handbook of Auditory Research (SHAR) provides comprehensive and up-to-date conceptual reviews on specific topics closely related to the sense of hearing. Previous SHAR volumes have focused primarily on either basic science or applied science. The present volume provides both an overview and examples of the translational research process, with translational research defined as the specific activities that allow basic scientific data to be "translated" first into clinical investigations and then into healthcare application. In this particular volume, the authors of each chapter were charged with describing the challenges and joys of translational research, the process whereby one moves from basic scientific inquiry all the way to clinical delivery. The chapters include examples of translational research programs drawn from across a broad range of relevant topics. The topic of this book was selected with the goal of emphasizing the critical importance of these translational activities to new advances in hearing healthcare and the goal of evidence-based practice (EBP), a principle defined by clinical practices that reflect approaches derived from compelling scientific evidence of efficacy.

In the United States and other countries, EBP has been conceptualized as the provision of clinical service with specific care decisions not only driven by the expert opinion of the clinician but also based on the best scientific data from current research literature. More recently, EBP was defined to also include patient preference; if patients are to make informed decisions about their healthcare preferences, it is incumbent on the care provider to not only be familiar with the research literature but also to be able to explain it to patients and make the information accessible to them so that they can make informed decisions about their care. Throughout the volume, there is therefore a focus on the essential precursors of EBP. These include the importance of robust basic science, critical review of existing findings, and the multiple steps required to move from basic science, through clinical trials, and ultimately to patient care. In the absence of valid controlled research reports, clinicians must rely on expert opinion, individual expert judgment, and patient preference in lieu of evidence-based guidance from the literature.

This initial chapter provides a brief introduction to translational research with themes that are expanded on in detail in Chap. 2. This is followed by an introduction to each of the specific case studies included in Chaps. 3–9. The final Chap. 10 reviews common themes that emerged across the case studies in each chapter and ends with commentary on two specific topics that were selected to highlight the translational nature of some of today's "hot" scientific topics. There is an urgent need to close significant gaps in our understanding of clinically relevant problems in hearing, so that clinical care reflects methods with the highest level of evidence of efficacy. These case studies provide a tool for introducing basic scientists to the concepts and ideas in translational science with the hope that basic scientists will think about scientific design with the potential for translation already in mind, to

protect opportunities for translation, and to ultimately close the gaps between benchtop and bedside. Closing these gaps will require enhanced collaboration among basic and applied scientists and clinicians. The overarching goal of this text is to provide a reference for scientists, clinicians, and other interested parties as to the important roles each plays in moving discoveries to healthcare delivery.

1.2 Clinical and Translational Research

Translational research is often described as "bench to bedside." It attempts to move basic science findings into clinical trials (translation 1, T1) and then data from clinical trials must be translated into clinical care guidelines that are based on the best scientific evidence (translation 2, T2). There is subsequent translation from guidelines into daily patient care as part of healthcare practice (translation 3, T3) and ultimately into population-based health assessment programs (translation 4, T4) (Meslin et al. 2013). Activities encompassed in each of these specific stages, and obstacles to successful translation, are discussed in Chap. 2 by Le Prell, with particular emphasis on T1 and T2.

The case studies in the chapters in this book largely focus on T1 and T2 research stages. When compelling basic science results fail to be assessed in clinical trials (i.e., failure to successfully navigate T1) or succeed in clinical testing but fail to successfully emerge as an approved drug agent, device, or other therapeutic intervention (i.e., failure to navigate T2), there can be no third phase of translation (T3) into patient care or any broader assessment of public health impact (T4). One of the earliest translational hurdles is the significant regulatory process that occurs as part of the move from basic scientific and preclinical investigations (using in vitro or in vivo methods with animal subjects) into human clinical testing, which involves an entirely different regulatory structure including not only institutional review boards (IRBs) or other national ethical review boards responsible for the oversight of the use of human subjects in research but also any agency responsible for the oversight of new drug development such as the US Food and Drug Administration (FDA). Indeed, the difficulty of this translational phase has resulted in the specific commentary that "bench to bedside" research may be more accurately defined as "bench to FDA to bedside" research because the regulatory process is so cumbersome (Knoepfler 2015). The myriad of obstacles that must be successfully negotiated as part of this process have led to the widespread definition of these translational phases as a "valley of death" from which many promising therapies never emerge (Hudson and Khazragui 2013; Meslin et al. 2013; Hammonds 2015).

The emphasis on translational research that has emerged in the United States is not unique; there is a global movement toward translational research and university-industry collaboration is often emphasized as a key element within the translational process. There are both commonalities and differences in the approaches to university-industry collaborations across countries, with the

approaches in the United States, United Kingdom, Canada, and Japan all having strengths and weaknesses (Miller 1995; Hudson and Khazragui 2013; Kneller et al. 2014). Butler (2008) highlights major investments in translational research in other countries, noting, for example, "In Britain, which is second only to the United States in biomedical research output, the government last year announced a doubling of the Medical Research Council's budget to almost £700 million (US$1.3 billion) by 2010, largely to finance a new focus on translational research" (p. 842). Indeed, there are translational centers and translational research funding programs all around the world (for specific examples, see Tralau-Stewart et al. 2009). Some of the efforts in individual countries are focused on specific directions. In India, for example, there has been a major push for the country to become a new "hub" for clinical trials (Bhowmik et al. 2010; Singh and Srivastva 2013), and there has been a drive to set up large "bio-banking" services, where tissues can be deposited and later accessed for use in future studies (Shankar 2015). Khanna (2012) highlights the reduced cost of trials not only in India but in China and Singapore as well. Singapore has been described as having had success stories specifically in fostering strong partnerships between scientists and clinicians to jointly advance translational medical programs (Wong 2014).

In any effort to promote translational research success, there will be a parallel effort to educate and encourage intellectual property protection (discussed in more detail in Chap. 2 by Le Prell). Nelsen (2004) specifically highlights the growing emphasis on translational research and, correspondingly, technology transfer at institutions around the world and points to some of the financial "lessons learned" from the US experience—specifically, the difficulty in licensing and profiting from academic intellectual property. One thing that is increasingly clear is that education in the translational sciences is urgently needed (Robinson et al. 2013; Manson et al. 2015). As part of this education process, education on team-based science is critical (Stokols et al. 2008; Roberts et al. 2012; Cooke and Hilton 2015).

The case stories in this book highlight many of the above themes and provide an introduction to activities encompassed in the phrase "translational research." This term is not a catchall nor is it simply a "buzz word" for the moment; translational research is a process that has specific steps that are fundamental to success in developing applications of basic science findings. The specific steps in the technology transfer process, and factors related to the likelihood of success, are discussed in Chap. 2. Although academics and industry historically have been considered "separate" entities with different goals (dissemination of knowledge vs. protected proprietary information), newer translational models encourage significant interaction between academics and industry in the United States and abroad (Pienta 2010; Emmert-Buck 2011; Hudson and Khazragui 2013). The National Institutes of Health (NIH) has also recognized the gap in translational success as an issue and has developed funding mechanisms that specifically support translational research. However, there is still criticism that the NIH has not done enough to bridge this gap given its overarching mission of public health improvement, and much work remains to address existing and emerging healthcare needs that are best served with robust translational research efforts (for discussion, see Butler 2008).

1.3 Translational Efforts Reviewed in This Volume

The final sections of this initial chapter introduce the topics and themes of each of the case studies addressed in subsequent chapters. The case studies were specifically invited, as they provide examples of the successful systematic progression of basic scientific inquiry into preclinical and clinical investigations.

1.3.1 The Scientific Continuum and Challenges in Translational Research

Chapter 2, by Le Prell, discusses the entire scientific continuum from basic science to clinical trials to the epidemiological assessment of public health, including careful attention to potential obstacles in the translational process that may be encountered at each of these stages. Chapter 2 includes a discussion of the sources of funding, including not only the NIH but also foundations and industry, as well as the need for and the steps involved in disclosure, patents, and licensing. The regulatory requirements, which are increased relative to those for basic science research, are discussed, with a specific case example drawn from a clinical trial assessing a dietary supplement for potential prevention of temporary threshold shift (TTS) (NCT00808470). In that case, the use of the supplement progressed through the same FDA review process used to regulate drugs (i.e., the Investigational New Drug [IND] application). Readers will find the experiences of different investigators with the FDA summarized in multiple chapters throughout this volume.

1.3.2 Diagnosis and Treatment of Central Auditory Processing Disorder

Chapter 3, by Kraus and Anderson, features a clinical disorder for which there are no widely accepted diagnostic criteria or treatment options (for review and discussion, see Fey et al. 2011; Bellis et al. 2012). Specifically, Kraus and Anderson discuss the challenge of diagnosing and treating central auditory processing disorder (CAPD), more recently termed auditory processing disorder (APD). APD was initially defined as a disorder of auditory perception despite normal hearing sensitivity, but the definition has now been expanded to also include abnormal hearing sensitivity with disproportionately poorer performance than would be expected given the hearing loss. One of the major challenges to clinicians has been disagreement of how to define APD, its causes, and its boundaries, particularly because APD is often comorbid with learning problems such as dyslexia or attention deficit hyperactivity disorder (ADHD). A second major challenge has been the lack of agreement on the "appropriate" tools for diagnosing APD.

A myriad of tests and test batteries exist, but clinicians disagree on the diagnostic criteria for APD (for discussion, see Wilson and Arnott 2012). In Chap. 3, a speech-evoked auditory brainstem response (ABR) metric that could be used as a tool to determine an "objective" criterion in the diagnosis of APD is described, including the translation of the data collection protocols into existing commercial equipment that can now be purchased by others interested in this research topic. Data from patients with APD are compared to data from controls, and from patients with other disorders, to provide a rationale for the diagnostic utility of this novel approach. In the latter part of the chapter, the therapeutic effects of music therapy on speech-evoked ABRs are described. In addition to describing a potential objective measurement tool for APD diagnosis, a major strength of the approach described in this chapter is the strong use of community partnerships to forge relationships with service providers who assist children and adults diagnosed with APD. The music therapy delivery was specifically modeled using time allowances for music classes to facilitate translation into public school curricula and real-world environments. Finally, the authors discuss new important directions for their research, such as determining optimal training programs and adaptability of these programs across diverse populations.

1.3.3 Sudden Hearing Loss

Chapter 4, by Montgomery, Bauer, and Lobarinas, describes a clinical disorder for which there *are* well-accepted diagnostic criteria and treatment options. The chapter provides an overview of the challenges associated with establishing etiology, formal assessment, and treatment of sudden hearing loss (SHL). Various mechanisms that have been proposed include autoimmune-mediated damage, viruses, vascular abnormalities, and abnormal cellular stress responses. A number of risk factors also play a role in development and severity of SHL. These include diseases of the cardiovascular system and circulatory system and chronic kidney disease. SHL has also been found to be a predictor of subsequent disease such as myocardial infarction and erectile dysfunction, suggesting a link with impaired perfusion and microvascular damage.

Owing to the varied proposed etiology, a number of treatments have been proposed. These include hyperbaric oxygen therapy, steroids, and a variety of alternative pharmacotherapy including antivirals, vasoactive drugs, and salvage therapy. Despite efforts at targeting specific proposed etiologies, oral steroids continue to be the standard of care for SHL. More recently, tympanic injections have emerged as an alternative method of administration for steroid treatment of SHL (for review, see Rauch 2008). Though assumed to be more effective, there have been few data to guide physician treatment decisions regarding whether or not to use this more invasive method of delivery to administer drugs directly to the site of "injury" or the more traditional oral treatment, leading to a recent large multisite investigation (NCT00097448). Interpretation of outcomes is complicated by the high rate of

spontaneous recovery, however. The clinical significance of this issue to evidence-based patient care has driven multiple clinical trials around the world in recent years. This chapter reviews the current practice, state of the science, and the challenges of treating SHL as well as the difficulties overseeing clinical investigations and determining efficacy. Control groups need to be carefully considered in any clinical investigation. As discussed earlier in this section, in the case of SHL, steroids are the standard of care. Interestingly, multiple systematic reviews suggest there to be little or no systematic evidence of benefit when steroid-treated patients are compared to patients who received a placebo (Wei et al. 2013; Crane et al. 2015). A number of individual studies suggest positive effects at the group level when treatment delivery is intratympanic (Filipo et al. 2013; Lavigne et al. 2015; Ng et al. 2015), but benefits are not consistent across investigations (NCT00097448). To deprive a control group of effective treatment represents an unacceptable alternative; thus, clinical investigations will often compare a new drug to the established treatment, with the study designed to show there is no difference between the agents (i.e., the new drug is at least as effective as the existing standard of care). In the case of SHL, steroid treatment may not have any benefit, but it is the standard of care, making it extremely difficult to recruit subjects if they may be randomized to placebo condition (Rauch 2015). As discussed in the chapter, the standard oral steroid treatment may not conclusively provide benefit, but patients prefer the knowledge that their symptoms are being treated with the best current strategy rather than taking the chance they will not receive any therapy.

1.3.4 Noise-Induced Hearing Loss

Chapter 5, by Lynch, Kil, and Le Prell, briefly describes the myriad of issues related to preclinical development of a drug, with the primary emphasis of the chapter being the issues that emerge with the transition to clinical testing. Examples and discussion of the clinical development of an agent being assessed for the potential prevention of noise-induced hearing loss (NIHL) is used as a case study. The regulatory environment is a key focus, with a detailed discussion of the process of developing a novel pharmaceutical, as well as an overview of some of the processes that drive the cost of new drug development, such as the development of specific manufacturing protocols including identification of contaminants, by-products, and metabolites that are produced biologically and safety assessments that are likely required for all of the above. The costs of developing a new drug are significant, commonly described as running more than US$1 billion per drug or pharmacological agent; this chapter explains where some of those costs come from and how the high number of "failures" increases the cost associated with each success (Munos 2009). Chapter 2 discusses conflict of interest and the requirement for transparency, and therefore it is highlighted here that as per the acknowledgments in Chap. 5, Lynch is the president and director, and Kil is the chief medical officer, of Sound Pharmaceuticals, Inc., a company that owns relevant intellectual property for

the protection of auditory function using Ebselen (Kil and Lynch 2004, 2010, 2012). Le Prell was the principal investigator of NCT01444846, which was conducted with funding provided by Sound Pharmaceuticals, Inc., and Lobarinas served as the lead audiologist on this trial. The final sections of this chapter describe similarities, and differences, in the way the development of other agents has proceeded.

1.3.5 Cisplatin-Induced Hearing Loss

Chapter 6, by Campbell and Fox, continues the theme of new drug development, discussing the challenges of translation of otoprotective drugs from testing in animal models into human trials. A major difficulty described in this chapter is the selection of specific test protocols to be used for measuring cisplatin-induced hearing loss, as there are a number of scales that have been used clinically and that could be considered for clinical trials on otoprotective agents. There are different definitions of what constitutes an ototoxic drug-induced hearing loss across scales, with robust threshold changes required to be observed to meet the criteria put forward by ASHA (American Speech-Language-Hearing Association 1994) and the AAA (American Academy of Audiology 2009), specifically, shifts that are greater than 20 dB at one frequency or greater than 10 dB at two adjacent frequencies.

This chapter describes, in detail, the potential application of ASHA/AAA strategies and other criteria-based categorization strategies to monitoring the prevention of cisplatin-induced ototoxicity; other strategies based on the absolute size of the threshold shift are also possible and have been used in completed studies (Campbell 2014). Multiple clinical trials on the prevention of cisplatin-induced hearing loss have been completed, are now in progress, or will begin in the near future, and these trials may serve as models for future investigations (Anderson and Campbell 2015). However, in preparing this chapter, Campbell and Fox noted that the selection of the specific scale or measure of hearing loss to be used as a primary end point is something that needs to be negotiated with the FDA as part of the approval process, and the "best" measure may differ from study to study. Thus, "cookbook" procedures cannot be offered, as every trial will be individually negotiated with the FDA. Readers are referred to a recent review from Campbell's team for details of ongoing studies (Anderson and Campbell 2015), with the caveat that different protocols may be best for different trials and all protocols must be approved as part of the IND process. A brief discussion of several agents is provided, including discussion related to the development of D-methionine, an agent for which Campbell is the sole inventor on relevant intellectual property (Campbell 2001, 2008). Campbell is also a founding member of MetArmor, Inc., a newly formed company that will be further developing a commercial formulation of D-methionine as a potential product for further testing for safety and efficacy in humans.

1.3.6 Drugs for Treatment of Tinnitus

Chapter 7, by Allman, Schormans, Typlt, and Lobarinas, transitions from prevention of hearing loss to treatment of tinnitus. Similar to the APD case study in Chap. 3 by Kraus and Anderson, the precise mechanisms underlying tinnitus are not well understood and are likely to vary from patient to patient. However, unlike for APD, there are a number of animal models of tinnitus that provide unique opportunities to study the potential pathophysiological correlates underlying tinnitus, particularly as these relate to NIHL.

Chapter 7 reviews a number of treatments that have been evaluated for tinnitus, the rationale behind their use, the "off-label" approach, proposed efficacy, and the discrepancies observed between data derived from animal experiments and human studies (for earlier detailed review, see Dobie 1999). The chapter also provides an overview of the controversies related to peripheral versus central origins of tinnitus, statistical versus clinical efficacy, self-selection bias, and the implications of these distinctions for treatment.

With respect to clinical trials, the chapter reviews the significant disagreement across investigators with respect to whether outcome measures should reflect changes in the auditory perception of tinnitus (i.e., decreases in perceived loudness in loudness matching studies) or changes in the emotional or psychological reaction to the sound of tinnitus, that is, tinnitus "disability." The challenges of interpreting the data are also compounded by varying study designs, varying subject and experimenter blinding, conflicting tinnitus perception and reaction outcomes, lack of statistical power, and strong placebo effects.

Despite the aforementioned challenges, there is significant interest in finding efficacious treatments for tinnitus. Evolving collaborations among interested parties include teams composed of physicians, audiologists, neuroscientists, and psychologists, with growing public awareness promoted across these disciplines. As discussed in the chapter, the future of tinnitus research will be shaped by forging important collaborative efforts, refining outcome measures, continued basic science, refined animal models, and robust evidence-based translational efforts leading to new best practices for patient care. Drugs are the topic of Chap. 7; for discussion of hearing aids, magnetic and electric stimulation, and counseling and masking therapies, readers are referred to other recent reviews (Nobel 2012; Folmer et al. 2014; De Ridder et al. 2015).

1.3.7 A Molecular Therapeutic for Restoration of Auditory Function

Chapter 8, by Staecker, Klickstein, and Brough, describes the development of a molecular therapeutic for treating profound hearing loss by inducing the regeneration of sensory cells in the cochlea. In the 1980s, there was a startling discovery

that sensory hair cells were regenerated after noise or drug insult in avian species such as chicken (*Gallus gallus domesticus*: Cotanche 1987a, b; Corwin and Cotanche 1988) and common quail (*Coturnix coturnix*: Ryals and Rubel 1988). Accompanying that regeneration, there was a full restoration of function (Saunders et al. 1991; Niemiec et al. 1994). Laboratories around the world quickly focused their attention on the developmental pathways involved in hair cell differentiation, with the hopes of inducing hair cell regeneration in mammals, although success in this goal was slow to be accomplished (Izumikawa et al. 2005). There is an abundance of basic science data showing the promise of gene therapy for restoration of hearing (for recent reviews, see Geleoc and Holt 2014; Chien et al. 2015; Fujioka et al. 2015), with *Atoh1* emerging as a compelling candidate (Richardson and Atkinson 2015).

All of the translational and developmental issues identified in the earlier case studies are amplified when the drug of interest is delivered via gene therapy, with intent to drive the generation of new cell populations to replace cells that have been damaged or lost. The chapter describes a host of challenges that must be navigated to launch any clinical investigation of a regeneration therapy with the drug to be delivered into the inner ear. The authors have firsthand insight into all of the challenges discussed in this chapter. Klickstein is the head of Translational Medicine, New Indications Discovery Unit at Novartis Institutes for BioMedical Research, and Brough is the chief scientific officer at GenVec, Inc. GenVec invented the drug CFG166. This drug is now being tested in partnership with Novartis and the University of Kansas, where Staecker serves as the principal investigator of NCT02132130, a study assessing CFG166 (see also https://pioneersresearch.org/node/182).

Many of the challenges launching NCT02132130 include the obvious difficulties in identifying the molecular pathway to the target, developing a strategy for safely delivering the therapy, determining a starting dose, and navigating the IND process through the FDA's Center for Biologics Evaluation and Research (CBER). Each of these issues is discussed in detail as well as less obvious challenges such as the identification of an appropriate patient population for an agent that induces hair cell regeneration. Such a population should include participants in which hair cell loss is specifically known. However, clinical testing often falls short of revealing a precise underlying pathology, making participant selection somewhat difficult. The authors also make a significant argument about the importance of establishing clear benefit, given that cochlear implants have been well established as a strategy for restoring not only awareness of sound but, in many cases, speech perception as well. For gene therapy to ultimately be successful, patients should receive at least as much benefit as that derived from a cochlear implant.

1.3.8 Cochlear Implants/Infrared Neural Stimulation

In Chap. 9, by Tan, Xia, and Richter, the potential for alternative cochlear implant designs that take advantage of new stimulation technologies are considered. The authors specifically review and consider three novel strategies for neural stimulation, including optogenetics, optoacoustics, and infrared neural stimulation, an approach that has emerged as a "hot" topic in hearing science, with growing attention at professional meetings and in the literature. The ultimate future application for this early science lies in the potential redesign of future cochlear implants, and the authors specifically discuss the potential advantages of light-based stimulation over conventional electrical stimulation.

The development of these potential next-generation implants is in its infancy, and the demonstration of both efficacy and safety of these devices for long-term use will be an important next step. Richter and colleagues describe advances in infrared neural stimulation in detail and highlight the prospects for translation. Lessons regarding necessary next steps can be readily drawn from the animal literature on implant technology. Early studies on infrared neural stimulation in animals will need to provide parametric data equivalent to that collected in electrical cochlear prosthesis studies on current flow, impedance, site of stimulation, and frequency–response relationships (Clopton and Spelman 1982; Spelman et al. 1982). Patterns of damage observed after electrode insertion and stimulation were of particular importance in these early studies (Miller et al. 1983; Duckert and Miller 1984, 1986). A wealth of work has focused on biophysics and physiology of electrical stimulation (for review, see Abbas and Miller 2004) as well as long-term effects of electrical stimulation (for review, see Leake and Rebscher 2004). It will be essential that any long-term damage related to infrared stimulation similarly be assessed. The development of databases over time has allowed careful mapping of structure–function relationships in which hair cell, neural, and other structural measures can be assessed for a relationship with electrically evoked function (Pfingst et al. 2011; O'Leary et al. 2013), and such parameters will need to be mapped for infrared stimulation. Given that speech processing is a major goal, strategies for processing stimulation will need to be optimized. Examples from the cochlear prosthesis literature include continuous interleaved speech (CIS), spectral peak (SPEAK), advanced combination encoder (ACE), and simultaneous analog stimulation (SAS) (for review, see Wilson 2004).

Changes in surgical procedure (i.e., "soft surgery"; see Rogowski et al. 1995; Giordano et al. 2014) were studied first in animal models and likely predict a similar developmental trajectory for infrared device implantation procedures. Data from animal models have provided insight into electrically evoked stimulus processing by comparing tone-evoked and electrically evoked activity in the inferior colliculus (Middlebrooks 2004; Snyder et al. 2004; Bierer et al. 2010) and auditory cortex (Bierer and Middlebrooks 2002; Middlebrooks and Bierer 2002); these tools have been used to show that transmission of information to the auditory cortex is impaired by some stimulus configurations (Middlebrooks 2008). Central response to electrical stimulation has been a major focus of cochlear prosthesis research (for review, see Hartmann and Kral 2004), and similar studies using infrared neural stimulation will be needed to optimize stimulation parameters.

There is a fascinating history of human testing and development of cochlear implants (for reviews, see Zeng 2004; Eshraghi et al. 2012). Some 50 years after the first implant procedures, the development of the electrical cochlear prosthesis is still active and ongoing, with current investigations into new electrode coatings (Tykocinski and Cowan 2005; Richardson et al. 2009), new implant materials (Gwon et al. 2015), and an exciting new prosthesis that is being actively modified to allow local drug delivery (Hendricks et al. 2008; Nguyen et al. 2009; Farhadi et al. 2013). No doubt, new information related to the development of infrared stimulation protocols will similarly emerge over an extended period if the device is ultimately translated to human testing. Taken together, the kinds of studies that set the stage for new surgical interventions are well established. As noted in several chapters, the device side of the FDA is well versed indeed in audiometric testing within clinical trials and there is a relatively clear path forward for the testing of new implantable devices to restore hearing in the profoundly deaf.

1.4 Summary

There are any number of translational topics that could have been selected for this volume. The topics included, however, were selected to provide a variety of different examples, some of which require INDs for approval to assess study drugs and others that discuss the development of devices (with the device used either diagnostically as in Chap. 3 or therapeutically as in Chap. 9) under a separate regulatory Investigational Device structure. In some case studies, the clinical disorder is well understood (as in cisplatin-induced hearing loss and NIHL), but in other case studies, the disorder of interest is not well understood (as in tinnitus, APD, and SHL). In some case studies, there is no accepted therapy, but in other cases, there is a current standard of care (such as the delivery of steroids in the case of SHL or the use of a cochlear prosthesis to rehabilitate auditory function). The ethics pertaining to appropriate control groups must be carefully considered where there is a standard of care. The collection of case stories provided by the various authors in this volume are intended to be useful to those seeking an introduction to translational research methods There are a variety of shortcomings to the evidence base available to guide hearing loss prevention and treatment decisions. Access to training, and improvements in existing training in translational research, are needed to allow researchers to successfully close the gaps in translation.

Compliance with Ethics Requirements

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Chapter 2
Current Issues in Clinical and Translational Research in the Hearing Sciences, Audiology, and Otolaryngology

Colleen G. Le Prell

Abstract Translational research is often described as "bench to bedside" because it builds on basic science findings to "translate" discoveries into potential interventions or therapeutics that can be tested in clinical trials and adopted into healthcare practice. This introductory chapter offers working definitions of the various phases of research spanning from basic research to clinical testing and ultimately to the implementation of these endeavors into evidence-based patient care. There are multiple challenges in moving from basic science to clinical trials and from clinical research into routine application in healthcare delivery. There are also clearly diverging interests of academics (creation of knowledge, education of the future workforce) and industry (meeting market needs and protecting exclusivity to generate revenue and increase shareholder value). However, academia and industry share the common goal of finding cures for patients in need. Whether patient care is advanced through industry-funded research within an academic laboratory or industry licensing of an academic patent is not important from the patient's perspective. What will benefit patients the most in the long run is the translation of novel therapies into clinical testing with subsequent translation of the most effective therapies into patient care, with the long-term goal of improving public health outcomes.

Keywords Clinical research · Evidence-based practice · Technology transfer · Translational research

C.G. Le Prell (✉)
Callier Center for Communication Disorders, University of Texas at Dallas,
1966 Inwood Road, Dallas, TX 75235, USA
e-mail: colleen.leprell@utdallas.edu

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2.1 Translational Research

This introductory chapter offers working definitions of the various phases of research spanning from basic research to clinical testing and ultimately to the implementation of these endeavors into evidence-based patient care. It also provides a brief overview of the diversity of individuals that scientists may need to interact with as part of the translational research process, including technology transfer officers, patent lawyers, and regulatory bodies such as the US Food and Drug Administration (FDA).

Translational research is often described as "bench to bedside" because it builds on basic science findings to "translate" discoveries into potential interventions or therapeutics that can be tested in clinical trials and adopted into healthcare practice. A number of translational research models have been proposed (Westfall et al. 2007; Dougherty and Conway 2008; Woolf 2008), and although the specific definitions vary from report to report, it is clear that there are multiple phases within the broader category of translational research. The first of these occurs at the intersection of basic science and clinical research (T1) and the second at the transition from clinical research to clinical practice (T2). There are multiple challenges in moving from basic science to clinical trials and from clinical research into routine application in healthcare delivery (Fears et al. 2010). Here, the different "phases" of research are identified and discussed.

Basic and clinical areas of research are often considered to be two distinct phases in the process of translation. As per the excellent review and summary of the National Institutes of Health (NIH) definition of translation research by Rubio et al. (2010, p. 471), "According to this definition, translational research is part of a unidirectional continuum in which research findings are moved from the researcher's bench to the patient's bedside and community. In the continuum, the first stage of translational research (T1) transfers knowledge from basic research to clinical research, while the second stage (T2) transfers findings from clinical studies or clinical trials to practice settings and communities, where the findings improve health." Basic science and its translation into clinical research in the T1 and T2 phases are really only the beginning of the journey toward effective healthcare. Dougherty and Conway (2008) propose third-stage (T3) activities intended to determine the extent to which these new clinical practices actually serve to improve the health of individuals and populations. Policy changes necessary to implement evidence-based treatments are also included in this T3 set of activities (Dougherty and Conway 2008). These T3 activities are distinct from T2 in that the end point becomes health improvement at the population-level, in contrast with health improvement for individual patients; population-level changes are studied using epidemiological research. Success is measured in this T3 phase as "changes in health-related behavior or other risk factors (in the shorter term), well-being or quality of life, or 'hard' morbidity or mortality end points (in the longer term)" (Ogilvie et al. 2009).

The gaps between basic research and adoption into practice (i.e., T1 and T2) are an ongoing challenge, often because some drug, device, or other therapeutic must be commercialized to become available for use by clinicians. A major obstacle is that basic discoveries coming out of academic institutions are often not sufficiently advanced to be attractive to companies as commercial opportunities (Handelsman 2009). The transition of research from a university setting to a corporate entity is termed "technology transfer" and is discussed in detail in Sect. 2.5. The topic of translational research has received significant attention from the NIH given their mission statement, which includes the protection and improvement of health as well as disease prevention (http://goo.gl/ro0nD8). Specifically, the goals of the NIH are as follows:

- "to foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health;
- to develop, maintain, and renew scientific human and physical resources that will ensure the Nation's capability to prevent disease;
- to expand the knowledge base in medical and associated sciences in order to enhance the Nation's economic well-being and ensure a continued high return on the public investment in research; and
- to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science."

2.2 Translational Research in Hearing and Balance

In 2004, the National Institute on Deafness and Other Communication Disorders (NIDCD) organized a workshop in Bethesda, Maryland, focused on the topic of translational research in hearing and balance (http://goo.gl/wMKltN) to determine how to support translational work in the hearing and balance sciences. Initial presentations reviewed the approaches of the National Institute of Mental Health (NIMH) and National Institute of Neurological Disorders and Stroke (NINDS). At the time, both institutes had already released program announcements requesting translational research applications for funding.

The workshop yielded positive outcomes, and on November 24, 2004, the NIDCD released PAR-05-023, "NIDCD Translational Research Grants," a program announcement that called for basic scientists and clinicians to jointly develop translational research projects appropriate for R01 or R21 funding mechanisms. The intent of the PAR was "to encourage basic research findings to have a practical impact on the diagnosis, treatment, and prevention of communication disorders" (http://goo.gl/hnlpRS). This program announcement was later divided into two new program announcements, one specific to R01 applications and the other calling for R21 applications. NIDCD currently has a call for R01 applications with the goal of translating basic hearing and balance research into clinical tools or applications (http://goo.gl/unLxrD), with application deadlines extending into February, 2017.

However, the last submission dates for R21s under that translational PAR were in 2013.

The importance of translational research to the NIH was further evidenced by the creation of the National Center for Advancing Translation Sciences (NCATS), launched in January 2012 (http://goo.gl/hV6Dj). One of the award programs housed under NCATS is the Clinical and Translation Science Award (CTSA), a program that supports "the development and implementation of national standards and best practices for translation, from basic discovery to clinical and community-engaged research." The NIH has been the major source of support for translational research in the United States and much of this chapter is organized around the NIH's mission, approach, and definitions. Clearly, the NIH is not the only source of funding for translational research and this approach is not intended to minimize the important contributions of foundations, other organizations, and industry. Action on hearing loss, for example, has put into place "The Translational Research Initiative for Hearing (TRIH)." This mechanism for funding explicitly excludes basic research as it is intended to move promising basic research into clinical trials (http://goo.gl/NVhmJf). Importantly, this program actively includes industry partners to facilitate the technology transfer process. Industry partners are invited to strategically fund, or cofund, projects in their area of interest.

2.3 The Translational Science Spectrum

The NCATS website provides a useful structure for organizing the continuum from basic research to population assessment (http://goo.gl/1mE15O). The specific stages in the spectrum of translational science include basic, preclinical, and clinical research; clinical implementation; and public health. In this model, public health issues should drive basic research, and basic research should yield information that provides rationale support for new therapeutic targets (see Fig. 2.1).

2.3.1 Basic Science

According to NCATS, "Basic research involves scientific exploration that can reveal fundamental mechanisms of biology, disease, or behavior. Every stage of the translational research spectrum builds upon and informs basic research…insights gained from the Center's studies along the translational spectrum can inform basic research" (http://goo.gl/AvA5tf). These principles broadly hold true regardless of funding source. Basic science is commonly considered to involve laboratory-based experiments. Such studies might be intended to increase general knowledge on fundamental mechanisms (as stated by NCATS), or these basic science studies might be intended to provide the foundation for clinical research (Rubio et al. 2010).

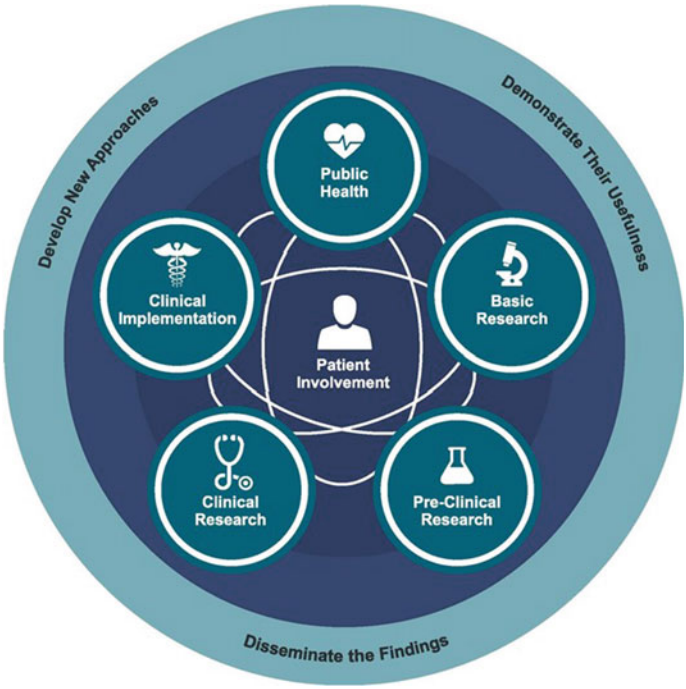

Fig. 2.1 Translational science spectrum. "The translational science spectrum represents each stage of research along the path from the biological basis of health and disease to interventions that improve the health of individuals and the public. The spectrum is not linear or unidirectional; each stage builds upon and informs the others. At all stages of the spectrum, NCATS develops new approaches, demonstrates their usefulness, and disseminates the findings. Patient involvement is a critical feature of all stages in translation" (http://www.ncats.nih.gov/translation/spectrum). Reprinted with permission of the National Institutes of Health/National Center for Advancing Translational Sciences

The importance of basic research within the NIDCD is made clear in a message from the NIDCD Director, James F. Battey, Jr., titled, "Advancing Research to Improve the Lives of People with Communication Disorders" (http://goo.gl/drU1c5). Dr. Battey points to genetic research, identification of genetic mutations linked to inherited hearing loss, and successes in gene mapping as fertile grounds for new discoveries "when we learn how to harness their potential to pause or reverse some types of hearing loss." He also points to research on inner ear sensory cell regeneration that "could one day offer a powerful treatment option, if not a cure, for hearing loss." The theme of translation of these and other basic findings into clinical use is made clear by his statement, "As we head toward new frontiers in scientific discovery and precision medicine, NIDCD-funded research is likely to produce more sensitive, individually tailored, and effective technologies for people with hearing loss."

The growth of the NIH can be traced at least in part to a landmark report to President Roosevelt by Vannevar Bush, the director of the Office of Scientific Research and Development at that time (Bush 1945). As reviewed by Crowley and Gusella (2009), a major outcome of Bush's ground-breaking suggestion was public funding of the nation's scientific endeavors via the NIH. The Bush report provided a major impetus to the expansion of basic scientific inquiry in the United States (Bertha 1996). Bush (1945, pp. 18–19) wrote,

> Basic research is performed without thought of practical ends. It results in general knowledge and an understanding of nature and its laws. This general knowledge provides the means of answering a large number of important practical problems, though it may not give a complete specific answer to any one of them. The function of applied research is to provide such complete answers. The scientist doing basic research may not be at all interested in the practical applications of his work, yet the further progress of industrial development would eventually stagnate if basic scientific research were long neglected.… Basic research leads to new knowledge. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn. New products and new processes do not appear full-grown. They are founded on new principles and new conceptions, which in turn are painstakingly developed by research in the purest realms of science…..A nation which depends upon others for its new basic scientific knowledge will be slow in its industrial progress and weak in its competitive position in world trade, regardless of its mechanical skill.

This report to the president is interesting in that it stresses that advances in science lead to more jobs, higher wages, more abundant crops, higher standards of living, prevention and cure of diseases, conservation of limited national resources, and a position of world leadership (Bush 1945). Subsequent to this report, there was a substantial increase in funding for research beginning in the early 1960s (Bertha 1996). The NIH website includes a short history of the Public Health Service (PHS) and the NIH, highlighting changes in funding after World War II as well as the incorporation of the National Cancer Institute (NCI) into the NIH through the 1944 Public Health Service Act. With respect to funding, "The entire NIH budget expanded from $8 million in 1947 to more than $1 billion in 1966. Between 1955 and 1968, NIH Director James A. Shannon presided over the spectacular growth that is now fondly remembered as 'the golden years' of NIH expansion" (http://goo.gl/FWQEhf). As funding for the NIH grew, it funded more basic research than clinical research (Moses et al. 2005; Crowley and Gusella 2009). According to the US Department of Health and Human Services (HHS), the NIH currently spends approximately 53–54 % of its budget on basic biomedical and behavioral research on the causes of disease onset and progression (http://goo.gl/LgujS4).

2.3.2 Preclinical Research

According to NCATS, "Pre-clinical research connects basic science and human medicine. During this stage, scientists apply fundamental discoveries made in the laboratory or the clinic to further understand the basis of a disease or disorder and

find ways to treat it. Hypothesis testing is carried out using cell or animal models; samples of human or animal tissues; or computer-assisted simulations of drug, device, or diagnostic interactions within living systems" (http://goo.gl/yxVjSD). Multiple examples of the transition from basic research to preclinical research are readily available within the field of hearing science.

The transition from basic to preclinical research has been rapid in the case of noise-induced hearing loss (NIHL), for example. After initial suggestions that intense metabolic activity might contribute to noise-induced pathology in the inner ear (Lim and Melnick 1971), Yamane et al. (1995) used immunocytochemical labeling to identify and localize noise-induced free radical formation in the marginal cells of the stria vascularis. Subsequently, Ohlemiller et al. (1999) reported a nearly fourfold increase in hydroxyl (OH) radical formation within 1–2 h of noise exposure. Later, free radical formation was reported as also being significant in outer hair cells, with continued postnoise production of both reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Yamashita et al. 2004). These basic scientific findings demonstrating noise-induced free radical formation quickly led to preclinical studies in which "antioxidant" substances that neutralize free radicals were assessed for potential prevention of NIHL in rodent models (for detailed reviews, see Le Prell et al. 2007b; Le Prell and Bao 2012). A number of these agents have now moved forward into clinical research investigations with human subjects (for detailed review, see Le Prell and Lobarinas 2015). Translational activities related to the development of a potential drug agent for the prevention of NIHL are described by Lynch, Kil, and Le Prell, Chap. 5.

Basic research yielded similar understanding of the mechanisms of aminoglycoside ototoxicity (for reviews, see Huth et al. 2011; Rybak and Brenner 2015) and cisplatin ototoxicity (for review, see Laurell and Pierre 2015). There has been significant preclinical investigation of agents that might prevent ototoxicity associated with these life-saving therapeutics (for reviews, see Abi-Hachem et al. 2010; Poirrier et al. 2010; Campbell and Le Prell 2012). Clinical trial data have been somewhat slow to emerge, however (for recent review, see Anderson and Campbell 2015). One potential challenge for the translation of otoprotective therapies into human patients being treated with aminoglycoside antibiotics or cisplatin is the requirement that the otoprotective agent must not interfere with the therapeutic antimicrobial or antineoplastic benefit of the therapeutic agent (for a brief review and discussion of cisplatin, see Rybak et al. 2009; for a brief review and discussion of aminoglycoside antibiotics, see Le Prell et al. 2014). Translational activities related to the development of a potential drug agent for the prevention of cisplatin-induced hearing loss are described by Campbell and Fox, Chap. 6.

2.3.3 Clinical Research

As reviewed by Rubio et al. (2010), the NIH has identified patient-oriented research, epidemiologic and behavioral studies, outcomes research, and health

services research as falling under the broad heading of Clinical Research. Clinical trials and other assessments of therapeutic interventions and new technologies thus fall under this category of patient-oriented research. According to NCATS, "Clinical research includes clinical trials with human subjects to test intervention safety and effectiveness, behavioral and observational studies, outcomes and health services research, and the testing and refinement of new technologies. The goal of many clinical trials is to obtain regulatory approval for an intervention" (http://goo.gl/rJZSXy). The NIH clinical trial registry maintained at the website www.clinicaltrials.gov is an excellent resource for the identification of currently ongoing clinical trials for a specific disease condition.

Because data are not published until a study is completed and negative results can be more difficult to publish for a variety of reasons, the clinical trial registry is a major advance in transparency as researchers (and patients) can readily search to see what studies are ongoing. Moreover, the results are required to be posted on this registry website within 12 months of the completion of the study. A helpful summary of the current guidelines for studies that must be posted in this registry is available at https://goo.gl/OP9IYg. HHS has proposed new requirements and procedures for registering trials and submitting results at the end of the study, so this should be considered a moving target.

In addition to HHS requirements to post studies, there are also FDA requirements for clinical trials conducted under their oversight. The FDA requires such trials be listed on clinicaltrials.gov. Similarly, the NIH requires that NIH-funded clinical studies be listed on this clinical trial registry website. Finally, an increasing number of journals will not accept human clinical research manuscripts describing outcomes from studies that were not posted on the clinical registry. It is universally understood that studies assessing potential health benefits of new drug agents fall under the oversight of the FDA (at least in the United States). Although the FDA is well known for its role in the regulation and oversight of new drug development and approval, readers are strongly cautioned that the assessment of other compounds, including dietary supplements, in a clinical trial is regulated under the same rules and requirements as any other novel drug agent when health outcomes are assessed. To illustrate the importance of these and other regulatory guidelines in the conduct of translational science, the following case study is offered.

In 2009, the study NCT00808470 was actively going through the institutional review process at participating sites including the University of Michigan and the University of Florida. During the review process at both supervising institutions, there was active discussion regarding whether an Investigational New Drug (IND) application was required prior to Institutional Review Board (IRB) approval. The guidance initially provided by commercial partners responsible for manufacturing the dietary supplements to be used in the studies indicated that foods and dietary supplements that are intended to make structure/function labeling claims do not meet the definition of a "drug" and therefore do not require the submission of an IND. Fortunately for the study team, that guidance was not accepted by the supervising IRBs and there was an explicit academic institutional requirement to pursue an IND. An IND application was therefore filed and ultimately approved

(IND application number 116027, allowed to proceed August 31, 2012). Specific guidance on the assessment of a dietary supplement in studies on the prevention of acquired hearing loss was later communicated to participants in the Pharmaceutical Interventions to Prevent Hearing Loss (PIHL) working group at a meeting organized by the Department of Defense (DoD) Hearing Center of Excellence (HCE). One of the presentations at that meeting was contributed by Eric Bastings, Deputy Director, Division of Neurology Products, FDA (E. Bastings, The FDA/IND Process and Recommendations, presented August 24, 2012, Baltimore, Maryland). Dr. Bastings, in his slides and commentary, noted that dietary supplements are not "lawfully marketed" drug products and as such they always need an IND before use in a clinical trial because any agent that is used to "diagnose, prevent, treat, or cure a disease" is considered a drug. The FDA defines disease as "…damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunction (e.g., hypertension); except that diseases resulting from nutritional deficiencies (e.g., scurvy, pellagra) are not included in this definition." A very helpful summary of the criteria used to distinguish health claims (related to disease prevention, mitigation, treatment, etc.) and structure/function claims (allowed for dietary supplements) is available in Guidance from the FDA (US Food and Drug Administration 2002).

As additional background on dietary supplements, it should be noted that the sale of dietary supplements is regulated by the FDA under the Dietary Supplement Health and Education Act of 1994 (DSHEA). DSHEA regulates substances including vitamins, minerals, herbs and other botanicals, amino acids, concentrates, metabolites, constituents, and extracts and any dietary substance intended to be used to supplement the diet and increase total dietary intake. Unlike drug agents, which must be proven to be both safe *and effective for their intended use* before marketing, DSHEA has no similar provisions requiring that the FDA review and approve dietary supplements for safety *or effectiveness* before distribution to consumers. To restrict the use of a supplement or force its removal from the marketplace, the FDA itself would have to show that the dietary supplement was "unsafe" before it could take any action. This aspect of their duties is facilitated only by the requirement that manufacturers and distributors of dietary supplements who receive a report that the use of their product was associated with a serious adverse advent must record, investigate, and forward that report to the FDA (for guidance see US Food and Drug Administration, Dietary Supplements 2015).

Particularly relevant to the case study introduced earlier in this section, dietary supplements are reviewed using the same criteria as drugs when a clinical trial assesses potential health benefits associated with use of a dietary supplement. The review of the IND application for the agents used in NCT00808470 was surely simplified by the categorization of the active agents as generally regarded as safe (GRAS) (http://goo.gl/NJt0X8), which reduced the requirements for toxicity data required as part of IND applications for new drug agents. However, despite GRAS components, the active agents were required to be manufactured to pharmaceutical standards, including stability testing, with all required manufacturing records provided in the section of the IND termed "Chemistry, Manufacturing, and Controls

(CMC)" (http://goo.gl/OGLUuf). The CMC section of the IND is discussed in detail by Lynch, Kil, and Le Prell, Chap. 5.

The Michigan Institute for Clinical & Health Research (MICHR) at the University of Michigan (UM), and in particular the MICHR IND/IDE Investigator Assistance Program (MIAP) (https://goo.gl/aOzKXU), was instrumental in the successful application for approval to proceed with NCT00808470. They were wholly responsible for assembling the IND application and filing updates and annual reports as required by the FDA, with the study team simply providing information for the applications and reports as needed. MICHR services were initially supported by the National Center for Research Resources (NCRR) (UL1RR024986) and are currently supported by NCAT (UL1TR000433). This is a compelling example of one of the ways in which CTSA funding from the NIH fosters clinical research at academic institutions.

2.3.4 Clinical Implementation

According to NCATS, "The clinical implementation stage of translation involves the adoption of interventions into routine clinical care for the general population. This stage also includes implementation research to evaluate clinical trial results and to identify new clinical questions and gaps in care" (http://goo.gl/8AT7Wv). Unfortunately, publishing data in an academic journal does not by itself guarantee this information is transferred to clinicians or into clinical practice (Meline and Paradiso 2003). Crowley and Gusella (2009) provide an interesting commentary on the impact of the Bush (1945) report on both basic research and clinical research in the United States. They highlight the positive impact in that medical schools and academic health science centers preferentially recruit basic scientists and support their research success through space allocations, promotions, and prestigious treatment. An unintended consequence, however, was that clinical work translating basic science discoveries into humans (i.e., clinical-translational research) was deemed the responsibility of academic hospitals and academic physicians (Crowley and Gusella 2009). Unfortunately, there are many basic researchers with little direct connection to an academic hospital and thus no immediate or obvious partners to oversee such clinical research. There is the partial exception in the clinician-scientist that has pursued dual training in research and clinical practice and maintains both an active clinical practice and an active research program, but many basic research scientists will not be directly involved in the clinical testing or clinical implementation of their research. Given lack of communication between basic researchers, clinicians leading clinical trials, and physicians in general practice, it is sad, but perhaps not surprising, that it can take 10 years or longer for technologies tested in teaching hospitals to make it into common application (for detailed discussion of "translational lag," see Milne and Kaitin 2009). None of the preceding comments should be taken to suggest that researchers cannot have an

active role in facilitating clinical implementation; these comments simply highlight ongoing challenges.

Attending and presenting at clinical professional meetings is a critically important component of facilitating the implementation of new research outcomes into clinical practice. Attending presentations by clinicians has added value in that scientists learn the key clinical issues for which new clinical solutions are needed, and in turn this can inform and guide new basic inquiry and new preclinical research study design. Clinical practice can, and should, inform research, with clinical observations guiding new research (for discussion see Apel 2011). The annual midwinter meeting of the Association for Research in Otolaryngology (ARO) is an example of a meeting that is attended by both basic scientists and clinicians. The annual conference of the National Hearing Conservation Association (NHCA) is a second example of a meeting that is widely attended by audiologists, industrial hygienists, professional service providers, physicians, nurses, and researchers. The Annual Scientific and Technology Conference of the American Auditory Society (AAS) is also worth mention here, as they specifically call for translational research presentations as part of the conference program. Other more clinical meetings that basic scientists may not have considered attending include the annual AudiologyNOW! meeting of the American Academy of Audiology (AAA), which is the largest gathering of audiologists in the world or the annual meeting and OTO EXPO^{SM} of the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS).

Outside of professional conferences, building strong relationships with clinical counterparts within an academic health science center is critically important. The development of a strong clinical trial design that can hopefully yield evidence that will be compelling to clinicians is contingent on the identification of relevant clinical metrics. Researchers are often accustomed to interpreting outcomes based on the statistical significance of a difference between two groups. Clinicians will be concerned not only about the reliability of the difference but also about the clinical significance. Using the example of NIHL, a drug that reliably provided an average 3-dB reduction in the amount of permanent threshold shift may not be useful for patients based on the minimal functional benefit, the cost of the drug, and the potential side effects, even if the 3-dB difference was statistically significant. In contrast, a drug that might not have reached statistical significance based on average group response, but was highly efficacious in a specific subgroup, could have significant clinical relevance because it may provide help for "some patients." This is a common conclusion in tinnitus studies in particular, based on the unknown etiology of the tinnitus in many cases (Dobie 1999; Langguth and Elgoyhen 2012). Statisticians do warn that subgroup analyses should be undertaken only with great care, however (Sleight 2000). Clinician partners can provide compelling insight into what would constitute a compelling clinical outcome so that studies can be designed and powered appropriately to support later clinical implementation. These and related issues are the heart of the movement toward "Evidence-Based Practice" (see Sect. 2.4).

2.3.5 Public Health

According to NCATS, "In this stage of translation, researchers study health outcomes at the population-level to determine the effects of diseases and efforts to prevent, diagnose and treat them. Findings help guide scientists working to improve interventions or develop new ones" (http://goo.gl/LNexCY). Longitudinal studies in large populations provide the best evidence for successful intervention outcomes. Although they do not include intervention components, there are several longitudinal studies on auditory function worth noting. One of the larger scale longitudinal studies that has provided valuable information on auditory function is the Epidemiology of Hearing Loss cohort from Beaver Dam, Wisconsin, and, more recently, the Beaver Dam Offspring Study, which now includes 5275 adults born between 1902 and 1962 (Cruickshanks et al. 1998; Nash et al. 2011). A second such study is the Baltimore Longitudinal Study on Aging, which started in 1958 and includes more than 1400 men and women in their 20s through their 90s (Brant and Fozard 1990; Moreira and Palladino 2011). Finally, the Blue Mountain Hearing Study (BMHS) is a population-based survey of age-related hearing loss (Gopinath et al. 2011). The study is a spin-off of the Blue Mountain Eye Study and includes prospective 5-year assessments (Mitchell et al. 2011). With longitudinal data collection, it becomes possible to prospectively evaluate hypotheses about factors that mediate hearing loss, such as dietary nutrient intake (Gopinath et al. 2011).

Longitudinal data are also available from the Health Professional's Follow-Up Study, which enrolled 26,273 men 40–74 years old at the time of the 1986 baseline (Shargorodsky et al. 2010a, c). However, it should be noted that the extent of the hearing loss assessment is a single survey question, "Have you ever had professionally diagnosed hearing loss?" Thus, to be identified as having hearing loss a participant must not only suspect he or she has hearing loss but also has to have followed through with a visit to a physician or audiologist to have the hearing loss professionally diagnosed. Thus, the survey is not sensitive to mild hearing loss, and researchers using this survey data will not correctly categorize participants who have hearing loss but have not had their hearing loss professionally diagnosed. It is difficult to determine what percent of individuals have hearing loss but have not sought help, given that these individuals, by definition, have not sought help. Duijvestijn et al. (2003) had a very clever approach to this problem in that they performed audiometric testing on 1419 individuals aged 55 or older who participated in a driving test study. A total of 483 individuals, 34 % of the sample, had a pure-tone average (PTA) threshold at 0.5, 1, 2, and 4 kHz exceeding 30 dB; however, fewer than half of the individuals who were identified as having hearing loss of 30 dB or more had visited a physician with complaints of hearing impairment. Worth noting, more than half of those individuals who had hearing loss but had not pursued any hearing healthcare services did in fact report they perceived their hearing as poor. Taken together, reliance on the self-report of professionally diagnosed hearing loss provides confidence all subjects with reported hearing loss

do have hearing loss, but there is certain to be significant underreporting of hearing loss by those who have not pursued diagnosis from a physician or audiologist.

Longitudinal data have also been collected in the Nurses' Health Study II (http://goo.gl/SKtfeM). Launched in 1976, the Nurses' Health Study was initially established to investigate potential long-term consequences of oral contraceptive use. In 1989, diet and lifestyle questions were added to the survey. In 2010, they added a question, "Have you ever had professionally diagnosed hearing loss?" The year of first diagnosis was requested if the response was positive. In 2012, this was modified to instead ask, "Do you have a hearing problem?" and "If so, at what age did you first notice a change in your hearing?" All of the surveys are available online (http://goo.gl/9LMShA), and the data can be accessed with permission subsequent to scientific review of the proposed analysis (http://goo.gl/qGWxOl). The 2012 data on "hearing problems" were used to explore the potential relationship between analgesic use and "hearing loss" (Curhan et al. 2012). The diagnosis of *hearing loss* based on a positive response to a survey question about *hearing problems* is potentially worrisome in light of new data showing some 12 % of a sample of individuals in the Beaver Dam study, with normal hearing confirmed in audiometric testing, self-reported hearing difficulties (Tremblay et al. 2015). Difficulties with speech-in-noise, for instance, may be caused at least in part by cognitive and perceptual changes, separate from changes in hearing thresholds (Füllgrabe et al. 2014). Certainly, some individuals with high-frequency hearing loss have difficulties understanding speech-in-noise because some parts of the speech signal are inaudible given their elevated thresholds (Quist-Hanssen et al. 1979; Badri et al. 2011). There is also a distortion component in which hearing-impaired listeners may perform more poorly than normal-hearing listeners even if all components of the speech signal are presented at audible levels (Plomp 1986). Speech-in-noise tests are essentially a "stress test" for auditory function (Wilson 2011), and, as per the review by Wilson, it was Carhart (1951) who first recognized that some patients have disproportionate difficulty hearing in noise. Later, Carhart and Tillman (1970) explicitly advocated that audiologic evaluations should include a measure of the ability of patients to understand speech in competing background noise in addition to the traditional pure-tone audiogram and speech discrimination in quiet. It is not clear what percent of the participants in the Nurses' Health Study II have threshold deficits (hearing loss) versus other auditory complaints falling under the general heading of hearing problems (such as difficulty discriminating speech in noisy backgrounds).

Population-level health data that are not longitudinal but include careful audiometric assessment of thresholds can be garnered from the National Health and Nutrition Examination Survey (NHANES) database. The NHANES is an ongoing cross-sectional survey of the civilian noninstitutionalized population of the United States, with data collected virtually continuously from new participants during each two-year test cycle. Specifically, approximately 10,000 individuals are selected at random every 2 years, with the demographic distribution in each cycle selected to yield a population that is representative of the US population (for detailed discussion of the historic and current sampling procedures, see Johnson et al. 2014). In

recent years, NHANES data have been used to assess relationships between hearing loss and a variety of factors including cognition (Lin 2011); depression (Li et al. 2014); smoking (Agrawal et al. 2009) and secondhand smoke exposure (Fabry et al. 2011; Lalwani et al. 2011); cardiovascular health (Agrawal et al. 2008; Nash et al. 2011); exposure to metals such as cadmium and lead (Choi et al. 2012); diet (Spankovich and Le Prell 2013; Choi et al. 2014); noise exposure (Mahboubi et al. 2013; Spankovich and Le Prell 2014); and skin color, race, and ethnicity (Lin et al. 2012). A wealth of data has been generated as these results, in deidentified form, are freely available on the Internet for download by interested researchers (http://goo.gl/FWFiV).

Readers are cautioned that outcomes from and interpretations of NHANES analyses vary as a function of the specific data incorporated into any given analysis. For example, both Shargorodsky et al. (2010b) and Henderson et al. (2011) assessed potential changes in the prevalence of hearing loss, including NIHL, in children and adolescents by comparing NHANES III (1988–1994) data to NHANES 2005–2006 data. Although neither author reported any reliable change in noise-induced threshold shift (NITS) (defined using the "notched" definition of Niskar et al. 1998), Shargorodsky et al. (2010b) reported a statistically significant increase in high-frequency hearing loss (PTA at 3, 4, 6, and 8 kHz greater than 15 dB HL) in NHANES 2005–2006 (16.4 %; 95 % CI: 13.2–19.7) relative to NHANES III (12.8 %; 95 % CI = 11.1–14.5) ($P = 0.02$). In contrast, when Henderson et al. (2011) assessed high-frequency hearing loss using slightly different criteria (PTA at 3, 4, and 6 kHz greater than 15 dB HL), there were no reliable changes in high-frequency hearing loss. A second major design difference was the exclusion criteria. Whereas Henderson et al. (2011) excluded participants who failed to meet normal tympanometric compliance criteria, Shargorodsky et al. (2010b) did not exclude data obtained from such participants. The different conclusions resulting from two different analyses of the same epidemiological data highlight the challenges of epidemiological research and the importance of coding all of the relevant variables. Related to this, if a single database is analyzed twice and the same conclusion is drawn each time, the second analysis cannot be considered to have independently confirmed the first study given that the subjects were identical. However, if two different (nonoverlapping) cohorts are analyzed, with the same pattern of results, then the conclusions are much more compelling as there are different participants in the different sample cycles. Taken together, data from various NHANES analyses and the handful of longitudinal studies to date provide a wealth of information on the prevalence of hearing loss and risk factors for hearing loss. Once a given intervention has been adopted and made its way into widespread clinical use, the real-world efficacy might perhaps be able to be studied using population-based approaches.

2.4 Evidence-Based Practice

There is a movement across healthcare asserting that decisions about a patient's care should be based on evidence that the recommended treatments or interventions are likely to benefit the patient. Quality, effectiveness, efficiency, and cost are key drivers of the movement toward evidence-based practice (EBP) (Moodie et al. 2011). EBP has quickly been adopted as the logic is self-evident: how can anyone argue against the idea that clinicians provide patient care based on the best available evidence (Valente 2005)? The ability to access, critically analyze, and interpret scientific literature is fundamental to the concept of EBP. Academic training will not provide clinicians with sufficient knowledge of the most efficacious approaches for the entire spectrum of cases that will be seen *over the course of a professional career* (Nail-Chiwetalu and Bernstein Ratner 2006; Bernstein Ratner 2011). The advice from Bernstein Ratner (2006) regarding the education of tomorrow's clinicians is compelling indeed: "Evidence is only helpful to professionals and their clients if health service providers seek it out, understand it, and apply it…We need to inculcate the value of reading the updated professional, peer-reviewed literature and help equip today's students with the understanding that this is the first step in EBP: When you do not know the best way to treat your client, look it up, and look in the right place. If you thought you knew it last year, check and see if it is still true" (p. 265). Academic researchers can facilitate this process by writing for clinicians rather than for their scientific colleagues, which specifically includes avoidance of jargon, explanation of clinical relevance, and clearly summarizing individual outcomes as well as group outcomes (Meline and Paradiso 2003). Contrary to strict reliance on the literature, however, EBP also requires that healthcare providers incorporate clinical expertise gained from patient care and patient preferences in making decisions (Dollaghan 2004; Moodie et al. 2011).

2.4.1 Levels of Evidence

Because EBP is firmly grounded in empirical evidence, it is critical to understand how to locate relevant literature and be able to critically evaluate evidence quality and relevance (Nail-Chiwetalu and Bernstein Ratner 2006; Limb 2011). The "level of evidence" pyramid provides a useful structure for ranking evidence (Cox 2005; Moodie et al. 2011). The highest level of evidence is meta-analysis (also termed systematic reviews) of randomized controlled trials (e.g., Agarwal and Pothier 2009; Phillips and Westerberg 2011). Systematic reviews are different from traditional reviews in that these are based less on narrative and more on numerical analysis across studies (McKibbon 1999, pp. 121–151). The original randomized controlled trial reports are the next level (e.g., Kramer et al. 2006; Suckfuell et al. 2014), followed by nonrandomized intervention studies (such as the study by Lindblad et al. 2011). In the level of evidence pyramid, these are followed by

nonintervention designs such as cohort studies, case-control studies, cross-sectional studies, case reports, and finally, "expert opinion" (for additional discussion see McKibbon 1999, pp. 1–31; Moodie et al. 2011). The text by Dawes et al. (2005) lays out a specific framework for critically assessing study designs.

Although expert opinions, including consensus statements, should be discounted if contradicted by compelling data from scientific studies, there may be cases where the paucity of data necessitates reliance on the opinions of experts as a primary source of information (Dollaghan 2004). The absence of data must not be interpreted as an absence of effectiveness when there is no research literature. In those cases, clinical expertise will necessarily be more heavily weighted. It must also be recognized, however, that not all research data are relevant to decisions in clinical practice. For example, basic research focused on underlying mechanisms is usually derived from animal models. These mechanistic data cannot be used as a basis for therapeutic treatment in humans *in the absence of subsequent clinical trial evaluation* (Dollaghan 2004). In other words, the basic science and preclinical data guide potential assessments in humans but do not provide a compelling rationale for immediate adoption into clinical practice. Additionally, even data from human studies can be, and should be, "ignored" if the study was not scientifically sound (Dollaghan 2004). Critical thinking includes identifying and critically evaluating an argument based on the specific supporting evidence; assessing trial design and potential shortcomings are essential (Finn 2011).

Only the higher levels of evidence are typically considered to warrant serious consideration of a change in clinical practice (Valente 2005). However, many times such evidence does not exist and yet treatment decisions must be made (Limb 2011). This situation can and usually does generate controversy among experts, as has been recently observed for treatment of tinnitus (Folmer et al. 2014; De Ridder et al. 2015) and the noise exposure exchange rate (ER) as regulated in the occupational noise standard 29 CFR 1910.95 (Occupational Safety and Health Administration [OSHA] 1983), with strong advocates for both maintaining the current 5-dB ER (Dobie and Clark 2014, 2015) and adopting a more conservative 3-dB ER (Morata et al. 2015; Suter 2015). While one can (and of course does) prospectively track subjects longitudinally as part of a hearing conservation program, variable use of hearing protection devices (HPDs) in the workplace remains problematic and actual daily exposures thus remain unknown for most workers. The evidence used to call for changes in healthcare, regulations, or other policy issues should be carefully evaluated as part of any call for change. Dobie and Clark (2015, p. 2) state, "It is unclear to us how a change in the ER would motivate employers to implement better HCPs and to put more emphasis on noise control, or how including more workers in those programs would motivate workers to more faithfully use HPDs." Based on this guidance, one might consider advocating for research that identifies and establishes *evidence-based* best practices for education and motivation of workers to achieve HPD use that is correct and consistent. Training on correct insertion significantly improves HPD attenuation achieved by

participants, although training strategies vary across studies (Tufts et al. 2013; Salmani Nodoushan et al. 2014). Fit-testing earplugs to verify achieved attenuation of a given earplug type provided to a worker also has the potential to improve hearing conservation outcomes, particularly when fit testing is used as a training tool to teach correct insertion, but the tools available for fit testing are still under investigation themselves (Neitzel et al. 2006; Voix and Hager 2009; Schulz 2011). In an EBP model, being critical about the quality of the evidence is a goal, not a character flaw (Dollaghan 2004).

2.4.2 *Statistical Significance Versus Clinical Significance*

In evaluating study outcomes for their potential relevance to patient care, it is important to consider not only statistical but also clinical significance (Meline and Paradiso 2003). The example of a small but statistically significant improvement in hearing outcomes was discussed in Sect. 2.3.4. Readers are reminded the *P* value generated during significance testing reveals nothing about the size or meaning of a group difference; the *P* value only serves as a test of how likely it is the null hypothesis (i.e., that there is no between-group difference) might be true, and a type I error (concluding there is a group difference when there is not) might be made (Altman 2000). This has led to a suggestion to assess effect sizes or confidence intervals to provide information about the size and impact of the group difference (Altman 2000; Dollaghan 2004). Confidence intervals specify a range of values within which the true population values are likely to fall (Altman 2000; Dollaghan 2004). A 95 % confidence interval specifies the range of values over which 95 % of the possible intervals would contain the true value, and a 99 % confidence interval specifies the range of values over which 99 % of the possible intervals would contain the true value; thus the 99 % confidence interval will be wider than the 95 % confidence interval. The confidence interval is explicitly intended to illustrate that if the same study were repeated on different subjects, the results would be different and thus we should be concerned about the range of values over which the true population value is likely to be found (Altman 2000) rather than the specific mean measured in the sample assumed to represent the population of interest.

Effect size provides a measure of the strength of a phenomenon. Effect size can be calculated as simple effect size (the difference between two group means), but it is typically calculated as the difference between the two group means divided by the standard deviation (SD), which accounts for variation across subjects and permits comparisons across studies (Meline and Paradiso 2003). There are multiple procedures for selecting the specific SD term that goes into the calculations (for review, see Coe 2002) and there are multiple strategies for interpreting the significance of the effect size (e.g., Cohen 1988; Ferguson 2009). Incorporation of SD into the calculation has an important influence on effect size. Readers will recall that SD is

calculated as the sum of the squared differences of each data point from the mean divided by the number of data points (for population data) or the number of data points minus 1 (for sample data). Thus, if the differences from the mean stay the same (the numerator) but the sample size grows (the denominator), the calculated SD will be smaller. When the effect size is calculated normalizing for SD, the calculated effect size will be larger if the SD (now the denominator) is smaller. Thus, even if they have equivalent outcomes with respect to mean group differences, larger studies will have larger effect sizes than smaller studies, increasing the importance of data from large studies and decreasing the importance of smaller ones when meta-analyses are performed.

2.4.3 The Gap Between Knowledge and Action

One might expect generally widespread agreement that EBP is "a good thing" given its emphasis on using the current best available information for making decisions about patient care. Chief concerns expressed by both otorhinolaryngologists and audiologists include lack of time to access and critically evaluate the literature (Bhargava et al. 2011; Moodie et al. 2011). This is a common concern across health-related professionals (Nail-Chiwetalu and Bernstein Ratner 2006; Bernstein Ratner 2011), as is the cost of acquiring full-text literature for clinicians not affiliated with an academic health science center and its libraries (Bernstein Ratner 2011). Nevertheless, relevant clinical professional societies are embracing EBP. For example, the AAA, in its Standards of Practice for Audiology document, states, "Audiologists implement evidence-based practices," (Standard IA2), and "Audiologists seek, critically evaluate, and apply research findings to promote evidence-based practice" (Standard VIA1). The Standards of Practice document and links to a variety of Clinical Practice Guidelines (CPGs) are available at http://goo.gl/QNUiye.

The AAO-HNS also offers a variety of CPGs based on systematic review of the evidence at http://goo.gl/IBbVM5. They explicitly support and endorse evidence-based medicine (EBM) when it includes clinical expertise, the best available external evidence, and also individual patient preference (http://goo.gl/uHd424). As discussed in Sect. 2.4.1, they offer an interesting caution that highlights the importance of all three of these components. Specifically, "the AAO-HNS also cautions that evidence based recommendations can change over time as data accumulates and our knowledge grows. Moreover, a current absence of data does not equate to an absence of effectiveness. As such, research evidence is often not the sole determinant of clinical decisions. Evidence must be interpreted in the context of each individual patient, and clinical decisions are usually made using the best available evidence in conjunction with clinical expertise and judgment."

2.5 Technology Transfer and the Valley of Death

Although there is generally good support for EBP, which by definition is based strongly on data from research investigations, there is clearly a failure for many promising drugs and technologies to make it into clinical trials, let alone into clinical practice. The gap between translational research and commercialization is a major problem, in part because basic discoveries coming out of academic institutions are often not advanced enough to be attractive to companies (Handelsman 2009). The transition of research from a university into a corporate entity is termed "technology transfer," and the all-too-frequent failure of promising basic science findings to make their way into use is termed the valley of death (Coller and Califf 2009; Meslin et al. 2013). "The technology transfer gap has always been with us, but in drug discovery it has widened to form a valley of death between the traditional finishing point of research supported by an academic grant, and the sort of programs industry is interested in licensing or venture capitalists are prepared to back through a startup" (Moran 2007, p. 266). Some blame the NIH for investing too many of their resources into basic science research, with not enough funding to support applied science (for discussion see Butler 2008), although, as noted in Sect. 2.2, the NIH (including the NIDCD) have put specific funding mechanisms into place for translational research and CTSAs provide programmatic support at an institutional level.

In addition to institutional support through CTSA-funded services, technology transfer offices are key players. Strong technology transfer offices facilitate translational research, generate income through licensing, and foster academic–industry collaborations (Martin 2002). There are five key aspects to the technology transfer process: disclosure, patent protection, marketing, negotiating, and licensing (Bertha 1996). The review by Patino (2009), providing perspective from a technology transfer office, is an excellent starting point for all of these. Helpful commentary from an inventor's perspective is also found in Marks (1991). Additional "required reading" is the article by Coller and Califf (2009), which provides a framework for assessing whether a basic science discovery is likely to succeed in the translation process.

2.5.1 Disclosure

Written disclosure by the inventor to the university is an essential first step; the university technology transfer office team then meets with the inventor to discuss the invention, including novelty, nonobviousness, and prior art, to determine the likelihood a patent will be allowed by the US Patent and Trademark Office (USPTO). *It is critical that the inventor have this initial meeting with the appropriate university officials prior to disclosing new data at professional meetings, in professional publications, and in other public releases.* Once data are in the public

domain, patent opportunities decrease. Although US law does allow a patent to be filed within the first year after an invention has been published or otherwise publicly disclosed, almost all other countries prohibit the filing of a patent once data are in the public domain (Nelsen 2004). Because receipt of patent protection does not guarantee a licensing partner will be found (Patino 2009), initial discussions with the Technology Transfer Office will often focus on many of the issues raised by Coller and Califf (2009) in their framework for assessing likely success. The technology transfer team will therefore also ask the inventor about potential licensees to ensure that if they invest in the patent preparation, submission, and defense, there are potential commercialization partners who may choose to invest in licensing the rights to the patent for product development purposes. Companies will typically be well versed in intellectual property management and will require nondisclosure agreements protecting against any public disclosure or other sharing of their proprietary information.

2.5.2 Patents

The cost for filing a patent application is fairly minimal, although there are significant legal costs incurred with the writing of the patent, which will directly vary with the complexity of the intellectual property, and there will be fees due at later times during the prosecution, award, and maintenance of a patent (for detailed discussion of factors that influence filing cost, see Patino 2009). One common sense solution is the filing of a provisional patent, which requires minimal information and minimal investment but protects the disclosure while the more time-consuming nonprovisional application is drafted by a patent attorney (Patino 2009). If the invention is deemed to meet specific criteria set by the USPTO (e.g., novelty, nonobviousness, and lack of prior art) when the utility application (i.e., the full application) is filed, a patent will be issued. *Patents provide necessary protection of a company's investment in the development of a product.* Without a patent and an exclusive license to protect against competition, it is not financially viable for a company to invest in the development of a new drug and clinical testing of that agent (Nelsen 2004; Patino 2009). Development of a pharmaceutical can cost nearly 1 billion US dollars (Peters 2004).

University opportunities to be part of the technology transfer process, through the filing of patent applications to protect faculty inventions, arose with the passage of The Patent and Trademark Law Amendments Act (the Bayh–Dole Act) of 1980. This act gave universities the right to own, manage, and profit from inventions developed using government funding (i.e., NIH or other governmental grants to academic institutions). Prior to the Bayh–Dole Act, the government owned all patents for inventions arising from research conducted using federal grant funds. There was limited licensing of these government patents by companies as the government would not allow exclusive licenses. Because corporate competitors could simultaneously license the rights to use those inventions in their own

competing products, there was little competitive advantage to be gained through nonexclusive licensing agreements. With the passage of Bayh–Dole, exclusive licensing of new inventions from universities to businesses became possible, and exclusive licenses have been more financially attractive to industry (University of California Technology Transfer Office 2015).

There continue to be strenuous objections to academic patents, however, based on arguments that development of proprietary information is fundamentally incompatible with an educational mission of collecting and evaluating knowledge, making that information available for students, and broadly enabling product development for the public good (Korn and Heinig 2005; Lempert 2005). The fiscal importance of the issue of ownership of intellectual property is made clear by Kesselheim and Avorn (2005). To advocate that universities should pursue intellectual property rights for the basic scientific results generated by their faculty, which are often precursors to actual commercial end products, they state, "restricting patenting rights to the end product alone ignores earlier scientific and financial contributions. Where intellectual property law draws the line has billion dollar ramifications for universities and academic medical centers attempting to support their research budgets, for patients who depend on the creation of innovative medical products, and for society, which ultimately benefits from and pays for these discoveries" (Kesselheim and Avorn 2005, p. 851).

One common tension during the negotiation of contracts for industry-funded research at academic institutions is management of potential new intellectual property (i.e., whether the university or the company owns any resulting patents, whether license agreements will be exclusive or not, and whether royalties will be required) (e.g., Kneller et al. 2014). Freedom of publication for the academic partner is another common tension (Kneller et al. 2014). Faculty are evaluated based on their publication records, and the mission of an academic research institution is creation and dissemination of knowledge. However, companies often need to protect trade secrets. One common solution is the requirement that faculty provide copies of papers and presentations to the company 30–90 days (depending on contract terms) before release so that companies can file patents as needed (Kneller et al. 2014).

2.5.2.1 Patents for Drugs That Mediate Auditory Trauma

Many of the compounds and molecules that are being investigated as potential otoprotective agents have been awarded patent protection as novel therapeutics that protect and/or preserve hearing. Ebselen, the subject of a case study in Chap. 5 by Lynch, Kil, and Le Prell, is the active agent in a formulation identified as SPI-1005; this patent is assigned to Sound Pharmaceuticals, Inc. (Kil and Lynch 2010). SPI-1005 was studied in a Phase I safety study (Lynch and Kil 2009) and was evaluated in a completed Phase II safety and efficacy study completed at the

University of Florida (NCT01444846; Kil et al. 2014).[1] Oral D-methionine, the subject of a case study in Chap. 6 by Campbell and Fox, is the active agent protected by multiple US and international patents (e.g., Campbell 2001, 2008). A proprietary formulation of β-carotene, vitamins C and E, and magnesium is the subject of several patents assigned to the University of Michigan (Miller et al. 2011, 2012, 2015)[2] and these patents are currently licensed to Hearing Health Science, Inc. This combination of active agents was assessed in animal models at both the University of Michigan (Le Prell et al. 2007a, 2011a) and Washington University (Le Prell et al. 2011b) before being assessed in clinical trials conducted in Sweden (in partnership with the Karolinska Institutet; see Le Prell et al. 2011c) and at the University of Florida (NCT00808470; Le Prell et al. 2016).

Other agents that act to reduce NIHL and/or noise-induced tinnitus are also being evaluated for potential efficacy in human subjects and developed as commercial agents by companies (for discussion of tinnitus therapies, see Allman, Schormans, Typlt, and Lobarinas, Chap. 7). For example, AM-111 is a patented JNK inhibitor (Bonny 2009) being developed by Auris Medical for human use in the inner ear; it has been assessed in recent clinical trials (Suckfuell et al. 2007, 2014). AM-101, patented for the prevention of tinnitus and other auditory complaints (Guitton et al. 2015), was also examined in a recent clinical study (Staecker et al. 2015). The novel surgical approach described for the delivery of adenoviral vector with E1/E3/E4 deletions (to allow transgene manipulation) described by Staecker (2008, assigned to the University of Maryland, Baltimore) is being used in NCT02132130 described by Staecker, Klickstein, and Brough, Chap. 8. The patents cited here are by no means an exhaustive list; these are provided simply to highlight relevant intellectual property associated with authors contributing chapters to this volume and to make the point that agents under investigation as potential otoprotective agents are routinely protected by institutional technology transfer offices if developed at academic institutions and by the corporate owners if they are developed by businesses.

2.5.3 Marketing, Negotiating, and Licensing

It must be kept in mind that a fundamental goal of the Technology Transfer Office is to promote the advancement of university intellectual property outside of the university through a licensing agreement and that the Technology Transfer Office is specifically tasked with protecting the best interests of the university (Patino 2009). In contrast, the company is tasked with protecting its own best interests, such as requiring a strong intellectual property position that ensures its ability to develop a

[1]Colleen Le Prell was the principal investigator on the contract between Sound Pharmaceuticals, Inc. and the University of Florida.

[2]Colleen Le Prell is an inventor on these patents; see references for detailed information.

product exclusively. Whereas exclusive licensing opportunities do increase the chances that a company will agree to a license, there is no guarantee that a license agreement will be negotiated. Even if a license agreement is successfully negotiated, there is no guarantee that the license agreement will lead to a new consumer product or process (Patino 2009). Licensing agreements will typically include milestones for development, and if they are not met, the licensing agreement can be terminated.

As patents for pharmaceutical agents grow older, they become less useful; therefore licensing and development must be pushed forward as quickly as possible by both the technology transfer office and the company. The Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch–Waxman Act of 1984, speeds the development of generic drug products by allowing the generic to reference all of the preclinical and clinical data that were collected by a pharmaceutical company during the development of the original name brand drug rather than conducting their own testing on the generic itself (Peters 2004; Knowles 2010). As reviewed by Peters (2004), although new drugs typically qualify for 20 years of patent protection, which stops competitors from marketing products with the same active ingredients, this 20-year "clock" begins *with the submission of the IND*. Because clinical testing and review and approval within the FDA can take multiple years, a large portion of a drug's patent life is lost during the testing period. The Hatch–Waxman Act does provide a mechanism through which some of this "lost patent time" can be restored, but "the maximum restored patent life is five years, and the maximum total effective patent life—meaning the time between FDA approval and a drug's patent expiration after any restored patent life—cannot exceed 14 years" (Peters 2004, p. 22). Thus, as patents age, there is less value associated with investing in clinical trials or additional development of the chemical entity if there will not be any significant protected sales period during which a generic equivalent cannot be made available to consumers. These kinds of challenges have led many universities to not only allow but also help faculty to spin-off startup companies that will license and develop intellectual property the faculty member developed at the university (Martin 2002; Nelsen 2004; Hammerstedt and Blach 2008).

2.6 Summary

This chapter provided a detailed overview of the T1, T2, and T3 phases of translational research, including provision of working definitions of different phases of research progressing from basic research through clinical testing and implementation into evidence-based patient care. There are many other tasks that must be accomplished to translate an agent from basic research into clinical testing, including, for example, development of dose–response curves, pharmacokinetic testing, two-species toxicity testing, and Phase 1 safety tests, all of which are discussed in more detail by Lynch, Kil, and Le Prell, Chap. 5, and by Staecker,

Klickstein, and Brough, Chap. 8. These studies are not attractive or appealing to many of the reviewers at the NIH who are accustomed to R01, R21, or other funding mechanisms where basic inquiry and generation of new mechanistic insight is the goal, but they are critically important to human translation.

Some of this work might be done within a university despite funding challenges, although many of these specific activities will occur postlicensing with leadership by a corporate entity. Worth noting, the NIH as part of its overall funding portfolio also offers Small Business Innovation Research (SBIR) awards, which companies can apply for to obtain grant funding that supports research that will foster new product development. Companies might also be able to obtain financial support from angel investors (individuals who support business development, typically investing between $25,000 and $100,000 in exchange for equity ownership) or venture capital (larger investments, also in exchange for equity ownership, and typically resulting in significant control over company decisions). All of the activities that must happen if a drug is to successfully move forward into Phase 2 efficacy testing have a price tag, and funds must come from grants, investors, or revenue streams from other existing products in the case of an established company with existing product lines. Academic inventors may interact with companies that license the rights to their inventions by partnering on grants, attending meetings with potential investors, or partnering on clinical testing of a licensed invention. Academic inventors who create a new spin-off company that will license and further develop the technology they invented have an even greater interest in furthering their own knowledge about all of the regulatory and financial challenges they will encounter.

With respect to translational research, Coller and Califf (2009) state that "the resources needed are substantial, the costs high, and the failure rates daunting." To navigate the many challenges successfully, there is a need for new funding models, changes to the regulatory environment to decrease bureaucracy and cost, and other policy changes necessary to accelerate the process (Fears et al. 2010). There are clearly diverging interests of academics (creation of knowledge, education of the future workforce) and industry (meeting market needs and protecting exclusivity to generate revenue and increase shareholder value). However, as argued by Ehrismann and Patel (2015), *there is an important common ground found in the mutual goal of advancing biomedical research, and finding cures for patients in need*. Whether patient care is advanced through industry-funded research within an academic laboratory, or industry licensing of an academic patent, is not important from the patient's perspective. What will benefit patients the most in the long run is the translation of novel therapies into clinical testing (T1) with subsequent translation of the most effective therapies into patient care (T2), with the long-term goal of improving public health outcomes (T3).

2.7 Closing Comments

The authors who describe the challenges and the obstacles and the myriad of "things you never even guessed you would need to someday know" when it comes to translational research are absolutely right—translation is slow and there is a steep learning curve. I have been asked if I would pursue a translational research program again, knowing what I know now about the slow pace of success in these kinds of activities. To all those reading this chapter to the very end, the answer is emphatically, enthusiastically, and without reservation yes. It is tremendously rewarding seeing each incremental step forward in the development of otoprotective agents. There are no FDA-approved drugs for the prevention of acquired hearing loss, but such agents are urgently needed. "Competitive agents" or not, there is a celebration of each accomplishment as data emerge across laboratories, and there are strong partnerships within and even among industry and academic investigators.

Compliance with Ethics Requirements

Colleen Le Prell has received contract funding from industry sources including Sound Pharmaceuticals, Inc., Edison Pharmaceuticals, Inc., Hearing Health Sciences, Inc., and MaxSound, Inc. She is a co-inventor on patents assigned to the University of Michigan and the University of Florida.

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Chapter 3
Auditory Processing Disorder: Biological Basis and Treatment Efficacy

Nina Kraus and Samira Anderson

Abstract Auditory processing disorders contribute to communication difficulties in children with language-based learning impairments and in older adults who have trouble hearing in background noise. Therefore, deficits in auditory processing are widespread among these diverse populations. For this reason, it behooves both scientific and clinical communities to consider optimum techniques for assessing and managing these deficits. The auditory brainstem response to complex sounds (cABR) provides an objective index of the biological health of the central auditory system. The cABR is also a sensitive indicator of training-induced neuroplastic changes and can therefore be used to assess treatment efficacy. Once integrated into clinical practice, use of the cABR may facilitate more widespread evaluation and treatment of auditory processing disorders.

Keywords Auditory aging • Auditory-based learning impairments auditory training • cABR • Central auditory function • Frequency following response • Objective assessment • Real-world environments • Speech in noise • Temporal processing

N. Kraus (✉)
Departments of Communication Sciences, Neurobiology and Physiology, and Otolaryngology, Northwestern University, 2240 N. Campus Dr., Evanston, IL 60208, USA
e-mail: nkraus@northwestern.edu
URL: http://www.brainvolts.northwestern.edu

S. Anderson
Department of Hearing and Speech Sciences, University of Maryland, College Park, MD 20742, USA
e-mail: sander22@umd.edu
URL: http://www.hearinbrainlab.umd.edu

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3.1 Introduction

The concept of an auditory processing disorder (APD) has been around for decades. Myklebust (1954) first defined APD as a disorder of auditory perception despite normal audiometric thresholds. In the 1970s, behavioral tests of auditory processing were developed and normative values were established based on performance of individuals with known cortical lesions. Now these behavioral tests are often used to assess auditory processing in children and adults who do not have identified anatomical abnormalities but have apparent hearing difficulties in difficult listening situations.

The most common manifestation of APD is difficulty understanding speech in noise. Deficits in auditory processing are prevalent in children with learning disabilities (Bradlow et al. 2003; Sharma et al. 2006). Children with dyslexia have poorer speech-in-noise (SIN) perception than children who are typically developing (Bradlow et al. 2003). They also have difficulty recognizing speech degraded by the removal of temporal fine structure cues, demonstrating that a speech perception deficit can occur in the presence of either external or internal noise (Ziegler et al. 2009). In addition to deficits in SIN perception, children with dyslexia have poorer performance compared to children who are typically developing on commonly used tests of auditory processing, such as the Pitch Pattern Sequence Test (Musiek 1994), the Dichotic Digits Test (Musiek 1983), and the Random Gap Detection Test (Dias et al. 2012). Given the evidence that children with learning disabilities often have APD, routine screening for APD may be beneficial in such children.

Older adults may also be affected by auditory processing deficits. Older adults have more trouble understanding speech in noisy environments than younger adults, even with audiometrically normal hearing thresholds (Gordon-Salant and Fitzgibbons 1993; Souza et al. 2007). These deficits may arise from decreased ability to process the fast temporal changes in speech (Grose et al. 2006; Gordon-Salant et al. 2007). Older adults have more difficulty identifying words that differ in temporal segmental speech cues (i.e., “dish” vs. “ditch” or “beat” vs. “wheat”) than young adults (Gordon-Salant et al. 2006, 2008), which may account for the older adult’s difficulty when trying to perceive these cues in compromised environments. Temporal processing deficits have also been revealed by electrophysiological studies. Older adults have delayed neural timing for the onset, offset, and consonant–vowel regions of the brainstem response to speech syllables compared to younger adults (Anderson et al. 2012; Clinard and Tremblay 2013) and they have decreased gap detection amplitudes in cortical responses (Lister et al. 2011; Harris et al. 2012). Current evaluation of hearing difficulties in older adults is typically limited to assessment of audiometric thresholds and speech perception in quiet despite the fact that the number one complaint of older adults is trouble hearing in noise. Therefore, assessment of auditory processing is warranted when an individual reports greater hearing difficulty than would be predicted from audiometric thresholds.

Referrals for APD evaluations from educators, psychologists, speech-language pathologists, and other professionals are increasing, and parents are demanding

these services when they learn of the existence of APD on the Internet and other media sources. Yet, despite the need for APD assessment and the availability of behavioral assessments, audiologists have been reluctant to include APD assessment in their clinical practices. A gap exists between the research supporting an auditory processing basis for learning impairments and speech perception deficits and the application of this knowledge in a clinical setting.

Several factors contribute to the lack of translation into clinical practice. One issue is a disagreement about whether APD exists as a separate entity apart from deficits in cognitive functions such as attention and memory (Cacace and McFarland 1998; Moore et al. 2010). Furthermore, APD is often comorbid with other learning problems such as dyslexia or attention deficit disorder (Sharma et al. 2009), with possible effects on the validity of the test results. Clinicians disagree on the criteria for APD diagnosis. Wilson and Arnott (2012) used nine different diagnostic criteria to determine the rate of APD diagnosis in 150 school-age children who completed an APD test battery and found that the rates of diagnosis varied from 7.3 to 96.0 %. Finally, clinicians are unsure of the efficacy of the treatments purported to improve auditory processing. Although benefits of training and/or FM systems for children with APD have been reported (Sharma et al. 2012), consensus has been hampered by disagreement about what constitutes an APD diagnosis and the paucity of outcome studies. Existing studies are difficult to compare because of methodological differences (Fey et al. 2011; Wilson et al. 2013). Conclusive outcome studies may be an unrealistic expectation given the different ways that APD is defined and the difficulties encountered when conducting longitudinal studies. In summary, some individuals have inordinate difficulty hearing speech in noise or paying attention to relevant sounds and excluding irrelevant stimuli, suggesting an auditory processing disorder. Large-scale studies in clinical settings combining behavioral and biological metrics are likely to be revealing and to provide guidance to clinicians.

Given that the attention and memory requirements of behavioral assessments of APD may reduce their validity, an objective assessment is needed for diagnostic evaluation and to document treatment efficacy. Electroencephalography (EEG) is the primary tool for evaluating infant peripheral hearing ability, but its use can be extended to evaluation of central auditory function. In children with learning problems, the ability to discriminate along a continuum of syllables differing in the spectral content of the formant transition correlates with the magnitude of mismatch negativity responses (MMNs) (Kraus et al. 1996). The middle latency response (MLR) has been used to diagnose APD and assess treatment benefits (Schochat et al. 2010). The use of the MLR is limited by between-subject variability, but this can be minimized by using between-ear amplitude differences rather than absolute amplitudes to determine the presence of an APD (Weihing et al. 2012). Typically, individuals with normal auditory processing have equivalent amplitudes when either the right or left ear is stimulated, but individuals with APD show unilateral deficits.

The auditory brainstem response to complex sounds (cABR; also called the frequency following response, or FFR) is another EEG evaluation that has recently been used to evaluate auditory processing disorders in a variety of clinical

impairments, including dyslexia, SIN perception deficits, APD, hearing loss, and aging. Because the cABR resembles the evoking stimulus acoustically and visually (Galbraith et al. 1995), the accuracy of encoding specific speech features, such as timing, pitch, and harmonics, is feasible to assess to an extent that is not possible when using slower, cortical potentials (MLRs) and late latency responses (MMNs). The following sections will describe the features of the cABR and its clinical applications for assessment of APD and therapeutic outcomes.

3.2 cABR: Objective Assessment of Central Auditory Function

The cABR's origins can be dated back to the frequency following response in the late 1960s and early 1970s. The term frequency following response (FFR) is used because the waveforms in the response reproduce the fundamental frequency of the stimulus (Marsh and Worden 1968). Moushegian et al. (1973) first demonstrated that the FFR can be recorded from the vertex of the human scalp. Initial experiments used simple sounds such as sine waves or tone bursts (Gardi and Merzenich 1979; Hall 1979), but in the 1980s Greenberg published the results of recording FFRs to vowels (Greenberg 1980) and to complex tones (Greenberg et al. 1987).

It was initially thought that the FFR could be used to assess infant hearing, but the FFR is more robust for low-frequency tones (Gardi et al. 1979), limiting its utility for the assessment of high-frequency thresholds. However, the last decade has seen demonstrations of the utility of the FFR for evaluating clinical disorders, including learning disabilities (Ghannoum et al. 2014; Malayeri et al. 2014), reading impairments (Banai et al. 2009; Hornickel and Kraus 2013; White-Schwoch et al. 2015), specific language impairment (Basu et al. 2010), autism (Russo et al. 2009), SIN perception deficits in children (Anderson et al. 2010a, b), APD (Billiet and Bellis 2010; Filippini et al. 2012), attention-deficit/hyperactivity disorder (Jafari et al. 2014), and age-related hearing difficulties (Anderson et al. 2013a, b; Clinard and Tremblay 2013).

The term cABR was adopted to differentiate these recordings from those made to simple and periodic stimuli (Skoe and Kraus 2010). Many of the aforementioned studies were conducted using the syllable [da], which contains an initial stop consonant burst, a consonant-vowel transition, and a steady-state vowel. Therefore, the cABR includes a response to a transient consonant in addition to the periodic, steady-state response that characterizes the traditional FFR. As mentioned earlier, the cABR's fidelity to the evoking stimulus permits evaluation of the encoding accuracy of speech components important for everyday communication—timing, pitch, and timbre (Fig. 3.1). The evaluation of these components has been useful in understanding the biological bases of the aforementioned clinical populations. For example, children with reading disabilities have delayed timing and reduced representation of the first formant harmonics in speech compared to children with

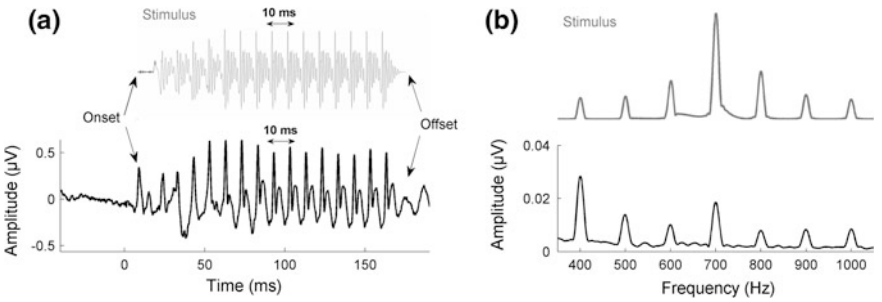

Fig. 3.1 When the stimulus waveform 170-ms [da] is temporally shifted to account for neural conduction, the stimulus timing of the onset and offset is apparent in the response waveform (average responses of 15 young adults with normal hearing). The periodicity of the stimulus waveform, with repeating peaks every 10 ms corresponding to the F_0 of 100 Hz, is also replicated in the response waveform (**a**). The harmonics of the response (average responses of 15 young adults) mirror those of the stimulus (**b**)

normal reading ability (Banai et al. 2009; Hornickel et al. 2009). Children with autism have less accurate pitch tracking than children who are typically developing (Russo et al. 2008). Finally, older adults with good SIN performance have better subcortical representation of the fundamental frequency (F_0) and less neural degradation in noise than older adults with poor SIN performance (Anderson et al. 2011). Each of these clinical communication disorders affects distinct components of the cABR, resulting in a unique neural signature for specific impairments (Kraus and Nicol 2014; Kraus and White-Schwoch 2015).

Another important feature of the cABR is its high reliability, a necessary condition for use in a clinical setting. Measures of pitch, timing, and timbre are reliable from session to session in school-age children (Hornickel et al. 2012a) and in young adults (Song et al. 2011). Further studies need to be conducted to determine cABR reliability in infants and older adults, two populations in which assessment may be unreliable due to immature development or variability associated with aging.

Finally, cABR features can be modified with experience. The cABR arises largely from the inferior colliculus (IC) in the midbrain (Chandrasekaran and Kraus 2010), a hub of intersecting connections of afferent and efferent fibers (Bajo and King 2012; Garcia-Lazaro et al. 2013). Animal models have demonstrated that connections between auditory cortex and IC are essential for auditory learning (Gao and Suga 2000; Bajo et al. 2010). Human studies have demonstrated that features of the cABR can be modified with online learning (Skoe et al. 2013b; Escera and Malmierca 2014), with as little as 1 week of training (Song et al. 2008), through classroom FM systems (Hornickel et al. 2012b) or through lifelong language experience (Krishnan et al. 2010; Krizman et al. 2012) and music training (reviewed in Kraus and White-Schwoch 2016). Therefore, given its reliability and its sensitivity to individual differences in auditory processing, the cABR may be ideal for evaluating the efficacy of APD training programs.

3.3 Integrating the cABR into Clinical Practice

A new EEG assessment has a high likelihood of being adopted into clinical practice if it can be incorporated into an existing platform used for other testing, such as hearing screening or diagnostics. The first clinical system, BioMARK, was built on an existing platform in common use in clinical sites in 2005. It was developed at Northwestern University by the Kraus Lab and was commercialized by Bio-logic Systems Corporation (Natus Medical, Mundelein, IL). King et al. (2002) first reported brainstem responses to a speech syllable in children with learning impairments, and Johnson et al. (2005) reported deficient sound encoding in children with learning or auditory processing disorders using the Bio-logic System. This particular system used a 40-ms [da], which contained an initial stop consonant burst followed by a consonant–vowel (CV) transition. The short length of the syllable makes it suitable for clinical assessment, as the total recording can be accomplished in less than 20 min. The inclusion of the CV transition permits evaluation of the most perceptually vulnerable region of the speech syllable (Miller and Nicely 1955). The system includes a template with marked peaks (onset peak: V, onset trough: A, FFR peaks: D, E, and F, and offset peak: O) to facilitate clinician peak picking (Fig. 3.2).

Since 2011, the cABR has been available as a research module from Intelligent Hearing Systems (IHS; Miami, FL). This version permits researchers or clinicians to use a variety of stimuli of different lengths. Using a full-length speech syllable is useful for comparing responses to different regions of the stimulus—the onset, transition, steady state, and offset (Fig. 3.3). Neural timing delays in clinical populations are often specific to the onset, offset, and transition regions of the stimulus (Anderson et al. 2010a, 2012).

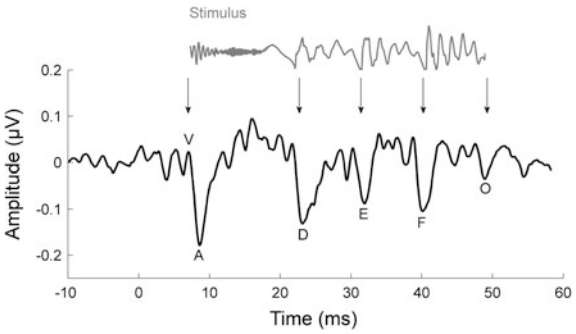

Fig. 3.2 The 40-ms [da] and its average response obtained from 25 infants aged 3–11 months using the BioMARK clinical EEG system. The onset peak and trough (*V* and *A*), FFR peaks (*D*, *E*, and *F*), and offset peak (*O*) correspond to the onset, FFR, and offset of the stimulus when it has been shifted to account for neural conduction time [Adapted from Anderson et al. (2015)]

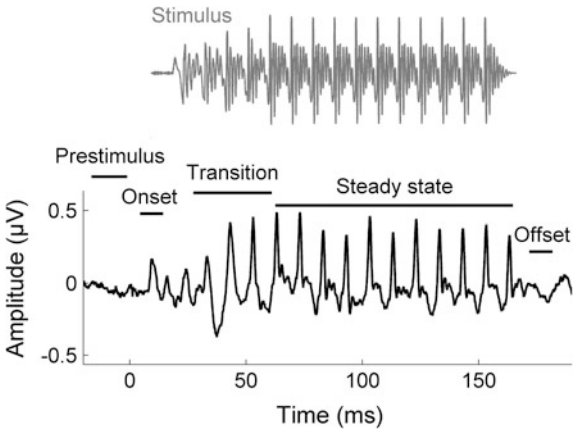

Fig. 3.3 The 170-ms stimulus [da] and the average response waveform of 15 older adults with normal hearing (aged 60–69 years). The prestimulus, onset (~8 ms), transition (20–60 ms), steady state (60–120 ms), and offset (~185 ms) are marked on the response waveform [Adapted from Anderson et al. (2012)]

Another benefit of the full-length syllable is the ability to compare phase differences between responses to two different stimuli. For example, an individual's responses to the syllables [ga] and [ba] should be in phase with each other in the steady-state vowel region, which is acoustically identical between the syllables. However, the responses to the consonant–vowel transitions should be out of phase, as differences between the stimuli in the formant transition are reflected in the phase of the response (Skoe et al. 2011). A cross-phase analysis allows the clinician/researcher to evaluate the extent of brainstem consonant differentiation in an individual (Fig. 3.4).

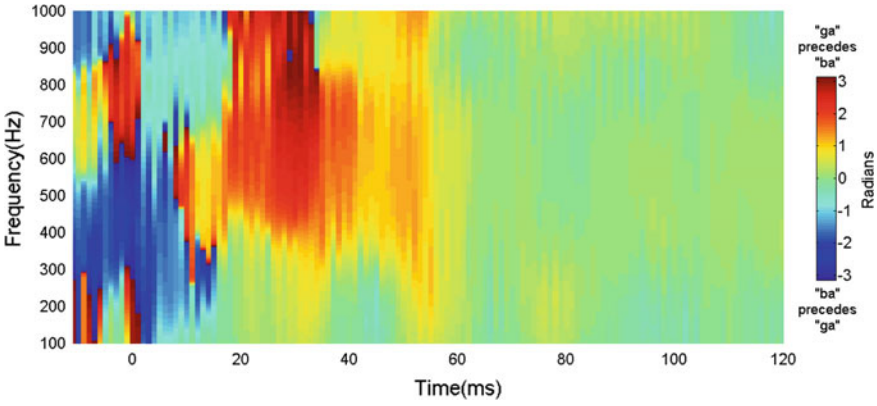

Fig. 3.4 Cross-phaseogram obtained from an individual 10-month-old infant. In the transition region (~20–60 ms), the phase of the response to [ga] leads [ba], indicated by the *red* color, in the formant transition region (400–720 Hz), as expected given tonotopicity of the auditory system. In the steady-state region (60–120 ms), the responses of the two syllables are in phase, as indicated in *green*

Clinical use of the cABR can expand the diagnostic capabilities of an evoked potential instrument. The current clinical protocol focuses on the ear; the cABR would expand testing to include auditory processing to the midbrain, reflecting influences of the corticofugal pathway, and would provide an objective assessment of auditory processing and treatment efficacy. Sections 3.4–3.7 describe how the cABR has been used to increase understanding of auditory processing impairments in children and in older adults and how it has been used to document treatment efficacy of training programs in real-world settings.

3.4 Evaluation of APD and Auditory-Based Learning Impairments

Some children with learning impairments, either dyslexia or specific language impairment (SLI), have deficits in auditory skills compared to typically developing children. For example, children with learning impairments may have difficulty perceiving rapidly presented auditory stimuli (Tallal 1980; Wright et al. 1997). Children with dyslexia may also have impaired perception of syllable onsets because of the inability to lock onto amplitude envelope modulations of speech (Goswami et al. 2002). Furthermore, there are no appreciable differences on auditory processing tests between groups of children with APD and with SLI (Miller and Wagstaff 2011). Therefore, objective and more granular evaluations of auditory processing skills in children with APD or SLI are warranted.

Similarities also exist between children with APD and children with auditory neuropathy spectrum disorder (ANSD), a disorder characterized by normal outer hair cell function with disrupted auditory nerve activity (Zeng et al. 2005). Individuals with ANSD have fluctuating hearing levels and may even have normal audiometric thresholds (Kraus et al. 1984, 2000). However, they exhibit poor temporal processing with elevated gap detection and temporal masking thresholds, and they have difficulty detecting signals in noise (Zeng et al. 2005). However, unlike individuals with ANSD, for whom the click-evoked ABR is absent, children with APD typically have normal click ABR latencies. The APD deficit is more subtle than that of ANSD and may be revealed only with the use of a complex stimulus (Filippini and Schochat 2009; Hornickel and Kraus 2013).

A pattern of cABR findings has emerged in children with reading impairments: they have delayed neural responses and reduced representation of higher speech harmonics (Banai et al. 2009; Malayeri et al. 2014) (Fig. 3.5). These findings may arise from a decrease in the synchrony of neural firing, which can lead to delayed response peaks and greater intertrial variability (Don et al. 1976; Schaette et al. 2005). Increased intertrial variability was found in a rat model of dyslexia (Centanni et al. 2014) and in poor readers compared to good readers (Hornickel and Kraus 2013). A similar neural difficulty is found in the FFRs of children with SLI.

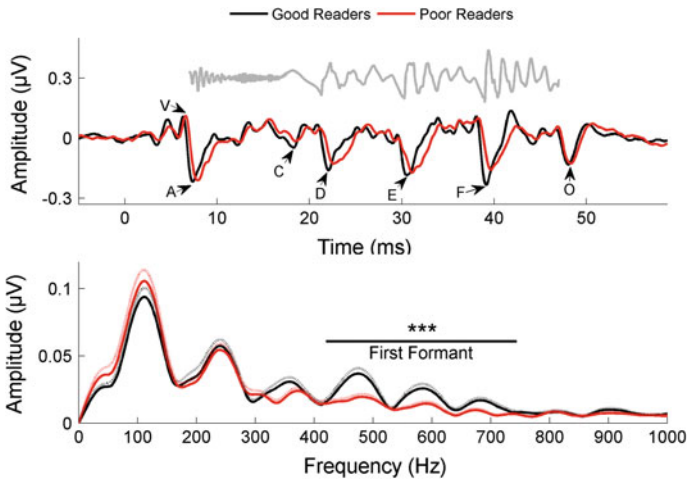

Fig. 3.5 Comparison of cABRs to a 40-ms [da] in children, ages 7–15, who were divided into groups of good ($N = 35$) and poor ($N = 28$) readers. *Top* Poor readers (*red*) have delayed latencies compared to good readers (*black*) for all seven peaks in the cABR. *Bottom* Poor readers have reduced representation of the first formant compared to good readers. *Dotted line* 1 S.E. ***$p < 0.002$ [adapted from Banai et al. (2009), *Cerebral Cortex*, 19(11), 2699–2707]

Compared to children with normal language abilities, children with SLI have degraded frequency tracking to tonal sweeps, especially at higher presentation rates, suggesting a disruption in sustained neural phase locking of the FFR generators in the brainstem (Basu et al. 2010). The inability to accurately represent the acoustic elements of speech that are critical for phonemic discrimination may impair the internal mapping of sound necessary to develop language or reading.

Delayed neural timing is also found in normal-hearing children with relatively poor speech-in-noise performance but only when comparing responses obtained in a background-noise condition to those obtained in quiet. The effects of noise on brainstem responses include delayed latencies and reduced amplitudes (Burkard and Sims 2002). Anderson et al. (2010a) found that 8- to 12-year-old children with poor SIN perception have greater noise-induced peak latency delays than age- and hearing-matched children with good SIN perception when comparing responses to a speech syllable obtained in quiet and in six-talker babble. This noise-induced delay was also seen in children who were divided into groups of good and poor readers (Fig. 3.6). Sperling et al. (2005) hypothesized that a noise-exclusion deficit prevents the formation of perceptual categories across sensory domains, contributing to reading difficulties. The finding of noise-induced delays in children with deficits in both SIN perception and reading suggests a common neural mechanism underlying these impairments.

However, children with reading versus SIN perception deficits appear to have distinct as well as the aforementioned overlapping neural signatures. Distinctions

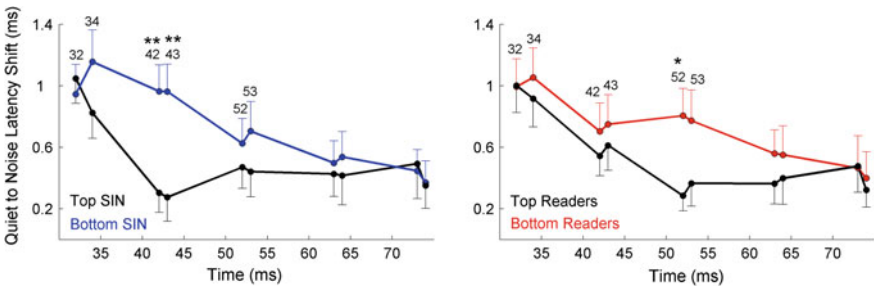

Fig. 3.6 Noise-induced latency shifts are greater for children with poor SIN perception (*blue*) than for those with good SIN perception (*black*), left, and are greater for children with poor reading (*red*) than for those with good reading (*black*), right. These latency delays were noted only for the consonant–vowel transition region of the syllable. Error bars = 1 S.E. $*p < 0.05$, $**p < 0.01$ [Adapted from Anderson et al. (2010a)]

are evident in the spectral content of their responses. Unlike children with reading problems, children with poor SIN perception have reduced amplitude of the F_0 rather than the higher harmonics (Anderson et al. 2010b). The F_0 and lower harmonics contribute to pitch perception (Meddis and O'Mard 1997), and pitch, along with spatial, timing, and harmonic cues, aids in speaker identification and auditory object formation (Oxenham 2008; Shinn-Cunningham and Best 2008). Locking onto a speaker's particular voice aids in stream segregation and is necessary to understand speech in a background of multiple talkers (Bregman 1990). Therefore, weak representation of the F_0 may impair the listener's ability to focus on a speaker's voice.

Few studies have used the cABR to investigate neural speech processing in children who have been diagnosed specifically with an APD independent of a reading or language impairment. Rocha-Muniz et al. (2012) compared cABR responses to a 40-ms [da] in three groups of children aged 6–12 years who were typically developing, diagnosed with an auditory processing disorder, or diagnosed with a SLI. They found that both the APD and SLI groups of children had abnormal cABR results compared to the normally developing group, but the abnormalities differed. Both groups with disorders had delayed peak timing compared to the typically developing group, but the timing delays in the SLI group were more pervasive than in the APD group. In addition, the SLI group had reduced amplitudes for the high-frequency region of the stimulus (721–1,154 Hz) compared to either the APD or typically developing group. These results are slightly different from those of the Banai et al. (2009) study, which found reduced amplitudes for both the mid (410–755 Hz) and the higher harmonics (755–1,130 Hz) in the group with reading impairments compared to the group with normal reading ability, but no information was provided regarding reading ability in the groups in the Rocha-Muniz et al. (2012) study.

Behavioral testing of APD is typically restricted to children older than the age of six because the language demands and testing requirements of memory and

attention exceed the abilities of younger children. The cross-phaseogram analysis, as mentioned in Sect. 3.2, evaluates subcortical differentiation of speech sounds. Impaired ability to accurately represent speech sounds is an example of an auditory processing disorder and may result in reading and language impairments. In a study of 3- to 5-year-old preschoolers, responses were recorded to the syllables [ba] and [ga] and cross-phaseograms were obtained (White-Schwoch and Kraus 2013). These children were also administered a phonological processing test (Clinical Evaluation of Language Fundamentals–Preschool-2, CELF-2P, Pearson, San Antonio, TX) and were divided into groups of low and high phonological processing skills. The children who had higher phonological processing showed greater phase differences in their responses between the [ba] and [ga] syllables than the children with lower phonological processing (Fig. 3.7). A follow-up study demonstrated that subcortical encoding of consonants in noise in preschool children predicts scores on tests of phonological processing a year later (White-Schwoch et al. 2015). Because reliable FFRs to a speech syllable have been obtained in

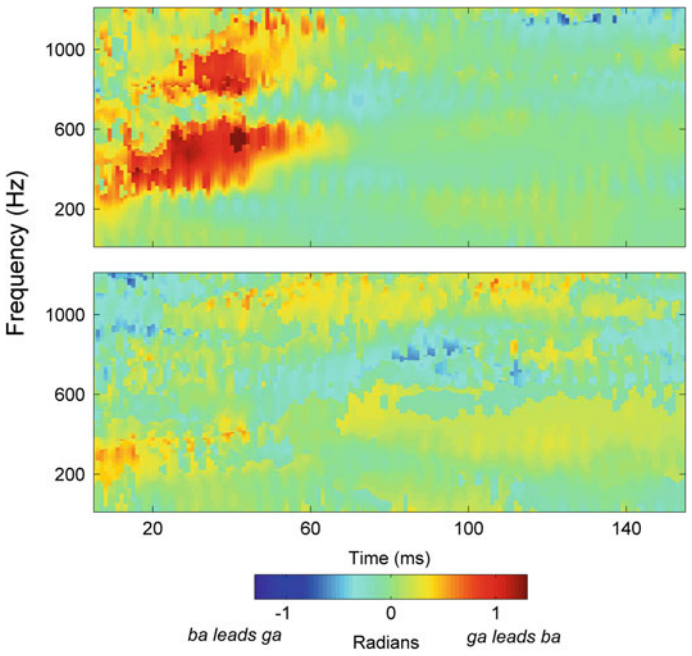

Fig. 3.7 Preschool children with better phonological awareness scores (*top*) have greater subcortical differentiation of stop consonants, as measured by larger phase differences, than age-matched children with poorer phonological awareness scores (*bottom*). The *red* region in the *top panel* shows the expected phase lead of [ga] before [ba] in the transition region, while there are no phase differences in the *bottom panel* illustrating data from children with less developed phonological (prereading) skills [Adapted from White-Schwoch and Kraus (2013)]

infants (Jeng et al. 2010; Anderson et al. 2015), perhaps these kinds of measures can be used to target at-risk infants and children who would benefit from intervention for language-based learning impairments.

3.5 Treatment of APD and Auditory-Based Learning Impairments

Other barriers to the inclusion of auditory processing evaluations in audiologic practices are the limited insurance payments for services and the belief by some clinicians that there are no effective treatment strategies for APD. The evidence of training benefits using electrophysiologic assessments is limited, but the click-evoked middle-latency response and the tone burst-evoked P300 may detect positive training outcomes in children with APD (Wilson et al. 2013). Because the cABR is reliable and meaningful in individuals and reveals myriad aspects of auditory processing, it can provide an effective assessment of the efficacy and nature of training benefits for auditory processing.

Two common interventions for APD are improving access to the signal through the use of an assistive listening device and providing auditory-based training to strengthen neural sound processing. FM systems are most often used in classrooms with children with hearing loss, but recommendations for its use with children with APD are increasing. Classroom noise often exceeds recommended levels (ANSI 2002; Knecht et al. 2002), putting the child with APD at a disadvantage compared to his or her peers. An FM system improves the child's access to the teacher's voice, effectively increasing the signal-to-noise ratio (SNR), and can be used to offset the deleterious effects of a noisy environment. The cABR was used to evaluate neural auditory processing and phonological skills in children with poor reading skills following 1 year of FM use (Hornickel et al. 2012b). Three groups of 8- to 12-year-old children were compared: an experimental group of children with reading impairments who used an FM system in the classroom, a control group of children with reading impairments who did not use an FM system, and another control group of children who were typically developing. Each group underwent a battery of tests before the beginning and after the end of the school year. The experimental group wore the FM system during school hours throughout the academic year. Two key findings emerged. In brainstem responses to a 170-ms [da], response consistency improved (intertrial variability decreased) in children who wore the FM systems, but there were no changes in response consistency in the other groups. Furthermore, the group who used the FM system was the only group that improved on phonological awareness (CTOPP) and basic reading (Woodcock–Johnson III Test of Achievement Basic Reading Cluster Score, HMH Riverside Publishing, Rolling Meadows, IL). Importantly, pretraining response consistency predicted the extent of improvement on phonological processing, suggesting that the cABR can be used to predict individual benefit from FM use (Fig. 3.8).

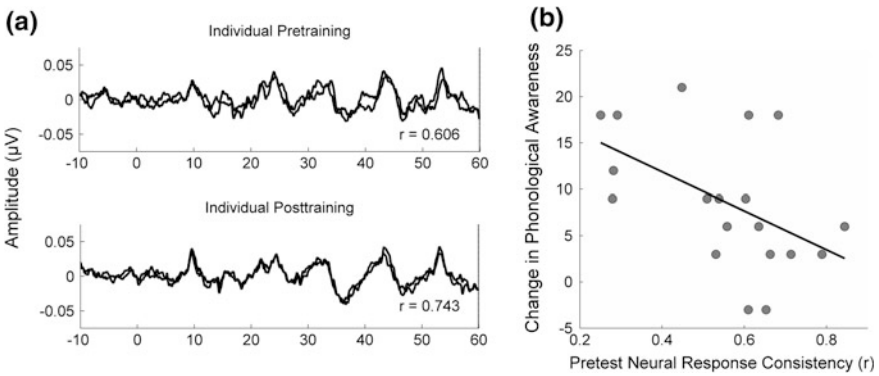

Fig. 3.8 cABR averages taken at two different times in the recording session (*gray* and *black*, respectively) in an individual child's response at pre- and posttraining sessions. The *r*-value is a measure of the degree of correlation (response consistency) between the two waveforms at each session. At the posttraining session, the waveforms are more closely aligned and have a higher *r*-value (**a**). The pretraining measure of neural response consistency predicts the change in phonological awareness after FM use during one academic year. Lower pretraining response consistency scores are associated with greater improvement in phonological awareness (**b**). [Adapted from Hornickel et al. (2012b)]

The cABR has also been used to document benefits from computer-based auditory training programs. Children with learning disabilities (8–12 years) underwent 35–40 h of Earobics training (Houghton Mifflin Harcourt Learning Technology, Boston, MA) over the course of 8 weeks (Russo et al. 2005). Earobics provides interactive training to improve phonological awareness, auditory processing, and language processing. The children's responses to a 40-ms [da] were elicited in quiet and in white Gaussian background noise (+5 SNR) before and after training. The responses in quiet and noise were cross-correlated to yield a measure of response degradation in noise—lower correlation values indicate greater noise degradation. Higher quiet-to-noise correlation values were seen after training, whereas no changes were seen in a control group. This training was accompanied by improvements in perception of sentences in noise, suggesting that more precise neural encoding of speech in noise is a factor in perceptual performance.

Training benefits were also documented with the cABR in children with SLI or APD. Responses to a 40-ms [da] were recorded in quiet and in white noise (+5 SNR) in four groups of children: typically developing ($N = 7$; no training), APD ($N = 9$, training), SLI ($N = 6$, training), and SLI ($N = 7$, no training). These children were also tested on a battery of behavioral APD tests, including a speech-in-noise test (details not provided), the Dichotic Digits (Musiek et al. 1991) or Staggered Spondaic Words Test (Keith et al. 1987), and the Pitch Pattern Sequence Test (Musiek et al. 1980). The training groups received 50 min of auditory training per week for eight weeks. The training consisted of practice on dichotic listening, pattern sequencing, and listening to speech in competing noise.

All four groups were tested before the initial visit and then 12 weeks later. Both the SLI and APD training groups had earlier brainstem latencies for the onset and initial peaks of the FFR elicited in noise but not in quiet, and no changes were seen in the control groups. Although the SLI and APD groups had significantly delayed latencies compared to the typically developing group before training, these differences disappeared after training. In addition, only the training groups had better behavioral performance on the Dichotic Digits or Staggered Spondaic Words Test and the Pitch Pattern Sequence Test at the second visit. No changes were seen on the speech-in-noise test in any of the groups. This study demonstrates the feasibility of using the cABR for evaluating treatment efficacy. However, the lack of an APD control group, random assignment, and small sample sizes limit interpretation of the results. More rigorous studies are needed to demonstrate efficacy of APD treatment.

3.6 Aging Effects on Auditory Processing: Spotlight on Hearing in Noise

Older adults, even those with audiometrically normal hearing, report trouble hearing in background noise, echoing one of the primary elements of APDs. This difficulty may arise, in part, from deficits in auditory temporal processing. Older adults are less able than younger adults to follow the fast-changing temporal cues that allow a listener to distinguish between words that differ on a single temporal dimension, such as voice onset time or formant transition duration (Gordon-Salant et al. 2006, 2008). Furthermore, older adults have more difficulty recognizing time-compressed speech (Gordon-Salant et al. 2007) and discriminating on the basis of temporal order compared to younger adults (Fogerty et al. 2010). Studies using speech materials may be affected by language or cognitive factors, but these deficits have also been found in studies using nonspeech materials. Older adults have larger gap detection thresholds (Schneider and Hamstra 1999; Phillips et al. 2000), larger duration discrimination thresholds (Fitzgibbons and Gordon-Salant 1995; Kumar 2011), and reduced temporal order discrimination compared to younger adults (Fitzgibbons et al. 2006; Shrivastav et al. 2008). Based on a review of 65 articles on central auditory aging, a task force concluded that the difficulties experienced by older adults may arise from a combination of factors including neurodegeneration along the auditory pathway and cognitive declines (Humes et al. 2012). The cABR is affected by both neurodegeneration and top-down cognitive influences (Kraus and White-Schwoch 2015) and is therefore a sensitive metric of auditory aging and can reveal a neural basis for central auditory processing deficits in older adults.

The use of the cABR permits evaluation of central auditory abilities in older adults without the confounds of linguistic or cognitive factors that may affect behavioral results. One primary finding across studies that supports a deficit in central processing is delayed neural timing (cABR peak latencies) in response to the

consonant–vowel transition of speech syllables (Vander Werff and Burns 2011; Anderson et al. 2012). This delay is similar to that seen in children with SLI, poor reading, and APD. These studies have been conducted in individuals with "clinically normal hearing." Because the definition of "normal hearing" may include thresholds ranging from −10 to 25 dB HL, it would be useful to determine if a relationship between latency and pure-tone threshold exists within this normal range, especially in older adults. Other characteristics in common with children with language-based learning deficits include decreased trial-to-trial response consistency and diminished representation of the higher harmonics in older adults compared to younger adults (Anderson et al. 2012). Furthermore, similar factors characterize children and older adults who are good or poor SIN perceivers. The neural signature underlying successful ability to hear in noise, robust representation of the F_0 and higher quiet-to-noise correlations, is present in both children and older adults (Fig. 3.9; Anderson et al. 2011).

To better understand the factors supporting speech understanding in older adults, structural equation modeling was used to determine the contributions of peripheral hearing status (audiogram, otoacoustic emissions), life experience (music, socioeconomic status, physical exercise), cognitive function (attention, memory), and subcortical sound processing (F_0 and first formant representation and quiet-to-noise correlations) to SIN perception (based on the QuickSIN and the HINT) in 120

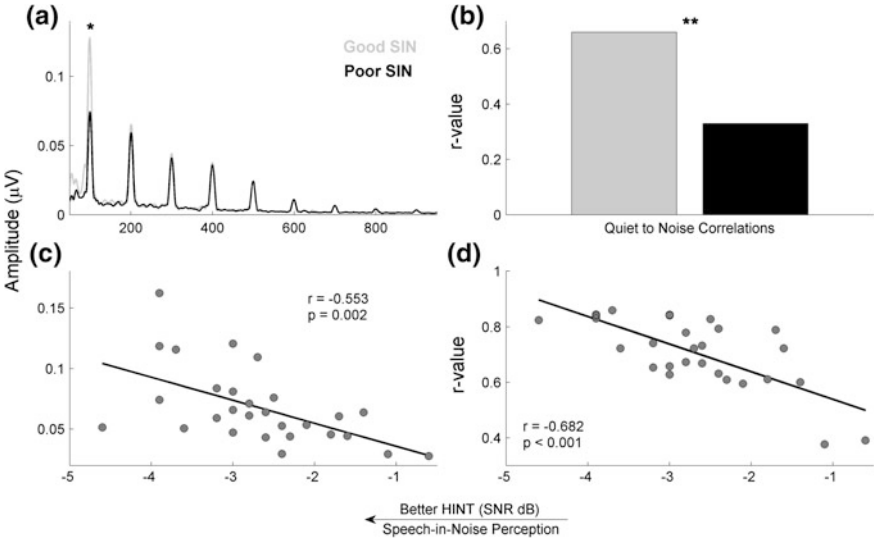

Fig. 3.9 Older adults with good SIN perception have greater strength of the F_0 than age- and hearing-matched older adults with poor SIN perception. All participants had clinically normal audiometric thresholds (**a**). Older adults with good SIN perception have higher quiet-to-noise correlation values than older adults with poor SIN perception (**b**). Better SIN perception is associated with higher F_0 amplitudes (**c**) and higher quiet-to-noise correlations. (**d**) $*p < 0.05$, $**p < 0.01$ (**c**, **d**). [Adapted from Anderson et al. (2011)]

middle- to older-aged adults, 55–79 years, with hearing levels ranging from normal to moderate sensorineural hearing loss (Anderson et al. 2013c). Both cognitive and subcortical processing contributed significantly to SIN perception, while neither life experiences nor peripheral hearing loss made significant contributions. However, it is expected that the contribution of peripheral hearing loss would be a significant factor in a data set that included more individuals with hearing loss. Furthermore, life experiences that are characterized by enrichment or deprivation may also affect neural speech encoding. For example, music training and language exposure can strengthen subcortical speech encoding (Wong et al. 2007; Parbery-Clark et al. 2012), whereas an impoverished upbringing may lead to decreased trial-to-trial response consistency and reduced representation of the first formant harmonics (Skoe et al. 2013a).

Although the cABRs in children with language-based learning impairments and older adults are influenced by peripheral and cognitive factors, there are likely different etiologies. In older adults, the deficits noted in the cABR may arise from peripheral neurodegeneration, cognitive declines, and changes in the balance of neurotransmitters. Animal models have demonstrated peripheral neurodegeneration after noise exposure in the absence of hair cell death. The degeneration can manifest as a delayed loss of auditory nerve fibers after recovery from noise exposure (Kujawa and Liberman 2006) or as an acute loss of auditory nerve terminals (Kujawa and Liberman 2009), although it remains undetermined if these noise-exposed animals have behavioral deficits processing sounds in challenging environments. Similarly, aging mice that have not had noise exposure experience cochlear synaptic loss and a decrease in auditory nerve fibers before there is detectable change in hearing thresholds or numbers of hair cells (Sergeyenko et al. 2013). This cochlear neuropathy is likely to affect the precision of sound encoding, particularly in the auditory brainstem where precise synchrony is required to produce a response (Bharadwaj et al. 2014). Therefore, the temporal processing deficits noted in the cABR in previous studies may arise, in part, from cochlear neurodegeneration. Additional studies in mice, assessing the cABR following exposures defined by Kujawa and Liberman (2009) as synaptopathic, would be useful in establishing the extent to which cABR changes are induced after noise exposure (cf. Shaheen et al. 2015). The cABR may also be affected by the local changes in the auditory brainstem and midbrain and top-down changes from auditory cortex. There is widespread speculation that decreased ABR amplitude after synaptopathic damage will specifically result in SIN deficits. Age-related changes in the balance of excitatory and inhibitory neurotransmitters occur in cochlear nucleus (Schatteman et al. 2008; Wang et al. 2009), inferior colliculus (Walton et al. 2002; Caspary et al. 2008), and auditory cortex (Hughes et al. 2010; Caspary et al. 2013). It is most likely, as stated in the Humes et al. (2012) consensus report, that temporal processing is affected by the interacting effects of an impoverished auditory signal and declines in day-to-day top-down modulation of responses.

Auditory processing deficits in children are likely to result from a failure to make effective sound-to-meaning connections that are necessary building blocks for learning language (Hornickel and Kraus 2013). This failure may result from a

genetic predisposition or from environmental factors, such as impoverished experiences, noise exposure, or ototoxic drugs, which result in a reduction in the quality of sound processing in the auditory brainstem and cortex. Decreased sensory input associated with hearing loss may also lead to degradation of auditory stimulus representation that interferes with the establishment of sound-to-meaning pathways (Balen et al. 2009). It should be noted that APD is a heterogeneous impairment that may arise from one or more sources of impairment or delayed development including auditory nerve, brainstem, auditory cortex, prefrontal cortex, corpus callosum, or other areas (Medwetsky 2011). The cABR may be influenced by impairments in these areas, but the neural signatures may depend on the specific nature of the impairment. For example, difficulty hearing in noise is associated with reduced representation of the F_0 whereas a reading impairment is associated with reduced representation of higher harmonics.

3.7 Treatment of Auditory Processing and Speech-in-Noise Perception Deficits in Older Adults

Auditory-based training induces neuroplasticity in adults that is reflected in changes in cABR and cortical evoked responses. Just 8 days of word-identification training on the basis of differing pitch contours leads to improved subcortical pitch tracking in young-adult nontonal language speakers (Song et al. 2008). This neuroplasticity is associated with real-world listening benefits. Young adults who used the commercially available Listening and Communication Enhancement program (LACE™, Neurotone, Inc., Redwood City, CA) had more robust subcortical speech representation in noise, and they also had improved scores on SIN tests (HINT and QSIN) (Song et al. 2012). Benefits of training are also seen in auditory cortex using the mismatch negativity response, with training on one stimulus generalizing to a novel stimulus (Tremblay et al. 1997).

Although training can modulate neural and behavioral responses in young adults and children, can similar benefits be achieved in older adults? Evidence from animal models is promising. Older rats that undergo frequency discrimination training have improved synchrony in auditory cortex and better perception; in fact, after training, the dot raster plots of older rats look similar to those of young rats (de Villers-Sidani et al. 2010). Therefore, one might expect similar results in older humans.

The use of computer-based auditory training, such as LACE, has become popular for a number of reasons. It permits adaptive fine manipulation of speech features and cognitive demands, allowing the user to proceed at an individual pace. The use of engaging software can increase compliance with the training (Bavelier et al. 2012) and can improve cognitive function in older adults (Anguera et al. 2013). Finally, the training can be performed at home, making it cost effective and efficient. Despite this potential, few studies have provided high-quality evidence for

the efficacy of computer-based auditory training, especially in individuals with hearing loss (Henshaw and Ferguson 2013). Recently, however, a randomized controlled study was conducted to determine the benefits of an auditory-based cognitive computer-training program in older adults with hearing levels ranging from normal to moderate sensorineural hearing loss (Anderson et al. 2013d). Older adults, aged 55–70 years, were randomly assigned to one of two groups. Those who were assigned to the experimental group received 40 h of home-based training over the course of eight weeks. The training consisted of six modules that adaptively increased levels of perceptual difficulty and memory load. Participants identified stimuli that differed in direction of pitch change or in the consonant–vowel transition duration. The stimuli were presented at a faster rate or were adaptively compressed as performance improved. Those who were assigned to the active control group also received 40 h of home-based training over the course of 8 weeks. They watched educational programs on their computers on topics ranging from art to history to science and answered questions about the content of the program. The participants were blind to the training group. Participants in the experimental group had faster subcortical peak latencies in response to a speech stimulus and reduced interpeak variability; these effects were most pronounced in noise (two-talker babble; +10 SNR) and in the response region corresponding to the consonant–vowel transition. The peak latencies in the active control group members did not change (Fig. 3.10). These neural changes were accompanied by improvements in SIN performance, short-term memory, and processing speed. Follow-up testing was performed 6 months after the completion of training. Faster timing and reduced interpeak variability were still present at 6 months, but of the behavioral variables, only processing speed benefits persisted, not the improvements in SIN performance or short-term memory (Anderson et al. 2014). Work is needed to determine the schedule of booster sessions necessary for maintaining performance. In addition, the training must be inherently reinforcing to the user to encourage continued participation in the program.

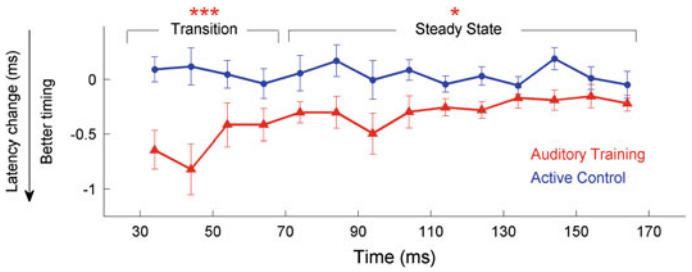

Fig. 3.10 After auditory training, older adults had earlier cABR latencies in response to speech presented in multitalker babble noise, especially in the consonant–vowel formant transition region. No latency changes were noted in the active control group. Error bars = 1 S.E. *$p < 0.05$, ***$p < 0.001$ [Adapted from Anderson et al. (2013d)]

The training studies carried out in children and older adults demonstrate the usefulness of the cABR for documenting changes in auditory processing, and that in children, aspects of the cABR can predict behavioral benefit from training (Hornickel et al. 2012a; White-Schwoch et al. 2015). More work is required to determine the predictors of training benefit in older adults. The cABR may also be useful in predicting success with other forms of intervention, particularly from the use of hearing aids. Cortical evoked responses are being used to determine benefit from hearing aids or cochlear implants in children with deafness, including those with ANSD (Roland et al. 2012; Cardon and Sharma 2013). The cABR may be similarly useful in predicting benefit in children or adults with sensorineural hearing loss that is not related to ANSD.

3.8 Challenges: Evaluating Training Efficacy in Real-World Environments

The aforementioned studies, although conducted in the home with computer-based programs or in the classroom with personal FM systems, were closely monitored and supervised by research personnel. To encourage widespread treatment for APD, it is important to document efficacy in more typical environments where rigorous control over treatment conditions may not be possible and to assess the impact of auditory training in community-based programs that have not been created by the experimenter. This has recently been achieved in two different studies that were carried out in at-risk children from lower socioeconomic backgrounds. Both of these studies used music as a medium for inducing neuroplasticity. Long-term participation in music training improves auditory expertise—SIN performance and auditory cognitive skills in children (Gerry et al. 2012; Strait et al. 2013) and older adults (Parbery-Clark et al. 2011). This enhanced behavioral performance is accompanied by improvements in the neural encoding of speech in noise (reviewed in Kraus and White-Schwoch 2016). Even a few years of music training in childhood and adolescence can partially offset age-related delays in neural timing in older adulthood (White-Schwoch et al. 2013; see also Skoe and Kraus 2012). Therefore, music may be an effective training strategy for inducing neuroplasticity and enhanced auditory function.

One study was conducted in the Chicago public schools (Tierney et al. 2013, 2015). High-school students chose between physical training (Junior Reserve Officers' Training Corps; ROTC) and music classes (choir or band); both options met three times per week. The students were evaluated with the cABR before their freshman year before the initiation of training and at the conclusion of each academic year. After 2 years, improvement was noted in subcortical timing in response to a speech syllable presented in a multitalker background in the music training but not in the ROTC group. This improvement was objectively evaluated in two ways:

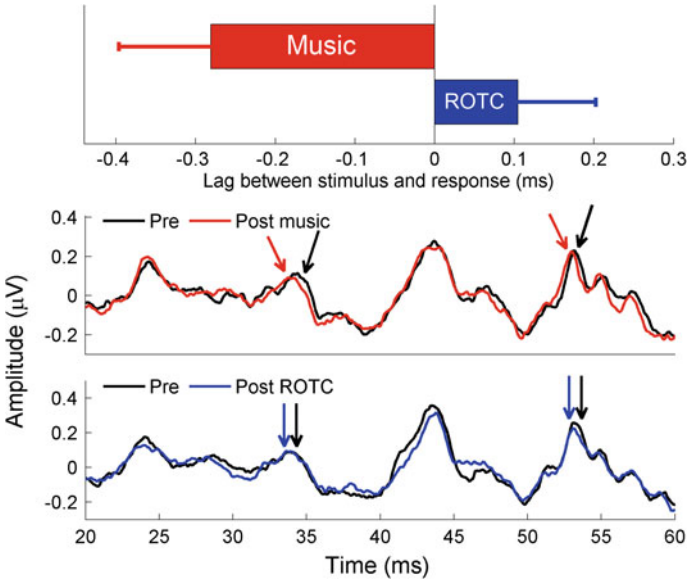

Fig. 3.11 *Top* The responses of adolescents to the syllable [da] presented in multitalker babble (+10 SNR) are shifted earlier in time after 2 years of music training, with decreased lag between stimulus and response. No changes were seen in the ROTC group. Decreased latencies are also seen in the post-waveform relative to the pre-waveform in the music group (*middle*) but not in the ROTC group (*bottom*). Error bars = 1 S.E [Adapted from Tierney et al. (2013)]

(1) identifying the response shift (stimulus-to-response lag) required to maximize the correlation between the stimulus and response, providing an objective measure of neural transmission delay at each test session, and (2) computing phase shifts between responses collected before and after training. Results indicated a decrease in stimulus-to-response lag and a negative phase shift indicated faster responses following 2 years of music training that did not occur in the physical training group (Fig. 3.11). These results demonstrate that even a modest amount of music training can improve the neural encoding of sound in adolescents (Tierney et al. 2015).

The second study (Kraus et al. 2014) was a randomized control design carried out in conjunction with Harmony Project (Los Angeles, CA), an award-winning community program that provides free music education to children in the gang-reduction zones of Los Angeles (http://www.harmony-project.org/, 2013). Children from the Harmony Project waiting list (ages 6–9 years) were randomly assigned to either defer their participation in music lessons for one year (termed Group 1) or start music lessons immediately (Group 2). The music lessons began with 2 h of musicianship classes weekly for approximately 6 months and then moved to group instruction for ≥ 4 hours per week on strings, woodwinds, or brass winds. cABRs were recorded to the syllables [ga] and [ba] before training, after 1 year, and after 2 years (Kraus et al. 2014). Results demonstrated increased

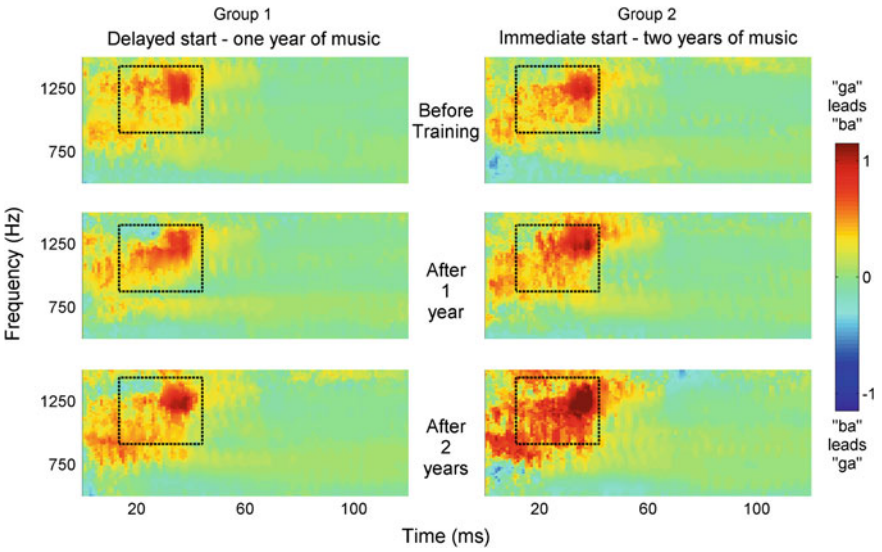

Fig. 3.12 Cross-phaseograms demonstrated an increase in subcortical differentiation between the syllables [ba] and [ga] after 2 years but not after 1 year of music training in school-age children. This increase was noted in the region corresponding to the second formant (0.9–1.5 kHz) at 15–45 ms post-stimulus onset [Adapted from Kraus et al. (2014)]

subcortical differentiation of the two syllables on the phaseogram after 2 years of music training in Group 2 (Fig. 3.12). The phase differences after 1 year were not significant in either group. It is likely that the number of hours of lessons after 1 year did not reach the threshold for producing a neurophysiological change, as the frequency of music lessons increased from 2 to 4 h per week after the first 6 months and was then more focused on a single instrument. One important aspect of this study is that the testing took place outside the lab setting in a classroom environment. Using the Intelligent Hearing Systems (IHS, Miami, FL) platform, the cABR was obtained in classrooms that were not electrically shielded, demonstrating the possibility of obtaining clean data in non-lab settings. One final point is that it takes time for music lessons to induce neuroplasticity, but these investments early in life are worthwhile because they have the potential for lifelong payoffs, as noted in White-Schwoch et al. (2013), who found that the benefits of music training in elementary and high school (earlier neural timing) persisted into older adulthood.

These two neuroeducational lines of work are important for a number of reasons. Most of the music studies cited in this chapter referred to individuals who had an extensive history of training leading to a professional music career. But these children received the amount of training that would be feasible to provide in the public schools, demonstrating the power of music education and the need to continue to maintain music in the public school curriculum. Furthermore, both groups of children came from environments of lower socioeconomic status with fewer

opportunities to engage in enriching experiences. Music training, an enriching activity with many possible social and recreational benefits, can at least partially ameliorate the deficits imposed by growing up in an impoverished environment. Finally, the studies demonstrate the feasibility of using the cABR to assess neurophysiological changes in real-world environments and in existing training programs, not just those that are experimentally created.

3.9 Future Directions

The biological nature of APD is poorly understood, in part due to the heterogeneous etiologies that may contribute to APD. Ideally, future studies of APD will include methodologies that clarify the sensory-cognitive interactions that are at play in this disorder. In addition to behavioral and cABR assessments, cortical evoked responses, functional magnetic resonance imaging, and magnetoencephalography will all contribute to a better understanding of the diverse nature of this disorder. cABR is likely to be especially viable in the clinic because of its documented reliability in individual subjects and its precision of reflective processing in the central nervous system. A better understanding of other potential causes of neurodegeneration of central auditory structures, such as history of exposure to noise, ototoxic agents, and traumatic brain injury, may also contribute to a better understanding of APD. The Kraus Lab continues to develop technology to bring the cABR into widespread clinical use as a measure of auditory processing.

The biological evidence for training efficacy is indisputable, but several questions remain unanswered. Future studies should determine optimal strategies for producing changes in different populations and how these strategies can be tailored to individual needs. The community-based studies described in Sect. 3.8 did not find improvements before two years of training. This fact is important for setting appropriate expectations. For example, a large study failed to find generalization effects after 6 weeks of online training, concluding that "brain training" does not improve general cognitive function (Owen et al. 2010), but perhaps the effects would have been realized after a longer training period. Determining factors that lead to changes in individuals will help to elucidate the biological mechanisms underlying these improvements. Large population studies are necessary to determine efficacy and to provide support for third-party payment. The cABR can be used to answer these questions.

Research on cABR/FFR is developing quickly across multiple domains (Kraus et al. In press). More work is needed to inform the efficacy of using the cABR in the assessment and management of APD in clinical settings. The projects in Los Angeles and in Chicago were successful, in part, as a result of relationships formed with community leaders who are committed to helping children achieve their potential despite the disadvantages that accompany an impoverished upbringing. Similar relationships need to be forged with clinicians and teachers serving children or adults with APD to bring assessment and treatment into real-world clinics and

other learning environments. The Kraus Lab neuroeducation work is an example of using community-based operations as laboratories in which to obtain scientific knowledge.

3.10 Summary

Although APD as an independent entity was identified several decades ago, the audiological community has not taken full responsibility for the assessment and management of this disorder. This reluctance is partly due to limitations in the current test battery, limited reimbursement, and a need for documentation of treatment efficacy. The cABR has proven to be sensitive to temporal processing deficits associated with auditory-based language impairments, including dyslexia, specific language impairment, and deficits in SIN perception across the life span. Because the cABR is a direct measure of auditory processing, an atypical cABR provides biological evidence of an APD. A few studies have specifically investigated cABR in children with an APD diagnosis, but more work is needed to develop criteria for classification of the cABR as typical or atypical. Furthermore, the cABR reflects neuroplastic changes in the midbrain, a hub of auditory learning, and can be used to assess efficacy of treatment. Therefore, the cABR has the potential to become an important component of the APD diagnostic and management test battery. Once integrated into clinical practice, use of the cABR may facilitate more widespread evaluation and treatment of APD.

Compliance with Ethics Requirements

Nina Kraus is chief scientific officer of *Synaural*, a company working to create a user-friendly measure of auditory processing.

Samira Anderson declares that she has no conflicts of interest.

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Chapter 4
Sudden Sensorineural Hearing Loss

Scott C. Montgomery, Carol A. Bauer, and Edward Lobarinas

Abstract Sudden sensorineural hearing loss (SSNHL) can have varying causes and etiologies and is considered a syndrome rather than a diagnosis. It is estimated that a cause is identified in only 10 % of patients diagnosed with the syndrome. Historically, there have been several proposed mechanisms for idiopathic SSNHL and today there are still questions and considerable debate regarding its etiology. Among the varied proposed mechanisms are immune-mediated disease, viral infection, vascular abnormalities, or a combination of multiple factors. This chapter reviews the current state of the science regarding idiopathic SSNHL, diagnosis, comorbidity, current therapeutic interventions, and emerging opportunities for disease management and treatment that are based on evidence-based practice. These include steroid treatment, hyperbaric oxygen therapy, drug therapy for viruses, intervention for vascular or ischemic etiology, salvage therapy, and posttherapy rehabilitation in cases of permanent hearing loss as well as the inherent challenges of providing intervention with varied evidence of efficacy.

Keywords Autoimmune inner ear disease • Coagulopathy • Herpes • Hyperbaric oxygen • Intratympanic steroids • Mumps • Perilymphatic fistula • Serology • Salvage • Tinnitus • Vertigo

S.C. Montgomery (✉) · C.A. Bauer (✉)
Division of Otolaryngology, Southern Illinois University School of Medicine,
301 North Eighth St., Springfield, IL 62794, USA
e-mail: smontgomery@siumed.edu

C.A. Bauer
e-mail: cbauer@siumed.edu

E. Lobarinas
Callier Center for Communication Disorders, University of Texas at Dallas,
1966 Inwood Road, Dallas, TX 75256, USA
e-mail: edward.lobarinas@utdallas.edu

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4.1 Introduction

Sudden sensorineural hearing loss (SSNHL) has many causes and etiologies and therefore is considered a syndrome rather than a diagnosis. It is estimated that a cause is identified in only 10 % of patients diagnosed with the syndrome (Schreiber et al. 2010). The lack of a common cause is particularly challenging for translational research efforts, both in narrowing down potential biogenerators for the disease process to guide basic research and for defining inclusion criteria for clinical trials. The most commonly accepted definition of SSNHL is based on symptoms rather than on a specific pathology. Diagnosis is generally based on the presence of sensorineural hearing loss greater than 30 dB at three consecutive frequencies in one or both ears on a standard audiogram occurring over 3 days or less (Stachler et al. 2012). In cases of unilateral loss, audiometric data are often not present before onset and the 30-dB differences are measured relative to the opposite ear. Idiopathic sudden sensorineural hearing loss (ISSNHL) is considered the diagnosis once an appropriate investigation has been completed and a cause has not been identified (Stachler et al. 2012). Historically, several mechanisms have been proposed for ISSNHL, and today there are still questions and debate regarding its etiology and whether it is immune mediated, viral, vascular, or a combination of multiple factors. Given these challenges, this chapter highlights the current state of the basic science, current therapeutic interventions and their relative level of evidence, ethical constraints regarding clinical research opportunities, and potential strategies to enhance translational research efforts.

4.1.1 Basic Science of SSNHL

Most cases of SSNHL are idiopathic and are classified based on the reported time course and severity of symptoms. The current treatment options available, as described in Sect. 4.5, are used primarily to attenuate and limit inner ear damage as opposed to addressing the unknown cause of SSNHL. Because the underlying mechanisms of SSNHL are poorly understood, most attempts at developing animal models are based on mimicking the symptoms of SSNHL via the introduction of viruses, vascular abnormalities (Schweinfurth and Cacace 2000), metabolic disturbances (Jing et al. 2006), and a host of other conditions that produce SSNHL-like symptoms. Similar to other hearing disorders, such as tinnitus and auditory neuropathy, the description of SSNHL as a syndrome is appropriate, and it is likely that several subtypes exist for which no one single treatment is effective. Further complicating the efforts of developing animal models are the high spontaneous recovery rates observed across individuals presenting with SSNHL. In addition, treatment of patients presenting with SSNHL cannot ethically be withheld or delayed, thereby limiting both the opportunities and design of clinical trials.

The path forward for basic science will require guidance from collaboration with clinicians and enhanced classification of SSNHL based on biological assays from

presenting patients and comorbid conditions identified in patients with SSNHL. In this chapter, we describe the magnitude of this important syndrome, the rationale and scientific support for current therapies, and proposed underlying mechanisms.

4.1.2 Epidemiology of SSNHL

The incidence of SSNHL varies across nations but is estimated to be in the range of 4–160 cases per 100,000 annually. In 2013, a population-based cross-sectional analysis (Alexander and Harris 2013) estimated an incidence of 27 per 100,000 in the United States. The study also found that incidence increased with age. Incidence among people age 65 and older was estimated at 70 per 100,000, data that are consistent with multiple other studies in Europe and Asia (Wu et al. 2006; Nosrati-Zarenoe et al. 2007; Teranishi et al. 2007). Men in the United States were found to be marginally more likely to be affected, with a male-to-female ratio of 1.07:1 (Alexander and Harris 2013). A slightly increased male-to-female incidence has been seen in multiple older studies outside the United States (Byl 1984; Wu et al. 2006), but a German study (Klemm et al. 2009) found a female preponderance, with a female-to-male ratio of 1.22:1. The reason for differences between the sexes is unknown, along with differences between national studies, but some have speculated that it may be due to culture differences in self-reporting of disease (Alexander and Harris 2013).

There are estimated to be more than 66,000 cases of SSNHL annually in the United States alone. Medical evaluation can involve extensive testing and multiple physician visits across multiple specialties including primary care physicians, emergency physicians, and otolaryngologists, leading to a significant burden on the healthcare system. Testing typically includes repeated audiometric assessment, magnetic resonance imaging (MRI), computed tomography (CT), and hematologic and serologic testing depending on the presentation. Consulting services such as cardiology or neurology may also be utilized in the diagnosis or for follow-up. The disease itself brings an obvious burden to the patients as well. A unilateral loss caused by SSNHL impairs sound localization and hearing in background noise. SSNHL also has a significant negative impact on quality of life as a result of feelings of exclusion, reduced well-being, and extensive use of speech perception strategies. This is true even in patients with only a unilateral loss (Wie et al. 2010). SSNHL occurring in the presence of an existing age-related hearing loss brings an additional impairment and communication burden, with concomitant psychosocial effects of social exclusion and reduced sense of well-being. SSNHL is frequently accompanied by tinnitus and dizziness (Byl 1984), each of which has its own impact on patient health, quality of life, and healthcare costs. Treatment options and associated costs are highly variable, consistent with the limited understanding of the pathology and the absence of targeted therapy. For example, hyperbaric oxygen therapy can be costly and time consuming, requiring daily sessions for several weeks, potentially taking time away from employment. Drug regimens can also be expensive and may have an array of side effects (Stachler et al. 2012). Aural rehabilitation for permanent hearing loss includes the expense of hearing

aids or surgically implanted devices and the lifelong follow-up maintenance of the devices. The impact of SSNHL on patients and the healthcare system as a whole is significant. Given the disabling nature of SSNHL, its costs, limited efficacy of its treatment, and apparent varied etiology there is an urgent need to apply a robust framework using translational research to move from T0 (basic science) through T1 (clinical insight and Phase 1 clinical trials), T2 (implications for practice via Phase 2 and 3 clinical trials), T3 (Phase 4 clinical trials, dissemination, and outcomes research), and ultimately T4 (population-level studies and public health). As highlighted in subsequent sections, the path forward in translation will require significant input from clinicians to optimize both basic science research efforts and clinical trials.

4.2 Clinical Presentation

Although, as stated in Sect. 4.1, SSNHL occurs over 3 days or less (Stachler et al. 2012), the loss frequently occurs over an even shorter time course, and most commonly, patients report SSNHL occurring during sleep (Mattox and Simmons 1977). Frequent associated symptoms are aural fullness, tinnitus, and vertigo or disequilibrium (Byl 1984). Unilateral loss is far more common than bilateral loss (Oh et al. 2007). Approximately 10 % of cases have an identifiable cause while the remaining 90 % are idiopathic (Penido et al. 2009). Spontaneous recovery rates are estimated to be from 32 to 65 % within 2 weeks of onset (Schreiber et al. 2010). The longer the duration the hearing loss, the more likely it is to become permanent. Multiple prognostic indicators are explored in Sect. 4.3.

Bilateral SSNHL, accounting for fewer than 5 % of patients with sudden loss, may be uniquely different than unilateral SSNHL. Bilateral SSNHL is rarely idiopathic and may have a lower rate of recovery, in one study estimated at 37.5 % for bilaterally affected patients compared to 56.5 % for those unilaterally affected (Oh et al. 2007). Compared to patients with unilateral SSNHL, bilateral SSNHL was more common in older patients, patients with lipid abnormalities, and patients with diabetes mellitus (Oh et al. 2007).

4.2.1 Autoimmune Inner Ear Disease and SSNHL

The presentation of autoimmune inner ear disease (AIED) has a significant overlap with SSNHL. At present, however, there is general agreement that these are separate disorders. AIED typically presents as a rapidly progressive, often fluctuating, bilateral loss that occurs over weeks to months. A retrospective review (Matsuoka and Harris 2013) of 47 cases at two tertiary medical centers in the United States identified fluctuating hearing loss for more than a year (100 %), tinnitus (95.7 %), ear pressure (93.6 %), and vestibular symptoms (51.5 %) as the most common symptoms of AIED. There is no gold standard diagnostic test and therefore AIED is

a clinical diagnosis. Many clinicians consider AIED a heterogeneous syndrome rather than a specific diagnosis. There is also a lack of agreement on a treatment regimen. The most commonly accepted treatment is a 4-week course of high-dose oral prednisone followed by a gradually decreasing dose known as a taper (Matsuoka and Harris 2013). The response to steroids is considered to be a critical diagnostic feature of AIED. Diuretics are often used to control vestibular symptoms, with the presumption that an increase in the endolymph volume of the inner ear, also known as hydrops, is a component of the disease. Drugs that alter the immune system, such as etanercept and methotrexate, have been tested but studies have shown no benefit over placebos (Harris et al. 2003; Cohen et al. 2005). The 72-h time frame for rapid hearing loss and presentation of associated symptoms is the only factor distinguishing the diagnoses of AIED and SSNHL. This somewhat arbitrary time frame may be inappropriate in light of the limited knowledge of the pathophysiology of these diseases and the possibly immune-related mechanism of SSNHL. Despite the lack of success of experimental drugs for AIED in clinical trials, there may be alternative opportunities to screen potential new drug candidates in animals based on work on the MRL-lpr mouse, a strain known to develop multisystemic nonspecific spontaneous autoimmune disease including degeneration of the inner ear that is similar to that observed in AIED (Ruckenstein et al. 1993). A specific treatment could be subsequently evaluated in clinical trials of individuals with AIED and SSNHL.

4.2.2 Etiology of Idiopathic SSNHL

There is growing evidence that SSNHL is a multifactorial syndrome with multiple etiologies rather than a disease with a single etiology. Putative causes of SSNHL are outlined in Table 4.1. There are numerous theories on the mechanisms ISSNHL, the most commonly accepted of which are detailed Sects. 4.2.3–4.2.7. As of yet, there is no direct causal link between any specific etiology and idiopathic SSNHL.

4.2.3 Membranous Breaks

One of the early theoretical mechanisms of ISSNHL was cochlear trauma with damage to the inner ear membranes. In 1968 Simmons proposed that rupture of Reissner's membrane was the cause of ISSNHL in a series of 15 patients with sudden onset of hearing loss. Most cases were accompanied by a "pop" or immediate-onset roaring tinnitus that occurred during strenuous activity, cough, or another event that increased intracranial pressure. This hypothesis was supported by two cases in which postmortem pathologic analysis showed evidence of Reissner's membrane rupture. Sudden hearing loss occurred in one of the cases as a result of barotrauma while flying (Gussen 1981).

Table 4.1 Causes of sudden hearing loss

Autoimmune	AIED	Neurologic	Multiple sclerosis
	Behçet's disease		Stroke
	Cogan's syndrome		
	Systemic lupus erythematosus	Otologic	Enlarged vestibular aqueduct
			Ménière's disease
Infectious	HIV		Perilymphatic fistula
	Meningitis		
	Lyme disease	Pharmacologic	Aminoglycosides
	Mumps		Chemotherapeutics
	Syphilis		Nonsteroidal anti-inflammatory drugs
	Toxoplasmosis		Salicylates
Neoplastic	Acoustic neuroma	Traumatic	Surgical/iatrogenic
	Cerebellopontine angle neoplasms		Temporal bone fracture

Simmons (1968) hypothesized that spontaneous mechanical rupture of Reissner's membrane would result in a syndrome of sudden hearing loss, tinnitus, and vertigo (Simmons 1968). Fee observed leakage of perilymph into the middle ear from the oval window in three patients with SSNHL after head trauma (Fee 1968). Goodhill further developed the link between perilymphatic leaks and SSNHL with a series of patients presenting with hearing loss after exertion, middle ear pressure changes, or a spontaneous popping sensation in the ear (Goodhill 1971). He hypothesized that increased middle ear pressure while straining could result in rupture of the round and oval windows and leakage of perilymph or perilymph fistula. Alternatively, membrane rupture could occur from transmission of intracranial pressure to the endocochlear fluid space via an enlarged or patent cochlear aqueduct or patent internal meatus at the cochlear modiolus.

Membrane breaks and spontaneous perilymphatic fistula may be responsible for a small proportion of patients with SSNHL. Direct clinical observation does not support these events as identifiable causes in the majority of cases. Membranous breaks are unlikely the predominant etiology in idiopathic SSHNL given that the majority of cases are not associated with an increase in activity or intracranial pressure and instead often occur on awakening from sleep (Chau et al. 2010). Perilymphatic fistula formation is a known cause of SSNHL after head trauma, barotrauma, and otologic surgery, but it is likely not the cause of the majority of cases for the same reasons described earlier. Two histological studies of temporal bones of patients with SSNHL found no evidence of Reissner's membrane rupture, membranous trauma, or perilymphatic fistulae (Schuknecht and Donovan 1986; Merchant et al. 2005), suggesting an alternative etiology in these instances. These findings are consistent with changes in hearing in animals with selective Reissner's

membrane ruptures. Findings from guinea pigs show less than 10 dB changes, results suggesting that Reissner's membrane ruptures alone are unlikely a significant contributor to the hearing losses associated with SSHNL (Gyo et al. 1994).

4.2.4 Viral Infection

Viral infections causing damage to auditory structures are well documented in adults. Otopathology has been linked to a number of agents, including varicella-zoster, Epstein–Barr, measles virus, and mumps virus. Inflammation caused by infection with or reactivation of a virus has been strongly suspected as one of the main etiologies of SSNHL, though there are very limited data proving a direct causative link (Kuhn et al. 2011).

A suggested pathway for viral infection affecting the inner ear structures is from primary viral infection in the cochlea or cochlear nerve after inoculation via the bloodstream, cerebrospinal fluid (CSF), or middle ear (Wilson 1986). Alternatively, SSNHL could be the result of reactivation of a latent viral infection (Wilson 1986). Several viruses are known to lie dormant within neural tissue and become reactivated at some later point, potentially causing inflammation leading to SSNHL (Fukuda et al. 1994). A third possible mechanism is a combination of viral and autoimmune etiologies. In this mechanism, a viral infection, either systemic or at a specific site outside the inner ear, leads to the creation of an antibody that cross-reacts with a critical inner ear structure or process (Merchant et al. 2008).

There are multiple serologic studies supporting a viral etiology to SSNHL (Fukuda et al. 2001; Chau et al. 2010). Live mumps virus was isolated from the inner ear of a woman who suffered SSNHL in conjunction with mumps infection of the parotid salivary gland (Westmore et al. 1979). Notably, despite increasing proportions of the population receiving immunization for mumps, measles, and rubella, we have not seen a resultant decline in the incidence of SSNHL, suggesting that these viruses are not likely responsible for the majority of cases. Herpesvirus particles are known to have a dormant phase in humans that can last the entire lifetime of the individual (Mandell et al. 2010). It is theoretically possible that reactivation of one of these viruses could cause SSNHL; however, there are no laboratory tests available to accurately diagnose viral reactivation. Animal studies of the effects of viral particle inoculation of the inner ear show histopathology findings of leukocytes, neural degeneration, and hemorrhage (Stokroos et al. 1998). Human histopathological studies have mostly shown atrophy of hair cells and supporting cells within the organ of Corti along with inconsistent damage to other structures within the cochlea such as the stria vascularis, tectorial membrane, cochlear neurons, and the vestibular end organ (Schuknecht and Donovan 1986; Linthicum et al. 2013). These lesions are similar to those found in temporal bones of individuals with progressive hearing loss attributed to known viral infections such as mumps, measles, rubella, or herpes (Merchant et al. 2008). Overall, there is correlational evidence indicating that viral infection or reactivation may play a role

in SSNHL, but there is no evidence that directly links viral infection to SSNHL, such as histopathological proof of viral particles within the inner ear.

4.2.5 *Vascular Occlusion*

Vascular occlusion of the vessels supplying the cochlea is another suspected etiology of SSNHL. Two branches of the labyrinthine artery, which arise from the anterior inferior cerebellar artery, supply the labyrinth and form a capillary network through the stria vascularis within the cochlea. The acute loss of hearing in SSNHL, along with its typically unilateral presentation, suggests that an ischemic event in these small blood vessels is a plausible mechanism. Vascular compromise could result from acute hemorrhage, occlusion from a traveling blood clot, vascular disease, decreased blood supply from spasm of blood vessels, or a change in blood viscosity (Kuhn et al. 2011). There are few data supporting vascular compromise as the sole explanation of SSNHL, but there is some evidence indicating it may at least play a role in some of the cases (Greco et al. 2011). In some studies, risk factors associated with vascular disease and ischemic stroke have been associated with SSNHL, including hypertension, hyperlipidemia, and cigarette smoking, while other studies have not found these links. Many of these comorbid conditions are found in older individuals but SSNHL often affects young, healthy people. A recent study suggested that altered autonomic regulation plays a role in SSNHL, arguing that dysfunctional blood pressure modulation may result in short-term blood pressure fluctuations and reduced cochlear blood flow (Schulz et al. 2014).

Gene analysis has provided evidence for bleeding and clotting disorders as causes of some cases of SSNHL. Polymorphisms of genes encoding thrombin, prothrombin, and Factor V Leiden have been associated with SSNHL and are discussed further in Sect. 4.3.1. Increased concentration of fibrinogen, a critical component of the clotting cascade, has been thought to contribute to SSNHL in some cases by increasing blood viscosity. In addition, there is a 1.6 times risk of stroke among patients suffering from SSNHL, indicating an underlying vascular abnormality (Patzak et al. 2005).

The labyrinthine artery supplies the cochlea and the vestibular organs. Occlusion of the labyrinthine artery would be expected to invariably result in auditory and vestibular dysfunction. In addition, one would expect vascular occlusion to result in a permanent rather than temporary hearing loss. One of the earliest studies examining vascular occlusion of the labyrinthine artery demonstrated hearing loss after 1 hour of occlusion. Hearing did not recover when blood flow was restored (Perlman et al. 1959). Furthermore, histopathologic studies provide only limited support for a vascular etiology for SSNHL. Fibrosis of the cochlea is the hallmark finding in vascular occlusion, as shown in animals after obstruction of the labyrinthine artery (Perlman and Kimura 1957; Belal 1979). Examination of temporal bones from patients who suffered from idiopathic SSNHL rarely reveal fibrosis (Yoon et al. 1990). A recent study compared temporal bones of seven patients who

suffered known vascular occlusion secondary to surgical procedures and the temporal bones of 11 patients with a history SSNHL. Fibrosis was present in six out of the seven temporal bones of patients with an associated vascular event but not in any of the temporal bones with SSNHL. Based on these findings, the authors concluded that vascular insufficiency was less likely a cause of this disorder (Linthicum et al. 2013).

4.2.6 Autoimmune Mechanisms

The autoimmune or immunologic hypothesis suggests that damage to the auditory system is mediated by autoantibody, immune complex, or T-cell mechanisms similar to the theoretical mechanism of AIED. This hypothesis is loosely supported by the steroid-responsive nature of SSNHL and associated elevation of the erythrocyte sedimentation rate, a nonspecific marker of inflammation (Chau et al. 2010). Antibodies that cross-react with inner ear proteins could potentially be formed directly or result from a reaction triggered by infection with a virus or other microorganism (Merchant et al. 2008). Autoantibodies to several inner ear–specific antigens have been detected in patients with SSNHL. Choline transporter–like protein 2 (CTL2), a glycoprotein found on supporting cells, has been identified as one possible target of an autoimmune reaction. In 9 of 20 patients with SSNHL, antibodies to CTL2 were detected on serologic testing (Disher et al. 1997). Other antigens within the inner ear that potentially are targets of autoantibodies include cochlin (Solares et al. 2004), beta-actin (Boulassel et al. 2000), beta-tectorin (Solares et al. 2004), and type 2 collagen (Yoo et al. 1983). A murine model of immune-mediated hearing loss using beta-tectorin and cochlin supports the idea of leukocyte infiltration of the cochlea as the mechanism causing hearing loss (Solares et al. 2004). Although elevated levels of antibodies to these antigens have been detected in association with autoimmune hearing loss, there are no large-scale studies showing their absence in a normal-hearing population or their presence in SSNHL. Others have called for direct evidence of these autoantibodies acting within the cochlea. Longitudinal studies examining titers over time as the hearing of patients with SSNHL fluctuates would add valuable evidence in support of the role of these antibodies in SSNHL (Merchant et al. 2008).

There is also evidence suggesting a more systemic autoimmune pathology may be involved in SSNHL. A group of autoantibodies targeting endothelial cell proteins, anti-endothelial cell antibodies (AECAs), may trigger vascular-mediated damage to the inner ear. A systematic review examined the evidence for the role AECAs and several other systemic autoantibodies in idiopathic SSNHL (Chau et al. 2010). Three of seven studies reported a statistically significant elevation of systemic autoantibodies in patients with SSNHL (Cadoni et al. 2002; Garcia Berrocal et al. 2002; Suslu et al. 2009). These antibodies included rheumatoid factor, antinuclear antibodies, anticardiolipin antibodies, and anti HSP-70 antibodies. Other immune factors, including decreased tumor necrosis factor-α and T-helper

cell populations, have been linked to SSNHL (Chau et al. 2010). The main critique of many of the findings is the lack of specificity to the inner ear.

Overall, there is converging evidence that suggests an altered immunity in SSNHL but as of yet there is no established direct causative link. As with the other possible etiologies of SSNHL, an autoimmune phenomenon may be responsible for only a portion of the syndrome or be one piece of a larger pathophysiological explanation that has yet to be elucidated.

4.2.7 Cellular Stress Response

Merchant et al. (2008) proposed that inappropriate activation of stress response pathways within the cochlea are responsible for idiopathic SSNHL. Transcription factors, such as nuclear factor-κ B (NFκB), may be pathologically activated by a variety of triggers such as viral particles, metabolic stress, or systemic inflammatory disorders. For example, a viral infection could lead to the creation of a circulating ligand that activates the cellular stress response without direct infection of the cochlea. This could provide an explanation for the lack of evidence of viral infection in temporal bones of individuals with idiopathic SSNHL. Furthermore, it is plausible that such a stress response could be localized to only one end organ, resulting in unilateral effects. The efficacy of steroids in treating SSNHL also supports this theory, as steroids are known inhibitors of NFκB (Amsterdam et al. 2002). Although this proposed etiology does theoretically explain SSNHL in many cases, as of yet there is no direct evidence of any specific transcription factor involved in the pathophysiology of SSNHL. There is also a lack of pathologic evidence from human temporal bone studies that specifically implicates an altered cellular immune response.

4.3 Prognosis

Spontaneous recovery rates for SSNHL are well documented, and several factors have been associated with clinical outcomes. These include patient demographics, audiologic findings, duration of hearing loss, and associated symptoms of vestibular dysfunction. Mattox and Simmons (1977) reported a 65 % recovery rate in a prospective study of patients presenting with SSNHL. Factors that were predictive of better recovery included the slope of the initial audiogram, hearing at 8 kHz, and the erythrocyte sedimentation rate inflammatory marker. If patients did have recovery of hearing, most showed hearing improvement within the first 14 days. In one study, a 40 % recovery to within 20 dB of the opposite ear was reported in patients who declined treatment (Guyot and Thielen 2000). Older age has been implicated as a negative predictor in many studies. A recent retrospective review comparing adults and children found that patients younger than the age of 18 were

more likely to partially and completely recover hearing (Chung et al. 2015). Profound hearing loss on initial audiometry was a negative predictor for recovery in both children and adults. Patients with higher thresholds at presentation tend to have worse outcomes in terms of hearing recovery. A 2014 study found that patients presenting with profound hearing loss, defined as hearing threshold of 90 dB or greater on pure-tone audiometry at four specific frequencies, had only a 3 % chance of hearing recovery (Wen et al. 2014).

The predictive value of other vestibular and audiologic diagnostic tests such as electronystagmography (ENG) and otoacoustic emissions (OAEs) is variable. There is some evidence linking abnormal ENG findings with poor recovery of hearing (Wilson et al. 1980; Xenellis et al. 2006), but this is not a universal finding (Fetterman et al. 1996). Otoacoustic emission abnormalities have a similarly weak evidence base, suggesting only a possible association with negative hearing outcomes. A small but thorough 2015 prospective study of 15 patients with SSNHL found that patients with detectable transient evoked OAEs and distortion product OAEs at 1 week follow-up were more likely to have hearing improvement at 3 months postpresentation compared to those with no response at the 1-week follow-up (Shupak et al. 2014). Although further investigation is needed with larger studies, OAEs show promise as prognosticators in ISSNHL and may provide useful information for clinicians and patients.

There have been efforts to develop predictive models of hearing outcomes for patients with SSNHL. A predictive model or algorithm could be useful in counseling patients and may offer valuable information to clinicians making treatment decisions. One difficulty with this approach is that modeling is typically based on a unique population of patients with SSNHL with its own mixture of presenting symptoms and risk factors. Generalization and application of the constructed model to other populations may have limitations. There is also no general agreement regarding relevant factors for inclusion. There is variable evidence supporting each prognostic factor. Based on each patient population, authors developing predictive models have found different statistically significant prognostic indicators (Mattox and Simmons 1977; Byl 1984; Suzuki et al. 2014). A recent multivariate analysis was able to predict posttreatment hearing level within a 40 dB range with 70 % certainty (Suzuki et al. 2014). This wide range and relatively low level of certainty indicate the unpredictability and limited value of the prognostic indicators that have been identified thus far. If creation of such a model or algorithm is possible, it will take a large multi-institutional study or meta-analysis.

4.3.1 Risk Factors

A number of risk factors for developing SSNHL have been identified. Predominantly, diseases of the cardiovascular and circulatory system have been associated with slightly increased risks of developing SSNHL. In addition, patients who have had SSNHL are at increased risk for subsequently developing myocardial

infarction, and some speculate a similar disease process between the two diseases (Keller et al. 2013; Lin et al. 2013b). Development of erectile dysfunction, another disorder with an etiology based on impaired perfusion and microvascular damage, is also increased in patients who have suffered from SSNHL (Hsu et al. 2013). Patients with chronic kidney disease, particularly those with comorbid diabetes, have also been found to be at increased risk for SSNHL (Lin et al. 2013a). As discussed in Sect. 4.2.5, the association of circulatory disease combined with the sudden nature of the disease gives credence to an ischemic etiology for SSNHL. Some of the more recently examined factors have included Factor V Leiden, prothrombin, thrombin, lipid profiles, obesity, and proinflammatory polymorphisms (Hiramatsu et al. 2012). In general, however, the strength of evidence implicating these risk factors is weak.

Dyslipidemia has been implicated as a possible risk factor in SSNHL and hypothesized to play a role in an increased inflammatory state in the inner ear. Several studies have shown that lowering of low-density lipoprotein cholesterol (LDL) levels by apheresis can potentially have positive effects on hearing recovery in certain patients (Bianchin et al. 2010; Canis et al. 2012). In contrast, a 2015 meta-analysis by Chang et al. examined six case control studies but could not establish serum LDL or total cholesterol abnormalities as prognostic indicators for SSNHL owing to a relatively small number of studies with wide variability in results among them (Chang et al. 2015).

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme involved in folate metabolism and polymorphisms of this gene cause increased plasma levels of homocysteine, a known prothrombotic factor. Polymorphisms of this gene have been proposed as possible risk factors in developing SSNHL, suggesting the altered enzyme may lead to a hypercoagulative state and thrombosis or ischemia of the inner ear. Meta-analysis of six studies found significantly increased risk of developing SSNHL among carriers of the C677T MTHFR polymorphism in European populations. No statistically significant risk was identified among Asian populations (Shu et al. 2014).

Overall, there is a growing body of evidence suggesting cardiovascular and prothrombotic risk factors are associated with SSNHL. As of yet, there are not enough data to recommend routine laboratory screening tests for any particular polymorphism. This is a developing area of research that may have clinical utility in the future and could play an important role in developing clinical trials for individuals identified as having cardiovascular abnormalities at the time of reporting SSNHL.

4.4 Diagnostics and Evaluation

4.4.1 History and Physical

All patients with complaints of sudden hearing loss should undergo a thorough history and physical examination. This is not only clinically prudent but could also reveal specific patterns identifying potential subtypes of SSNHL. It is important to look for clinical features that are associated with an identifiable cause of the patient's hearing loss. Historical elements such as trauma, ear pain, ear drainage, fever, and neurologic symptoms can potentially identify specific pathology. A physical examination including otoscopy is strongly recommended to search for signs of a treatable cause of the hearing loss such as conductive hearing loss. A neurologic exam is also recommended in the initial workup (Stachler et al. 2012) to help determine if the hearing loss is due to an ischemic event such as a stroke or a transient ischemic attack.

Pure-tone air and bone conduction audiometry should be performed on every patient with suspected SSNHL to determine the degree and configuration of the hearing loss. The 2012 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) clinical practice guidelines (Stachler et al. 2012) recommend ear-specific speech recognition thresholds, word recognition scores, tympanometry, acoustic reflex thresholds, and acoustic reflex decay. These measures are crucial to obtaining the correct diagnosis and guide treatment for each patient who presents with SSNHL symptoms.

In addition to their use in diagnosis and as prognosis assessment indicators, audiometric findings are critical for follow-up of patients with SSNHL. Serial audiometry is an important part of monitoring the response to treatment and for recognizing progression of hearing loss in the affected or a new loss in the unaffected ear, and data regarding the time course and pattern of changes can help in the design of clinical trials. With respect to management, changes in hearing should be assessed within 6 months of initial diagnosis of SSNHL (Stachler et al. 2012) and in patients without complete recovery auditory rehabilitation or assistive devices may be needed.

In addition to inner ear damage, SSNHL could be associated with retrocochlear disease. In these cases, ABR testing is useful for evaluating pathology affecting the cochlear nerve and central auditory pathway, such as an acoustic neuroma, particularly when patients are unable to undergo MRI. One study estimated the sensitivity of ABR at 71 % with a specificity of 74 % in patients with asymmetric sensorineural hearing loss and MRI-confirmed retrocochlear tumors (Cueva 2004). The gold standard for screening of retrocochlear pathology in patients with asymmetric hearing loss continues to be MRI with gadolinium contrast enhancement. However, ABR can provide a useful alternative in certain scenarios in which MRI is contraindicated, such as in patients with metal implants and claustrophobia.

Otoacoustic emissions (Shupak et al. 2014) and electronystagmography have been implicated as prognostic factors in some studies, but there is insufficient

evidence to support their routine use in patients with SSNHL. Importantly, neither normal ENG nor otoacoustic emission findings can reliably rule out retrocochlear pathology. Brainstem auditory evoked potentials (BAEPs) and electrocochleography (ECOG) recordings have been shown to be abnormal in patients with ISSNHL (Habib et al. 2011) and could be used as objective measures in clinical trials. It is worth noting that whereas BAEP and ECOG can aid in the diagnosis of ISSNHL, there is no evidence that they provide any additional prognostic value over behavioral audiometry.

4.4.2 Laboratory Testing

There are no universal laboratory tests or imaging techniques that are diagnostic for idiopathic SSNHL or have specific utility for directing targeted therapy. This does not imply that laboratory testing should never be done in SSNHL. If history, physical exam, or other testing suggests a particular underlying disease process, it may be wise to perform laboratory tests and these could aid in identifying subtypes of SSNHL. Diagnostically, it is also important to perform these tests because some forms of SSNHL can arise from infectious causes. In these cases, there is often historical or demographic information that would guide the clinician to conduct further diagnostic testing.

There is active research in the area of identifying new risk factors and prognostic factors associated with SSNHL. Given the possibility of increased risk of acute myocardial infarction in patients who have suffered from SSNHL and the association of several cardiovascular risk factors with SSNHL (Lin et al. 2012), some authors suggest further laboratory investigation in patients with a family history of cardiac disease. However, the widespread use of laboratory-based screening tests under these conditions would likely yield many false positives and would not be cost effective. Several hematologic genetic and nongenetic laboratory studies of the circulatory system have been examined for their association with SSNHL. In the future, these may act as useful markers for disease, but as of now, the studies supporting individual laboratory tests have not provided enough evidence to make a recommendation in support of routine testing.

4.4.3 Imaging

The classic pattern of hearing loss from vestibular schwannoma is a slow progressive decline, and a sudden loss is uncommon, occurring in only 10 % of cases. Nevertheless, the possibility of retrocochlear pathology as the cause of SSNHL must be considered. MRI of the internal auditory canals, brain, and brainstem with gadolinium has a high sensitivity for detecting vestibular schwannomas and is considered the most sensitive test for detecting retrocochlear pathology in general

(Fortnum et al. 2009; Stachler et al. 2012). A recent meta-analysis suggests that the presence of a high 3-D fluid-attenuated inversion-recovery (FLAIR) MRI signal in the inner ear of patients with ISSNHL indicated a more severe initial hearing loss and was associated with a higher incidence of vertigo. These results suggest that MRI findings may be a strong predictor of poorer prognosis (Gao and Chi 2014). Given the time course and pattern of hearing loss associated with vestibular schwannoma and its readily identifiable cause, clinical trials for SSNHL should screen out or subtype individuals with signs of retrocochlear pathology.

4.5 Treatment

Treatment in cases of SSNHL due to a known etiology will vary based on the specific etiology. The information in this section reviews current treatment of ISSNHL and the relative strength of evidence in support of each of the interventions.

4.5.1 Steroids

Systemic corticosteroids, either alone or in combination with intratympanic steroids, are the most common treatments for ISSNHL. The specific mechanism of action of steroids within the cochlea is not known, but they are presumed to decrease inflammation as they do elsewhere in the body (Tabuchi et al. 2011). The typical dosing regimen is 1 mg/kg/day of oral prednisone up to 60 mg daily for 10–14 days given in a single dose (Stachler et al. 2012). Extensive research, including multiple meta-analyses and a Cochrane review, has examined the efficacy of steroids in treatment of SSNHL. Wilson et al. (1980) first described the efficacy of systemic steroids in improving hearing outcomes, and this study is still referenced frequently today despite multiple larger studies with arguably better methodology finding contrasting results (Crane et al. 2015). A 2006 Cochrane review with updates in 2009 and 2013 had three trials meet the inclusion criteria, all of which were double blind and placebo controlled. Two trials showed no significant improvement with steroid administration, whereas the other showed significant hearing improvement in 61 % of the steroid-treated group and only 32 % in the control participants. The recommendation for steroid use was inconclusive because of the contradictory results from these studies (Wei et al. 2013). A 2014 meta-analysis (Crane et al. 2015) examined the same three articles for systemic steroid therapy versus placebo and found no statistically significant improvement in hearing outcome. The 2012 AAO-HNS clinical practice guidelines offered no strong recommendations for or against systemic steroids for treatment of ISSNHL, stating that clinicians may offer this initial treatment. This conclusion was based on the relatively low risk of steroid treatment compared to even a small possible benefit

of improved hearing, particularly in patients presenting with a profound loss. The current practice of systemic steroid treatment is not well supported because of a proven benefit, but because of the relatively low risk of treatment, this approach continues to be common practice owing to a possible therapeutic benefit. Given the mixed reports on systemic steroid treatment and the potential heterogeneity of ISSNHL, additional studies or analyses could be performed with careful selection of patients. It is possible that a specific subtype of ISSNHL could benefit significantly from treatment, whereas others may be unresponsive.

Intratympanic steroid administration has also been studied extensively. The potential benefit of this route of administration is the increased concentration near the suspected site of disease and the lack of systemic symptoms that accompany oral steroids. Consequently, this approach may offer an alternative to patients unable to tolerate systemic therapy. The risks of intratympanic steroid injection include the pain of the injection, transient vertigo, infection, and tympanic membrane perforation. The concentration of steroid and frequency of administration varies widely among authors. There is evidence based on histology studies in guinea pigs that intratympanic steroids may result in higher concentrations of steroid in the cochlea and even improve cochlear blood flow (Shirwany et al. 1998). A meta-analysis examining intratympanic steroids versus systemic corticosteroids found no significant difference in outcomes (Crane et al. 2015). Of six trials meeting inclusion criteria, only one showed a benefit of intratympanic steroids over systemic steroids for initial treatment of SSNHL. These results were similar to a 2012 meta-analysis (Garavello et al. 2012). The 2012 AAO-HNS clinical practice guidelines offered no strong recommendations for or against intratympanic steroids for treatment of ISSNHL for the same reasons as mentioned earlier in this section.

4.5.2 Hyperbaric Oxygen

Hyperbaric oxygen (HBO) therapy was first identified as a possible treatment for SSNHL and tinnitus in the 1960s. The therapeutic concept is rooted in the theoretical mechanism of inner ear ischemia causing hearing loss (Bennett et al. 2012). Therapy involves the administration of 100 % oxygen at a pressure greater than 1 atmosphere in a sealed chamber to deliver high oxygen content to a patient's tissues. The usual course is 5–40 sessions of 1- to 2-hours treatments over the course of several weeks. Risks of undergoing HBO therapy include damage to the lungs, ears, and sinuses from the pressure change along with temporary vision change, claustrophobia, and oxygen poisoning. Other negatives of HBO include the disruption to the patient's daily life given the length and frequency of the therapy along with a high cost. A 2012 Cochrane review examined seven randomized controlled trials and found a 22 % increase in the possibility of hearing improvement following HBO therapy along with a significant improvement (15.6 dB) in average pure-tone audiometric thresholds. Given its low risk and potential for improvement of hearing, the 2012 AAO-HNS clinical practice guidelines stated that clinicians may offer adjunct HBO

therapy up to 3 months after diagnosis but warned that the data supporting this therapy are limited and have significant shortcomings.

4.5.3 Other Pharmacologic Therapy

A plethora of pharmacologic agents have been tried in the treatment of ISSNHL, and whereas many have showed positive effects in small studies, these same agents have been subsequently shown to be ineffective in larger studies and meta-analyses. Viral infection–mediated inflammation is one of the more prominent etiologic theories for ISSNHL, and thus extensive research has been performed on antiviral therapy. A 2012 Cochrane systematic review included four randomized trials comparing steroid treatment with steroid plus antiviral treatment (Awad et al. 2012). None of the four studies found statistically significant differences in hearing outcomes between the two groups. This finding was in agreement with a previous systematic review and meta-analysis (Conlin and Parnes 2007). Given this evidence, antiviral therapy should not be used routinely in the treatment of ISSNHL.

The vascular or ischemic etiology for ISSNHL has also led to several targeted pharmaceutical studies. Multiple vasoactive drugs have been used based on the circulatory and cardiovascular system risk factors associated with ISSNHL. A Cochrane review concluded a lack of significant benefit for these pharmacologic agents because of too poor methodology in the identified studies along with heterogeneity of results, despite all three studies showing evidence of hearing improvement relative to placebo (Agarwal and Pothier 2009). The 2012 AAO-HNS clinical practice guidelines agreed with the findings of the Cochrane reviews and recommended against routine use of antivirals, thrombolytics, vasodilators, vasoactive substances, or antioxidants in the treatment of SSNHL.

4.5.4 Salvage Therapy

Salvage therapy is treatment given after a failure to respond to initial treatment. Many of the same agents used for initial treatment have also been used for salvage therapy, the most successful of which is intratympanic steroid injection. A recent meta-analysis of six studies found a significant treatment effect of intratympanic steroid injection with an odd's ratio of 6.04 (Crane et al. 2015). These findings are confirmed by an earlier meta-analysis analyzing many of the same studies. Although this result is encouraging, there is a cautionary tone from the authors, who express concern that certain studies with positive findings could be considered outliers given their questionable reliability and perhaps should not have been included in the meta-analysis

A recent prospective randomized trial compared salvage therapy with intratympanic steroid injection to HBO therapy (Cvorovic et al. 2013). As expected, both HBO therapy and intratympanic steroids led to an improvement in hearing

recovery. In addition, patients with hearing thresholds less than 81 dB and age younger than 60 years receiving HBO therapy tended to have better hearing outcomes than patients with profound hearing loss and those older than 60 years of age. These findings suggest that both HBO therapy and intratympanic steroid injections are viable salvage therapy options for individuals with SSNHL in select patient populations. Another study compared HBO therapy, intratympanic steroid injection, and combination therapy in patients with refractory SSNHL (Yang et al. 2013). Their findings corroborate the early studies showing benefit in all three experimental groups. They also found that combined therapy resulted in greater improvement in word recognition scores, hearing gain, and rate of recovery compared to the other groups, suggesting combination therapy may be the most efficacious treatment option for salvage therapy. Further randomized prospective trials are needed to elicit the true therapeutic value of these treatments.

4.5.5 Counseling and Amplification

It is recommended that patients who fail to respond to treatment and suffer permanent loss from SSNHL should receive counseling from a clinician and be provided with rehabilitation resources, including information on assistive listening devices and hearing aids. Even a unilateral hearing loss results in significant disability that impacts social interactions and communication (Wie et al. 2010). At a minimum, clinicians should provide information counseling their patients regarding appropriate treatment options and outcomes. It has been shown that professional counseling can also ameliorate the self-perceived handicap (Hawkins 2005). Many patients with SSNHL experience tinnitus, which is also perceived as a handicap (Chiossoine-Kerdel et al. 2000), and thus referral to audiologists or other professionals trained in tinnitus management is recommended. Clinical trials should be used to evaluate which rehabilitation strategy or protocol is most beneficial to these patients.

4.5.6 Clinical and Experimental Significance

The various clinical studies presented throughout this chapter have shown weak or conflicting evidence for existing SSNHL treatment. Whereas no treatment reliably reaches statistical significance, it appears that subsets of patients have been helped by some of these therapies. In some cases, there has been substantial attenuation of SSNHL, so it may be premature to abandon these treatments. Conversely, trial and error of varied treatments with weak evidence, despite good intentions, is not good long-term clinical practice. As a result, there is an urgent need for additional research that is fueled by collaborative efforts from clinicians, basic scientists, and translational scientists. Among the goals will be identifying responder subtypes and common pathophysiology to better design clinical trials that determine both

statistical and clinically relevant efficacy. This second point is essential, as a statistically significant effect could be marginal or clinically irrelevant if the effect size is small. Future clinical trials could initially focus on identified subtypes who are more likely to respond and progressively expand to larger groups. In cases in which treatments fail, additional research is also needed to determine the most efficacious rehabilitative approaches based on relevant research findings.

4.6 Summary

As a disorder, SSNHL has provoked controversy in its definition as well as treatment. Much of the controversy arises from the challenges of studying SSNHL. In a clinical setting, with such a high rate of spontaneous recovery, it is ethically difficult to offer invasive, costly, or risky treatments. This same dilemma pervades much of the research in SSNHL. While considering the high rate of spontaneous recovery, clinicians must also weigh the morbidity of a possible permanent hearing loss. The clinician and patient must choose between a limited number of treatment options with strong scientific evidence and other treatments with low risk and weaker evidence but which have the potential to benefit the patient.

Despite being first described in 1944, the etiology of SSNHL is still a mystery. Since the 1940s, a tremendous body of research has been developed, yet we have found very little concrete evidence suggesting one potential cause over another and also very little information that can improve patient outcomes. Although this is somewhat discouraging, modern research techniques, from basic science advancements to mining large patient databases, provide an opportunity to make progress where it was previously not possible. With current research exploring nearly every facet of this disorder, there is hope that we can soon learn to identify patients at higher risk for SSNHL and effectively treat those who develop hearing loss with evidence-based therapies.

Although clinical trials have failed to conclusively identify efficacious treatment, there is some evidence that steroids, HBO, and vasoactive compounds may help a subgroup of patients. These subgroups present an enormous research opportunity in potentially identifying underlying mechanisms or for developing inclusion criteria for targeted therapies, information that is particularly relevant in T0 through T2.

Ultimately, the success of future treatments will largely depend on robust collaborations between clinicians, who are in a position to collect valuable data that can be used to subtype various forms of SSNHL, and their basic science counterparts, who can then take these findings and feed them forward through the translational process.

Compliance with Ethics Requirements

Carol Bauer declares she has no conflict of interest.

Scott Montgomery declares he has no conflict of interest.

Edward Lobarinas declares no conflict of interest.

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Chapter 5
Development of Drugs for Noise-Induced Hearing Loss

Eric D. Lynch, Jonathan Kil, and Colleen G. Le Prell

Abstract Current efforts to translate laboratory findings into clinical drugs for preventing or treating sensorineural hearing loss (SNHL) are reviewed in this chapter. Since no drugs have been approved for any inner ear indication involving SNHL, including tinnitus, this is a novel area of both clinical development and regulatory oversight. An overview of FDA guidance, and sponsor interactions or meetings with the FDA, involving preclinical data to clinical trial design and regulatory approval are reviewed. Specific steps on how to evaluate the safety and efficacy of an investigational new drug through a series of well-controlled preclinical (nonhuman) and clinical (human) studies are provided. The information presented is designed to assist researchers and clinicians in mapping out and executing an effective drug development program. In this chapter, regulatory considerations for the development of a new or existing drug that reduces, mitigates, prevents, or treats noise-induced hearing loss (NIHL) are reviewed, including both preclinical and clinical FDA interactions, followed by a detailed discussion of the investigational drugs that are furthest along in clinical testing.

Keywords Clinical trial · FDA · Investigational new drug · Noise-induced hearing loss · Otoprotection

E.D. Lynch (✉) · J. Kil
Sound Pharmaceuticals, Inc., 4010 Stone Way N, Seattle, WA 98103, USA
e-mail: elynch@soundpharma.com

J. Kil
e-mail: jkil@soundpharma.com

C.G. Le Prell
Callier Center for Communication Disorders, University of Texas at Dallas,
1966 Inwood Road, Dallas, TX 75235, USA
e-mail: colleen.leprell@utdallas.edu

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5.1 Introduction

In developing drugs for preventing or alleviating sensorineural hearing loss (SNHL), an important question is whether the use of the drug will be ethical. Although seemingly obvious, this question bears significant regulatory meaning. In the US Food and Drug Administration (FDA), in Europe's European Medicines Agency (EMA), and in Japan's Pharmaceutical and Food Safety Bureau (PFSB), the concept of an "ethical drug" is largely agreed to be a drug that has proven to be both safe and efficacious. This is demonstrated through a series of well-controlled preclinical (nonhuman), and clinical (human) studies aimed at understanding the pharmacologic and toxicologic effects of the investigational drug for a specific disease, disorder, or condition. Although the regulatory environment varies from country to country, the international community has adopted guidelines set forth by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use with regard to drug development and marketing.

In the United States, FDA guidance is clear. An investigational new drug (IND) application is required when clinical studies intended to evaluate the safety and efficacy of an unapproved drug are proposed. In addition, any clinical evaluation that changes the dose, route of administration, formulation, or indication generally requires an IND or a waiver from the FDA. Research groups seeking to develop ethical drugs for the prevention and treatment of SNHL are encouraged to review and understand the regulatory aspects governing their development program. One helpful resource to be consulted early in the process is the Center for Drug Evaluation and Research (CDER) at the FDA, which offers a Pre-Investigational New Drug Application (PIND) Consultation Program. For investigators at academic institutions, assistance with regulatory support or other relevant resources may be available through a clinical trial management office or clinical translational research center.

Before beginning the costly and lengthy process of performing the requisite preclinical safety studies in support of an IND, the investigational compound should be well vetted for safety and efficacy in at least one relevant animal model of the human condition or disease. Developing a new drug is expensive and it requires years of sustained effort. Current estimates for the costs of developing a new chemical entity (NCE), a new drug that has never been approved by the FDA, can exceed $1 billion. Higher costs are associated with biologics (e.g., recombinant proteins, gene therapy) and agents that act on the central nervous system (CNS) (DiMasi et al. 2003; DiMasi and Grabowski 2007), since clinical testing typically requires 10+ years (see Fig. 5.1; for additional discussion, see Morgan et al. 2011). Setting a foundation based on solid preclinical evidence is crucial. Publication of results and methods from animal studies affords a greater potential for useful discoveries to be validated by independent parties. Before publicly disclosing or otherwise sharing new discoveries, however, intellectual property protection must be considered. The importance of protecting data generated in

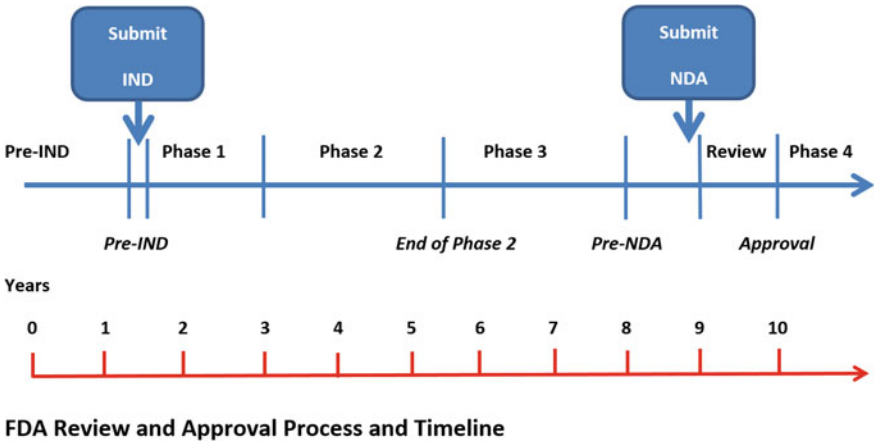

Fig. 5.1 The timeline for the FDA review and approval process. Preclinical research generating data required for the filing of an investigational new drug (IND) application are shown here as 18 months, which is likely an idealized situation. In many cases, preclinical research and the necessary toxicological, pharmacological, and pharmacodynamic safety research may proceed over multiple years before first-in-man studies. Phase 1 studies are typically limited to safety and Pk/PD parameters, whereas Phase 2 studies include both safety and efficacy. Phase 3 studies are the larger safety and efficacy registration studies that are necessary to seek permission for health claims from the US FDA

preclinical testing is not discussed in detail in this chapter but is an essential step in the translational process, and Chap. 2 by Le Prell should be reviewed for discussion on this step. In this chapter, specific regulatory considerations for the development of a drug that reduces, mitigates, prevents, or treats noise-induced hearing loss (NIHL) are reviewed, including both preclinical (Sect. 5.2) and clinical (Sects. 5.3 and 5.4) development, followed by discussion of the investigational drugs that are furthest along in clinical testing (Sect. 5.5). Readers well versed in preclinical test methodology may choose to go directly to Sect. 5.3. Section 5.2 highlights issues in developing preclinical datasets prior to human testing.

5.2 Preclinical Efficacy: Designing "Proof-of-Mechanism" Studies with Translational Value

There are multiple variables in the design of preclinical efficacy assessments for NIHL prevention and treatment. A key issue in NIHL research is the lack of standardized animal models or protocols for the evaluation of lead or candidate compounds, which reduces the ability to make direct efficacy comparisons between different compounds. Effective preclinical disease models should closely replicate the human disease in both pathology and physiology and involve routes of drug

administration or treatments that translate directly to their intended clinical application or indication. Animal models for NIHL are numerous. The adoption of common models with respect to experimental variables including noise exposure (Sect. 5.2.1), species selection (Sect. 5.2.2), route of administration and dose–response testing (Sect. 5.2.3), and auditory assessments (Sect. 5.2.4) are necessary to compare lead compounds for their relative safety and efficacy.

5.2.1 *"Replication" of the Human Disease: Laboratory Sound Exposures*

In daily life, individuals are exposed to different types of noise based on their occupation, recreational interests, and other everyday activities. Therefore, in defining noise exposures for use in preclinical studies, investigators need to determine the target population for which they want to model relevant noise exposures. NIHL has two phases: a temporary threshold shift (TTS) hearing loss following a noise exposure and a permanent threshold shift (PTS) hearing loss that does not resolve to baseline after a noise exposure. Although there is some debate over when hearing loss should be defined as permanent, there is generally good agreement that most TTS will resolve within the first 14 days, and by 30 days postnoise, any remaining threshold shift is a PTS. Investigators must select a level and duration of noise to elicit a desired TTS or PTS based on their population to be modeled (Hu 2012). In addition to intensity and duration, spectral characteristics of the exposure, such as whether the exposure is an impulse noise or a continuous noise, may be important (Henderson and Hamernik 2012). The potential for repeat insults within the human population of interest should also be considered as part of the animal model.

Beyond the basic selection of broadband, octave band, narrowband, or impulsive noise, investigators need to select a method of delivery for the noise insult. Important considerations include free field versus closed field, binaural versus monaural, restrained versus unrestrained, and awake versus anesthetized animals. Unfortunately, anesthetics have the potential to alter the pharmacology and toxicology of otoprotective compounds or drugs. In addition, the anesthesia used to immobilize the animal before and during the noise exposure may alter the animal's response to the noise trauma (Chung et al. 2007).

Noise exposure paradigms often vary across laboratories, making comparisons difficult, if not impossible. Common noise exposures for preclinical testing among different laboratories would facilitate drug comparisons (for detailed discussion, see Le Prell and Miller 2016). That said, because human noise exposures outside the laboratory are highly variable from one setting to another, there is a need for multiple agreed-on protocols, including broadband, octave-band, and impulse noise exposures at a minimum and narrowband and pure-tone exposure as an option. The issue of TTS and PTS within these noise protocols needs careful consideration,

given that both are clinically relevant and may involve similar or disparate drug targets.

5.2.2 *Species Commonly Used in Otoprotection Research*

Rodents are the most commonly used laboratory models in preclinical NIHL studies. Here, various mouse and rat strains, *Cavia porcellus* (guinea pig), and *Chinchilla lanigera* (chinchilla) are briefly discussed. In any model, it is preferable to work with specific pathogen-free (SPF) organisms from qualified commercial vendors to reduce the potential for subclinical diseases or conditions that may confound experimental results.

5.2.2.1 Mouse Models

Mice are relatively easy to breed and easily housed in large numbers, and a wide variety of genetically modified strains are commercially available. However, mice can be difficult to dose orally and often require significantly higher drug doses than other rodents based on their very rapid metabolism. Owing to their small size, small deviations in dosing volume tend to impact both pharmacokinetic (Pk) and pharmacodynamic (PD) values. In addition, mice have an "audiogram" or range of hearing that is shifted to a higher frequency range than humans. Noise exposure paradigms in mouse studies typically include extended high frequencies (i.e., >8 kHz), largely above the range considered critical for human hearing. Auditory function has been documented in a large number of inbred mouse strains (Zheng et al. 1999). Some of the most common mouse strains used in NIHL studies are the CBA/Ca and CBA/CaJ. Another common strain is the C57BL/6J, although this strain carries a Cadherin 23 (Cdh23) mutation that dramatically influences the age of onset and rate of progression of hearing loss across the life span. Age is an important factor, as mice exhibit an increased sensitivity to noise in the first 4–8 weeks of life (Kujawa and Liberman 2006), with vulnerability decreasing across the remaining life span (Henry 1982). Interestingly, these differences vary across strains (Li et al. 1993) and some strains appear more resistant to NIHL than others. These differences raise important questions about which is the "best" strain to use to model human NIHL, in addition to questions about whether mice are the "best" rodent species as a whole given differences in hearing and metabolism.

5.2.2.2 Rat Models

Relative to mice, the rat's larger size makes certain aspects of auditory testing and drug dosing easier to accomplish. Consequently, rats are popular in hearing research, and auditory thresholds have been reported across a number of strains

(Borg 1982). Some of the most commonly used strains for NIHL research are Sprague-Dawley, Long-Evans, and Fischer 344. This again raises questions about which is the "best" strain and "best" species. Like mice, rats are more sensitive to higher frequency sounds than humans and exhibit increased sensitivity to noise in the first 6 weeks after hearing onset (Lenoir et al. 1979).

5.2.2.3 Guinea Pig Models

The use of guinea pigs as laboratory animals is highly regulated by the US Department of Agriculture (USDA). As a "covered species," there are additional considerations regarding their acquisition, monitoring, and reporting of their use for biomedical research (National Research Council 1996). Sourcing of SPF guinea pigs can be problematic because of endemic cytomegalovirus (a leading cause of unilateral SNHL) in many commercially available colonies, but generation of SPF colonies is possible. Guinea pig breeding is also more challenging owing to lower fecundity and longer gestational periods relative to mice and rats (Ediger 1976).

Despite the aforementioned challenges, there are multiple advantages to using guinea pigs for studies on NIHL otoprotection. First, guinea pigs have better low-frequency hearing than most mice and rats (4–8 kHz). Second, guinea pigs have significantly larger mastoid cavities or bullae and cochlear volumes than mice or rats, making local or inner ear drug delivery possible. Drugs and investigational compounds can be delivered directly to the cochlea via a cochleostomy (a hole drilled through the bony wall of the cochlea) or through the round window membrane (RWM). RWM application techniques include acute topical applications (Lemke et al. 2009), surgical implantation of an infusion cannula (Brown et al. 1993; Miller et al. 2007), and drug-diffusing gels such as Gelfoam® (Lemke et al. 2009; Eshraghi et al. 2013). Because differences exist in the noise vulnerability of albino versus pigmented animals (Pye 1987), strains must still be selected carefully with respect to "best" modeling of the human condition of interest.

5.2.2.4 Chinchilla

The final rodent species to be discussed here is chinchilla, a species also covered by the USDA. Chinchillas have a long history of use in auditory research because their range of hearing is similar to that of humans, with increased hearing sensitivity and noise vulnerability at 4 kHz. Like the guinea pig, the cochlea and round window can be readily visualized for local or inner ear drug administration. However, SPF sourcing, vivarium housing, and oral dosing considerations place them in line with guinea pigs as one of the more challenging species to work with from a technical and regulatory perspective. In addition, the pharmacology (Pk and PD) of many approved and investigational drugs are not known in chinchilla, as they are not widely used in studies beyond the peripheral auditory system.

5.2.3 Route and Timing of Administration

Injection (subcutaneous, intramuscular, or intraperitoneal) is the common route of administration for drugs in most animal studies. Although oral dosing as a route of administration has not been widely adopted in otoprotective studies, translation to human clinical trials and ultimate approval will likely require oral administration. Oral gavage is more time consuming and technically challenging than injection and can result in trauma to the oropharynx and inhalation of the drug into the lungs. Some studies have instead delivered compounds in the animal's food (Le Prell et al. 2011a, 2014) or water (Ojano-Dirain et al. 2013); however, this results in uncertain dosing and Pk/PD parameters because dietary consumption is difficult to measure accurately, particularly in the case of multiple animals housed in the same cage. Even with single-animal housing, water bottles may leak or chow might be removed from the dispenser without being consumed.

In addition to dosing methodology differences across studies, there are significant differences with respect to the start of dosing. The start of dosing might be hours or days before the noise exposure, and once begun, dosing might continue for hours, days, weeks, or even months after the noise exposure. Although some studies do include postnoise treatment dosing, dosing in most otoprotective animal studies begins prenoise to establish steady-state Pk. It is unclear whether this dosing strategy will be effective in pivotal or Phase 3 clinical trials that are required for drug product registration or a new drug application (NDA). Perhaps the most important issue with respect to dosing, however, is the failure of most preclinical investigations to establish a dose response or lack of dose response, as would be expected for any drug development effort (Spruill et al. 2014).

The route of administration of a drug can significantly impact its safety and efficacy profile as well as its potential marketability. For the prevention or treatment of occupational NIHL, oral delivery will likely be required. Oral administration is one of the least invasive and easiest methods of drug delivery for humans, particularly for chronic indications or treatment. If a drug is limited by moderate or potentially severe adverse events (AEs) or side effects, then local delivery by intratympanic injection (ITI) may be more favorable. However, this route of administration has its own side effect profile, including pain, perforation, and infection, and requires a trained physician or otolaryngologist to administer. In a single-center study involving 11 subjects, the drug AM-111 was administered by ITI postnoise exposure for the treatment of acute acoustic trauma (Suckfuell et al. 2007). Here, 13 AEs were reported in 5 subjects. Similar side effects have also been reported in larger studies using ITI drug administration for other indications including local steroid treatment after idiopathic sudden hearing loss (Rauch et al. 2011) or ITI dexamethasone (OTO-104, a sustained release dexamethasone hydrogel) to treat Ménière's disease (Lambert et al. 2012). Intravenous (IV) administration may be an alternative to oral delivery or ITI administration for drugs with poor oral bioavailability or where ITI is not possible. Although there do not appear to be any well-controlled IV-based clinical trials involving NIHL, IV

administration of drugs has been used after sudden sensorineural hearing loss (Mora et al. 2003; Kang et al. 2013).

5.2.4 Auditory Assessments in Preclinical Models

The auditory brainstem response (ABR) and otoacoustic emissions (OAEs) are the most commonly collected data in preclinical tests, whereas human studies typically assess pure-tone threshold sensitivity behaviorally and perhaps include OAEs. Brief descriptions of these and other metrics are described in Sects. 5.2.4.1–5.2.4.6.

5.2.4.1 Auditory Brainstem Response

Prevention of TTS and PTS in preclinical models is most commonly assessed using the acoustically evoked ABR threshold. The ABR is a tone or click-evoked synchronized neural response to calibrated sounds such as tone pips or clicks. The evoked activity along the ascending auditory pathway is recorded in humans using electrodes placed on the scalp and earlobe or mastoid, and it is recorded in anesthetized animals using subcutaneous electrodes. The specific test frequencies vary as a function of species (e.g., chinchillas and guinea pigs have lower frequency audiograms than rats or mice and are therefore tested at lower frequencies). Although ABR threshold testing is not commonly used for the diagnosis or monitoring of NIHL in humans, it is widely used in both preclinical and clinical settings. It would therefore be beneficial to develop a common preclinical ABR testing methodology to allow comparisons among studies and across compounds.

In addition to the common threshold metric, amplitude has been suggested as an important new clinical test metric (for review, see Kujawa and Liberman 2015), but specific clinical deficits due to decreased ABR wave 1 amplitudes have not been shown. Therefore, several clinical studies are needed before this method becomes an adopted clinical end point (Le Prell and Lobarinas 2015; Le Prell and Brungart, in press). Although the ABR could be used to define specific thresholds and threshold shifts clinically, there is a significant challenge to using ABR threshold testing in humans. Specifically, there is a much greater noise background that arises in part because humans are tested in an awake state to avoid anesthesia-related complications and cost as well as the increased noise from the greater distance between the scalp electrode and the brainstem generator in human heads relative to laboratory rodents.

5.2.4.2 Otoacoustic Emissions

Outer hair cell (OHC) function is routinely inferred using OAEs. OAEs are sounds recorded in the ear canal via a microphone that are generated by nonlinearities

produced by OHCs that are reliable correlates of inner ear health (Kemp 2008). All vertebrates studied to date are capable of generating some level of OAE either spontaneously [spontaneous otoacoustic emission (SOAE)], evoked by a transient sound [transient evoked otoacoustic emission (TEOAE)], or evoked by two tones and measured at a different distortion frequency [distortion product otoacoustic emission (DPOAE)] (mammals, see Lonsbury-Martin and Martin 2008; amphibians, see Manley and Van Dijk 2008). Despite the variety of cochlear shapes and mechanics present across the broad class of vertebrates studied, the widespread existence of OAEs suggests a common mechanism among vertebrates likely associated with the amplification and fine tuning of the auditory system for optimal sensitivity (Bergevin et al. 2015).

Although not a test of hearing, changes in DPOAE amplitudes have been proposed as an early identifier of NIHL, with potential application in occupational noise-monitoring programs (Konrad-Martin et al. 2012). OAE metrics may reveal damaged OHCs in the absence of overt hearing loss, but the utility of OAE measurements as a metric for noise-induced OHC damage in clinical trials will require additional validation studies before this measure can become a routine aspect of drug development. As such, although helpful in understanding the pathology of hearing loss, OAEs will probably remain an exploratory or secondary clinical end point (for discussion, see Le Prell and Lobarinas 2015). In summary, OAE measurements are now quite common and routinely supplement pure-tone audiometry in published works, but pure-tone audiometry remains the gold standard for clinical testing and the determination and progression of acute and chronic NIHL.

5.2.4.3 Behavioral Audiometry

Because ABR thresholds closely match behaviorally derived thresholds in mammals (Le Prell et al. 2004), there is often little incentive for investigators to undertake the time and expense of training animals to perform an operant response for reporting the detection or discrimination of different features of acoustic signals. Trained behaviors are usually maintained using positive reinforcement such as food or water for correct responses or by shock avoidance paradigms where animals are punished with a transient foot shock for failing to make correct responses. The training time required, and the increased costs associated with the long-term care and personnel time, generally reduce enthusiasm for this approach. This comment should *not* be taken to suggest there is no utility in operant experiments. Psychophysical investigations using operant conditioning have been used to measure frequency selectivity (Serafin et al. 1982; Prosen et al. 1989), sensitivity to intensity changes (Prosen et al. 1981; Le Prell et al. 2001), amplitude modulation (Moody 1994), formant frequency (Sommers et al. 1992), phase (Moody et al. 1998), rise time (Prosen and Moody 1995), and masking (Le Prell et al. 2006). Animals can also be trained to explore other phenomena such as categorical perception (Kuhl 1986; May et al. 1989). Collection of these measures may be

increasingly important in the future given suggestions that noise insult results in suprathreshold processing deficits that are "hidden" in an otherwise normal audiogram (for review, see Kujawa and Liberman 2015).

5.2.4.4 Audiometry Using Suppression of Reflexes

An alternative to operant tasks is the use of acoustic signals to mediate reflexive responses. For example, the acoustic startle reflex is a whole body motor response to unexpected high-level sound present in both animals and humans. This response can be attenuated by presenting a lower level "cue" stimulus before the louder startle stimulus, a phenomenon termed prepulse inhibition (PPI). PPI has been used to generate "audiograms" with threshold estimated based on the minimum sound levels at which prepulse signals effectively inhibit the acoustic startle reflex (Ison et al. 2002; Tziridis et al. 2012). Prepulse signals that are inaudible should not suppress the acoustic startle response. Detailed discussion of the acoustic startle reflex in auditory tests is provided by Allman, Schormans, Typlt, and Lobarinas in Chap. 7.

5.2.4.5 Otoscopy and Tympanometry

During otoscopy, the ear canal is inspected and the tympanic membrane is visualized. Tympanometry then provides measurements of the mobility and impedance of the tympanic membrane and middle ear ossicles. This validated measure is not a viable end point but is frequently included as part of the screening criteria in NIHL studies, with individuals who have conductive or mixed hearing loss excluded. For preclinical studies, otoscopic evaluation of the animal is sometimes completed, but tympanometry is rarely performed. Protocols are available for guinea pig (Darrouzet et al. 2007; Dai and Gan 2008), chinchilla (Margolis et al. 2001; Akinpelu et al. 2015), rat (Popelar et al. 2003; Bielefeld et al. 2008), and even mouse (Zheng et al. 2007). Because changes in tympanic membrane compliance can account for some individual variability observed between animal subjects, tympanometric testing may be worth including in preclinical investigations.

5.2.4.6 Tinnitus Tests

A variety of issues have made it difficult to study subjective tinnitus in animals; correct reinforcement or punishment for sound reporting responses in animals that *might* have experimentally induced tinnitus are particularly problematic as the investigator has no a priori knowledge regarding which animals develop tinnitus or how severe an individual animal's tinnitus might be (Moody 2004). A new paradigm for the identification of tinnitus has emerged that involves a modification of the PPI paradigm (Turner et al. 2006). Instead of using an acoustic PPI cue in a

silent background, a silent gap in a continuous background noise is used to modulate the acoustically evoked startle response. Presumably, when the background noise is similar to the animal's tinnitus spectrum, the animal cannot reliably detect the silent gap, and the gap fails to modulate the startle response. This loss of gap prepulse inhibition as a measure of tinnitus has been demonstrated in both salicylate- (Yang et al. 2007) and noise- (Longenecker and Galazyuk 2011; Nowotny et al. 2011) induced tinnitus models. Use of gap detection for tinnitus has not been validated clinically and has not been used in NIHL clinical studies or trials; therefore it is not discussed further here. Use of this test is discussed in detail by Allman, Schormans, Typlt, and Lobarinas in Chap. 7.

5.2.5 *Histological Assessments to Elucidate Mechanisms of Protection*

Preclinical evaluation of the effects of noise on the mammalian cochlea have generally focused on OHC damage or loss, swelling of the stria vascularis, afferent dendrite swelling, and the loss of presynaptic and postsynaptic elements between the inner hair cell and auditory nerve. These measurements require postmortem collection of cochlear tissues and significant technical expertise in the subsequent processing and analysis. Histologic evaluation of the human cochlea is not generally performed except in cases where temporal bones have been donated for medical research (as in Makary et al. 2011, for example). In preclinical studies, histologic analysis can reveal the site or mechanism of action of the drug and further elucidate what audiometric assessment may best reveal a physiologic change in human studies (DPOAE, electrocochleography, or ABR). The timing and methods chosen for sample collection, preservation, and processing substantively affect histological quality, and protocols should be developed in consultation with the relevant literature.

5.2.6 *Summary of Preclinical Testing Issues in Translational Investigations*

It would be beneficial to the field if agreement on common animal models were achieved. The diversity of models emphasized by different laboratories developing individual agents has made comparisons of relative efficacy difficult. Appropriate rationales for selecting specific species for otoprotection research should include their similarities to humans both in terms of auditory function as well as in pharmacology and pharmacodynamics of the drug of interest (see Sect. 5.3). From a drug development perspective, it is problematic that there is no agreement on either the most appropriate animal species or most effective noise exposure in translational

auditory research. To speed the development of promising drugs, standardization of the multiple variables in the design of preclinical NIHL studies is needed. In Sect. 5.3, translation of an investigational new drug from preclinical assessment into human testing is discussed. An IND (Sect. 5.3) is required to proceed with clinical studies, which are identified as falling into four stages (Sect. 5.4).

5.3 The Investigational New Drug Application

5.3.1 Pharmacokinetic Assessment

Pharmacokinetics (Pk) is the study of the time course of drug absorption, distribution, metabolism, and excretion (ADME) whereas pharmacodynamics (PD) refers to the effect of the drug on the body and is often determined by a change in a circulating biomarker (Spruill et al. 2014). Ultimately Pk and PD information is used to optimize dose, dose schedule, and the relationship to an efficacy end point in pivotal studies (see Fig. 5.2). Pk and PD information can drive modification of chemical structure to optimize drug activity. NCEs are often developed from parent or lead molecules that have been chemically altered based on their structure–activity relationship (SAR), ADME, Pk, or PD response observed in earlier studies. Basic scientists rarely have training in SAR, ADME, Pk, or PD tests, but they are an integral part of progressing a new agent from animal testing to first-in-man (FIM) studies.

In addition to Pk and PD, there needs to be an early assessment of toxicity, which is generally performed in mice. However, it is also important to select an animal species that metabolizes the drug similarly to humans. The FDA requires the selection of a nonrodent species such as a dog, minipig, or monkey that best represents the ADME, Pk and PD of the drug in humans for all in vivo toxicology or toxicokinetic studies. Metabolic profiling is critical to the IND process because the drug's metabolite may exert important biologic activity and affect both the drug's safety and efficacy. When a compound successfully "passes" early in vitro and in vivo assessments, there is still significant work that must be done to establish appropriate manufacturing procedures.

5.3.2 Chemistry, Manufacturing, and Controls

When a candidate compound is selected for further investigation, efforts to establish the most efficient route of synthesis in terms of cost, yield, and impurities will be made. This becomes of particular concern if exotic intermediates are required for the synthesis, as they may be difficult or impossible to obtain at commercial scale.

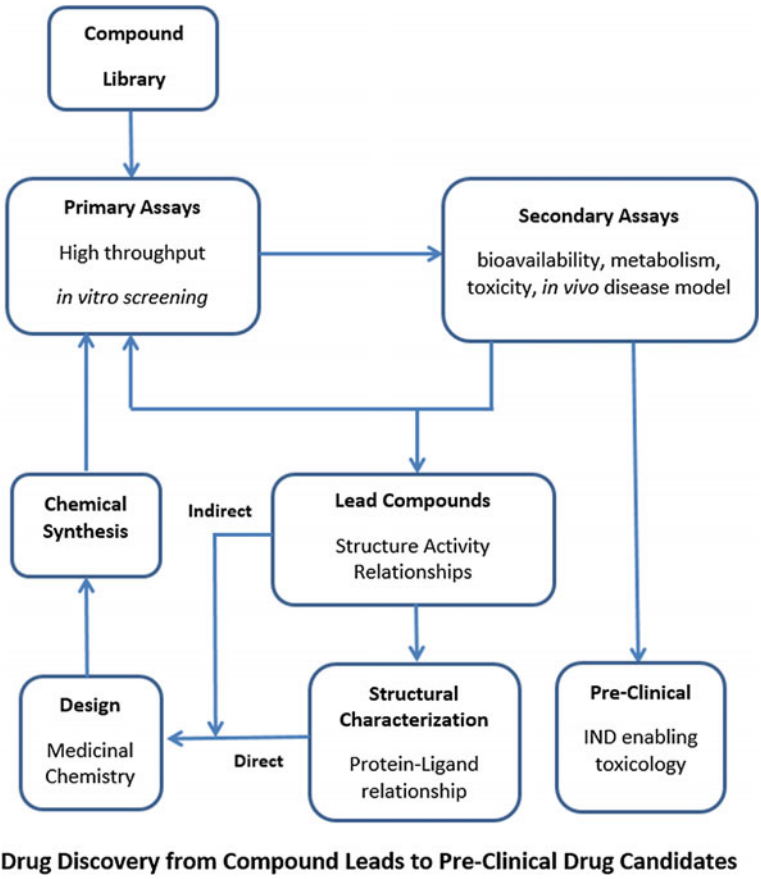

Fig. 5.2 Drug discovery: the preclinical activities required in the translation of an agent from a library of compounds into an investigational new drug candidate. After identification of an agent of interest, a series of in vitro and in vivo tests are required to screen both safety and efficacy. From these assays, candidates emerge and go through further development to understand better the chemistry of the agent and biochemical effects, and to design chemical formulations that are bioavailable, with each new chemical iteration undergoing new assays for safety and efficacy. Completion of this process is achieved when data are adequate to allow approval of an Investigational New Drug (IND) application to the FDA, for first-in-man studies. Results of those studies may drive further iterations of the process illustrated here (Adapted from https://commons.wikimedia.org/wiki/File:Drug_discovery_cycle.svg)

Medicinal chemists provide significant developmental input at this stage; their expertise allows modification of the compound to improve stability and solubility as well as increase scalability for manufacturing. It may be necessary to establish an early-stage reference supply of the compound for comparison to subsequent batches generated by the same or alternative synthesis routes. After the major metabolites are identified, these need to be synthesized for use as a reference material for subsequent bioanalysis of the parent and metabolites in IND-enabling toxicology

studies and later in clinical studies. Methods for determining the identity and purity of the parent compound and associated impurities must be developed and validated for use on subsequent batches analyzed in IND-enabling toxicology studies. The ultimate goal of these activities is to optimize the manufacturing protocols, determine all materials (metabolites) that need to be assessed for safety, and define the release specifications for the drug substance and drug product (see Fig. 5.2). All of these tests are required to be performed using good laboratory practice (GLP), which is a set of standards that ensure consistency, reliability, and reproducibility of the data through uniform, validated procedures completed with calibrated equipment.

5.3.3 IND-Enabling Toxicology

Questions that lead to a thorough understanding of the mechanism of action, possible side effects, dose-limiting toxicities, route of administration, drug half-life, drug metabolites, elimination routes, and possible drug–drug interactions must be asked and adequately answered after preclinical efficacy has been established. A major goal of the IND-enabling toxicology is to determine a recommended dose and schedule for a FIM clinical safety study. An essential component of the IND package will include in vitro and in vivo mutagenicity and carcinogenicity studies. These are typically in the form of an Ames test in bacteria for mutagenicity, a chromosomal aberration test in cultured cell lines, and a micronucleus test in vivo. These requirements may change based on past history of testing of the components in the NCE, given the known risk factors. As availability of the new candidate drug may be limited during early development and characterization steps, a number of contract research organizations (CROs) also offer non-GLP microversions of these tests using smaller amounts of the NCE. The much more costly GLP studies require larger volumes of the active pharmaceutical ingredient (API).

When assessing an NCE in toxicology studies, impurities should be present at a level above what is present in the final marketed drug product to ensure adequate testing of the impurities. In general, during process development, the impurity levels are reduced with manufacturing refinements. However, when scaling up to commercial batch sizes, these improvements may be lost and impurity levels can increase. Depending on the complexity of the synthesis and cost of the starting raw materials or intermediates, the price for manufacturing of the drug substance under good manufacturing practice (GMP), and the development and validation of test methods to characterize the drug substance, run into the hundreds of thousands of dollars for production of sufficient qualified material appropriate for the preclinical toxicology studies. These figures can be increased dramatically for biologics or compounds with extraordinary synthesis routes.

Depending on the proposed route of administration and duration of exposure, the requirements for IND-enabling toxicology may vary significantly. For most drugs given orally, FDA will generally require at least two routes of administration be

evaluated for acute administration. Typically, these are oral and intravenous acute toxicity studies performed in one rodent and one nonrodent species. In these studies, it is imperative that exposure to impurities and metabolites be sufficient to identify toxicity signals in the species chosen in order to be considered reasonably predictive of human toxicity. If multiple doses in human clinical studies are predicted or proposed, chronic toxicity studies of a duration equal to or preferably greater than the exposure duration in human trials will be required in generally one rodent and one nonrodent species. For all of these studies, careful attention to and documentation of efforts to improve the formulation chosen for delivery to optimize exposure in the test animals need to be included. Frequently, non-GLP pilot studies are performed to evaluate potential formulations and perform dose–response assessments before performing costly and time-intensive GLP toxicology studies. Pilot studies may ensure that the toxicology studies performed under GLP are able to identify dose-limiting toxicities and/or establish maximum feasible dose criteria for the studies before their performance. Consultation with a regulatory toxicology expert to plan and perform an acceptable IND toxicology program is highly recommended.

5.3.4 Filing an IND

5.3.4.1 eCTD Format

Current regulatory filing with the FDA is performed using the "electronic Common Technical Document" (eCTD) format developed by the ICH Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). The eCTD is a hierarchical HTML electronic structure developed to assist in the transfer of regulatory information to the FDA. Before submission of an IND in eCTD format, a sponsor is required to contact the e-submission support team and arrange to submit a sample eCTD or standardized data set. On review and approval of the validated structure, you are then invited to submit an eCTD IND. There is extensive documentation on the FDA website to guide in the development and filing of an eCTD IND. In general, specialized software packages are very helpful to address the regulatory requirements of eCTD filing, submission, and maintenance. It is of course possible that regulatory filing procedures or software requirements will change over time and therefore it is highly recommended to work with or engage a regulatory expert or group familiar with the eCTD process to accelerate submissions and ensure adherence to current FDA and ICH guidance.

5.3.4.2 Indication for Use

Determining the indication for use for a drug to prevent and/or treat NIHL is challenging in that this remains an area with no currently approved drugs and thus

no marketed products with approved labels and indications. Typically, indications for use are constrained by acute, intermittent, or chronic use. For NIHL, acute or intermittent use may be appropriate if it is related to treatment at or near the time of the acute noise exposure or injury. However, for workers exposed to hazardous noise on a daily basis, chronic daily treatment across an occupational career may be indicated. A decision on the intended use of the drug product should be made early on. Although a target product profile (TPP) is not required at the filing of an IND, a draft TPP should be created early in the development process. The TPP is typically the goal of an end of Phase 2 meeting with the FDA. Major modifications to an indication (e.g., change in target population) may require the filing of a new IND application, especially if the disease is covered by a different division of the FDA. An example of the components of a TPP for a drug that prevents or treats NIHL is provided in Table 5.1.

5.3.4.3 FDA Division

Currently, the Division of Neurology Drug Products (DNP) at the FDA has been involved in the filing, review, allowance, and oversight of most, if not all, clinical trials for NIHL. Over the last decade, the DNP has gained significant experience in working with companies seeking to develop drugs for the prevention and treatment of NIHL as well as other acquired forms of SNHL. As of the writing of this chapter, there are no drugs that have been approved by the FDA for the prevention or treatment of any SNHL disease or disorder, let alone NIHL. As NIHL is a novel therapeutic indication with no marketed products, DNP is playing a significant role in reviewing the criteria for early-, middle-, and late-stage clinical studies. DNP has established a liaison with the DoD Hearing Center of Excellence to learn about audiology and otology. In general, the medical device industry for hearing loss is much more advanced because of the decades of work in approving hearing aids and cochlear implants in adults and children. It is not uncommon for review teams within the DNP to consult with their colleagues in the Center for Devices and Radiologic Health (CDRH) that contains a Division of Ear, Nose, and Throat (ENT) devices.

5.4 Clinical Safety and Efficacy

5.4.1 Phase 1 Studies

Phase 1 studies include FIM safety and pharmacokinetic tests of the investigational drug. They are intended to determine the tolerability, dosing, and AEs or side effects associated with dosing of the drug. Phase 1 studies can be randomized controlled trials (RCTs) that include a placebo comparator and blinding to the

Table 5.1 Sample target product profile (TPP)

Product description/mechanism of action	Small molecule, hormone, peptide, or antibody by oral delivery or injection. Drug X increases the activity of an inner ear antioxidant enzyme critical to hearing function
Indication	Prevention and treatment of NIHL
Efficacy end points	Reduction of NIHL using pure-tone audiometry
Primary efficacy end point	Reduction in the magnitude of the TTS/PTS (dB HL)
Secondary efficacy end point	Reduction in the loss of word recognition scores (WRS)
Clinical assessment of success	Clinically relevant improvement in HL by ≥ 25 %
Contraindications	List situations in which the drug should not be used because the known risk outweighs any potential benefit. Known hazards from clinical studies. If no known contraindications exist, state "none known"
Warnings	List serious drug-related adverse reactions from clinical studies and potential safety hazards. Describe the preclinical and clinical data that indicate the product's potential carcinogenic, mutagenic, and/or fertility side effects
Precautions General Carcinogenesis Mutagenesis Impairment of fertility Pregnancy Nursing mothers	Describe any special care to be exercised by the physician or patient for the safe and effective use of the product, e.g., precautions not listed under any other section. Describe the animal studies performed to evaluate the pharmacology, toxicology, carcinogenicity, mutagenicity, and reproductive toxicities. If no nonclinical studies have been done, state this Identify Pregnancy Category A, B, C, D or X. If no nonclinical studies have been done, state this List information about excretion of the drug in human milk and the effects on the nursing infant. If no nonclinical studies have been done, state this
Adverse reactions	List drug-related adverse events seen in clinical trials or anticipated from preclinical pharmacology and toxicology
Dosage and administration/market size	List recommended route (oral, IV, transtympanic, inhaled), regimen (e.g., twice daily), dosage (mg), and duration of treatment (e.g., 10 days). US market size for acute and chronic NIHL could be 10–30 million adults
How supplied	Describe product and administration configuration

The TPP is a living document that is good to start at the beginning of a drug development program and to update after each completed phase of development and as more information is accumulated on the drug's safety and efficacy as well as any changes to the clinical indication, intended use or specific population, packaging, and labeling [Adapted from Scannon (2012); see also http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf]

subject and clinician or observer. Single ascending doses will typically start in a healthy adult population. Multiple ascending doses are typically started in healthy volunteers and then extended to subjects with the disease, especially if the elimination or clearance of the drug is altered by the disease and/or the intended Phase 2

population has impaired renal or hepatic function. Multidose testing is also performed to establish steady-state kinetics for multiday dosing protocols and involves a series of peak and trough plasma measurements to determine the concentration of the drug and its major and minor metabolites. PD assessments can also be addressed in Phase 1 studies, especially if a potential AE involves a drug–drug interaction or the intended Phase 2 clinical end point is a PD assessment. PD assessments are often measured during and after the treatment period to determine if any beneficial change in a biomarker can be elicited. While the FDA does not differentiate between Phase 1a and Phase 1b studies, the pharmaceutical industry typically designates Phase 1 studies in a diseased population as a Phase 1b study. The remainder of this section describes a case study in the form of SPI-1005.

5.4.1.1 Safety Assessments for SPI-1005

Lynch and Kil (2009) describe a Phase 1 clinical trial with ebselen (SPI-1005), an investigational new drug for the prevention and treatment of NIHL, in a randomized double-blind placebo-controlled single ascending-dose study. Thirty-two normal healthy subjects were consented, screened, and enrolled at a single clinical site (MDS Pharma, Lincoln, Nebraska) for a 72-h inpatient stay. History and physical (H&P) examinations, vital signs including orthostatic measurements, 12-lead electrocardiograms (ECGs), hematology [complete blood count (CBC) with differential], serology (Chemistry-20, also termed Chem-20, a complete chemistry screen that measures 20 different substances), and urinalysis were repeated over a 2-week period. AE monitoring was conducted repeatedly over the 3-day inpatient period. This study was completed and published in a peer-reviewed scientific journal. There is no requirement for Phase 1 studies to be published or listed on clinicaltrials.gov but as per the introductory comments, release of data in a peer-reviewed format may facilitate development and acceptance as well as driving new preclinical assessment of investigational drugs in other laboratories. The test battery is listed in detail here to highlight the multiple components monitored within a Phase 1 study as part of initial safety assessments.

5.4.2 Pharmacokinetics

A key component of Phase 1 testing is Pk assessment. As part of this Phase 1 study, Lynch and Kil (2009) reported data on peak plasma concentration (C_{max}), the time after ingesting the drug that it takes to reach maximal concentration (T_{max}), and half-life ($t_{1/2}$), which is the time it takes for 50 % of the drug to be eliminated from plasma. Finally, the total concentration or exposure (AUC_{0-t}) for ebselen and its three metabolites were calculated, as well as the plasma selenium concentration. Data generated in this Phase 1 study were a necessary step in the drug development process, ultimately setting the stage for a Phase 2 study assessing safety and efficacy

of SPI-1005 (NCT01444846; Kil et al. 2014). Details are shared here to illustrate the kinds of data that are sought in preclinical and early Phase 1 clinical testing for an NCE.

Critical to the discussions with the FDA is a robust review of any AEs at each dose level tested. This is essential in guiding the acceptable dose range and schedule and the potential allowance of additional clinical studies. If multidose schedules are proposed in future studies, supporting toxicology studies performed in appropriate species over a duration of time equal to or greater than the clinical dosing schedule need to be provided and reviewed. The data gathered in Phase 1 studies allow sponsors to make an informed decision on what dose ranges are well tolerated and guide establishment of a risk-to-benefit ratio in relationship to the pursued indication. In the case of the SPI-1005 Phase 1 data, with no AEs reported at all doses tested (single oral dose up to 1,600 mg) but no multidose testing, approval for multidose Phase 2 studies relied on preclinical toxicology studies run in multiple species for 28 days.

5.4.3 Phase 2 Studies

Phase 2 studies include larger numbers of subjects than Phase 1 studies and are intended to provide an initial assessment of efficacy in the affected population. They also further assess safety in the affected population. This section introduces the Phase 2 clinical trial of SPI-1005 in the prevention of NIHL (NCT01444846).

5.4.3.1 Trial Design

This single-center study recruited healthy volunteers 18–31 years of age at the University of Florida; enrollment was completed in November 2013. This was a dose-escalating design with three treatment arms. Participants in Arm 1 were randomized to take oral SPI-1005 at a dose of 200 mg twice daily or matching placebo. Participants in Arm 2 were randomized to take oral SPI-1005 at a dose of 400 mg twice daily or matching placebo, and participants in Arm 3 were randomized to take oral SPI-1005 at a dose of 600 mg twice daily or matching placebo (see Fig. 5.3). Dosing was continued over 4 days, starting 2 days before a calibrated sound challenge (CSC) and continuing the day of the CSC and 1 day post-CSC. This was a double-blind design; neither the subjects nor the study team knew the treatment condition of any subject during the course of the study. During the CSC, subjects listened to prerecorded rock or pop music on an iPod® using insert earphones that were set to a specific SPL (averaging 100 dBA in coupler measurements) for a fixed exposure duration (4 h). In a pilot study using this CSC (n = 12), the TTS at 15 min postnoise exposure ranged from 0 to 14 dB, with the group average of 6.3 ± 3.9 dB at 4 kHz (the most affected frequency) (Le Prell et al. 2012).

Pure-tone audiometry was the primary audiometric assessment; TTS was calculated for each tested frequency in each ear over time. The TTS was defined as the difference between the post-sound exposure threshold and the baseline threshold measured immediately before the CSC. Hearing tests were conducted at the time of screening and enrollment (clinic visit 1), immediately before the CSC on the third day of dosing, as well as 15-min, 1-h 15-min, 2-h 15-min, and 3-h 15-min post-CSC (clinic visit 2). Audiometric testing was repeated the following day (clinic visit 3) and 1 week later (clinic visit 4).

5.4.3.2 Medical Monitoring

Subjects had a detailed H&P examination at the time of the screening to determine if they satisfied the inclusion and exclusion criteria. Subjects who passed the H&P and all other laboratory criteria, including audiometry, hematology (CBC), serology (Chemistry-20), and radiology (chest X-ray), were enrolled. The H&P, including

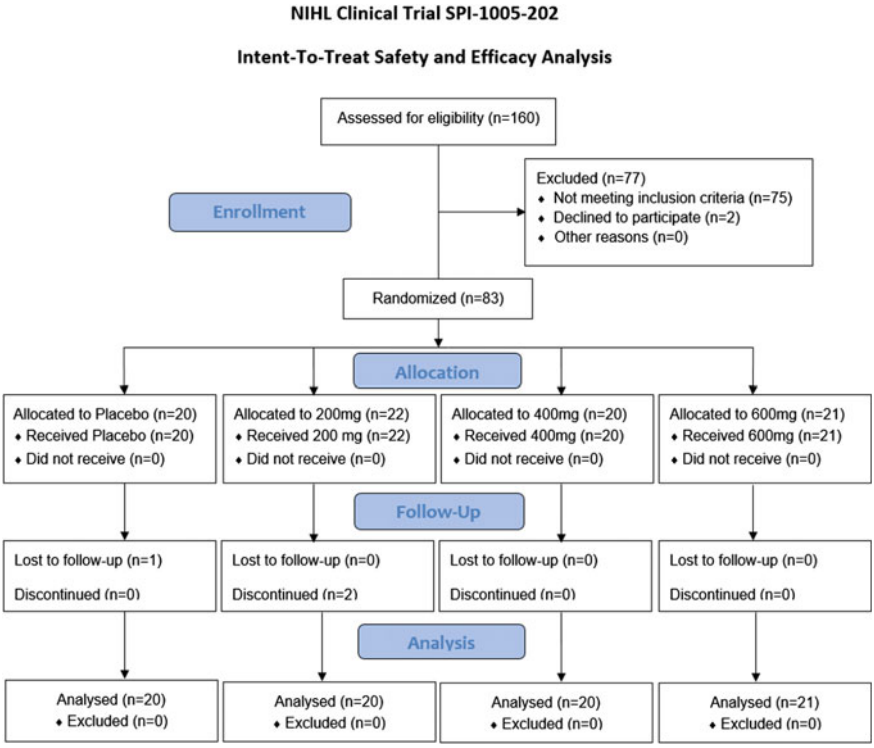

Fig. 5.3 The number of subjects in the Phase 2 clinical trial of SPI-1005 (NCT01451853) are illustrated here. In an intent-to-treat analysis, all subjects are included, regardless of compliance with protocol

Medra queries about AEs, was repeated at clinic visits 2, 3, and 4. Additional blood samples were drawn and all baseline assays repeated at clinic visits 2 and 4. Chest X-ray exams were repeated at clinic visit 4. Details are shared here to illustrate ongoing medical monitoring in Phase 2 studies, akin to that in Phase 1 studies.

5.4.3.3 Pk

Pk assessments are also completed in Phase 2 studies. Here, blood was collected for analysis of plasma ebselen and its metabolites, as well as total plasma selenium, at clinic visit 2. The Pk data from the Phase 1 study with SPI-1005 indicated a plasma $t_{1/2}$ of approximately 6–8 h, suggesting that twice-daily dosing would be appropriate in a multidose protocol. The Pk data also indicated that ebselen reaches C_{max} in approximately 2 h. These data informed decisions for the timing of blood draws to quantify ebselen and its metabolites after the achievement of steady state in Phase 2. In the Phase 2 study, Pk samples were drawn on the morning of the third day of dosing, just prior to the morning dose and 2 h after the morning dose.

Subjects were exposed to the CSC after the second (steady-state) blood sample was drawn. Based on prior preclinical data, efficacy of ebselen is best achieved when dosed at least 1 h before noise exposure (Lynch et al. 2004; Yamasoba et al. 2005). By analyzing Pk samples, exposures to drugs in test subjects can be confirmed and exposure–response relationships can be determined. For studies with multiple dose levels, study sponsors and reviewers can assess whether higher doses of the drug result in higher exposure levels of the drug and metabolites or if there is a saturation effect. One additional parameter that can be evaluated with Pk sampling is confirmation of a subject's compliance with the dosing schedule. One subject assigned to the 600-mg group, who reported compliance with the dosing protocol, showed no detectable levels of ebselen or metabolites in the Pk assessment [using validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method]. In addition, the subject's plasma selenium levels were not elevated above those of placebo subjects and showed no increase from baseline to treatment [using a validated inductively coupled plasma mass spectrometry (ICPMS) method]. These bioanalytic data were not available in real time and were available only several weeks after the study was completed, as is typical for many studies, and, moreover, as required for any double-blind study in which treatment codes are not available until the data are "locked." The study coordinators made every attempt to recall this subject for an interview to discuss this noncompliance issue but did not receive a response. The retained clinical trial material for this subject was sent for analysis, which confirmed the presence of study drug in the remaining capsules at the expected levels. Ultimately, this subject was included in the per protocol efficacy analysis despite strong evidence that the subject was noncompliant with the dosing protocol as there was no conclusive evidence available. Multiple Phase 2 studies are often performed in an effort to adequately define dose range, end points, and power estimates before proceeding with Phase 3 pivotal studies.

5.4.4 Phase 3 Studies: Pivotal Studies

Phase 3 studies often include a large number of subjects. During Phase 3 studies, effectiveness is (hopefully) confirmed, side effects are monitored, and there may be comparisons to other common treatments if there is an established standard of care. The use of a placebo group should be carefully considered in Phase 3 studies, as there are special ethical issues related to care for sick or diseased patients (Hernandez et al. 2014; Keranen et al. 2015; Niemansburg et al. 2015). For the indication of NIHL, a placebo group comparison to active dose group(s) is justifiable given that there are no other currently approved treatments. There is a caveat, however, in that in any study where PTS is expected in the absence of experimental drug intervention, every effort must be made to ensure that all subjects are appropriately educated about the effects of noise on hearing and provided with hearing protective devices as per regulatory agency guidance (OSHA 1983; DoD Instruction 6055.12 2010).

Typically, a NCE for a nonorphan indication will need to be tested in a large number of subjects in two separate pivotal Phase 3 trials, which should result in similar outcomes. Study repetition allows for comparison and evaluation of repeatability by the FDA when submitting a NDA for approval to market a drug for a given indication. In general, exposure to the NCE-containing drug product should include upward of 600 subjects and is commonly composed of 300 drug-exposed subjects in each of two Phase 3 trials. The precise numbers of drug-exposed subjects will be negotiated with the FDA review team and is based on known or potential risks identified in earlier trials as well as power estimates for achieving a statistically robust result on agreed on primary end points for the trial. If the results of the two pivotal Phase 3 trials differ significantly in their outcomes, the FDA may recommend additional confirmatory studies be completed prior to submission of an NDA. A special protocol assessment (SPA) for clinical protocols is a declaration from the FDA that a Phase 3 trial's design is adequate or acceptable for FDA approval. An SPA will seek to reach agreement between the sponsor and the FDA on the pivotal protocol design, end points, safety assessments, and the statistical analysis plan prior to enrollment of the Phase 3 clinical trial.

Given the novelty of NIHL as an indication and the efficacy end points being employed, sponsors may choose to request an SPA by the FDA review team. Clinical protocols for Phase 3 trials where data outcomes form the primary basis for an efficacy claim, if the trials had been the subject of discussion at an end-of-Phase 2/pre-Phase 3 meeting with the review division, may be eligible for an SPA agreement under the Prescription Drug User Fee Act (PDUFA) goals. A request for an SPA must occur before initiation of the pivotal Phase 3 trials. If granted, an SPA agreement can provide an opportunity to get input and buy-in from the FDA on the scientific, regulatory, and statistical rigor of the planned clinical trial. SPAs can also be requested for nonclinical carcinogenicity protocols and CMC stability protocols.

In performing Phase 3 studies, it is imperative that drug developers utilize a drug product consistent with that which will be filed for registration with the FDA. Any

changes in the dose, formulation, form, and manufacturing methods of the drug substance or drug product between the clinical supplies used in the pivotal trials and the drug product in the NDA must be disclosed and could put the approval at risk. If the FDA concludes that the drug product tested in the pivotal trials is not clearly equivalent to what is being proposed for registration or market approval, further studies of the proposed drug product may be required to prove bioequivalence. Typically, a minimum of two registration batches of qualified drug substance and drug product must be manufactured and batch records made available to the FDA to allow adequate review of the processes for use in commercial manufacturing of the drug product.

5.4.5 NDA and Approval

Legal requirements for safety and effectiveness for a drug to be approved have been interpreted as requiring scientific evidence that the benefits of a drug outweigh the risks and that adequate instructions exist for safe use in the intended indication. Well-controlled clinical trials, adequately descriptive labeling and instructions, appropriate and supportive toxicology reports, and well-delineated CMC all are components of a successful NDA approval. Perhaps most interesting to readers of this chapter would be a coherent discussion of the relevant end points for efficacy assessment of an approvable otoprotective drug. The challenge here is that there is no precedence to cite, as there are no approved drugs for the prevention and treatment of NIHL. There are, however, guidance statements from multiple organizations that might prove helpful.

5.4.5.1 Guidance from Professional Societies

Although there is no specific guidance from the FDA as discussed in Sects. 5.3.4.2 and 5.3.4.3, it seems reasonable to predict that noise otoprotection health claims are likely to be based on preservation of threshold sensitivity or perhaps preserved speech test performance given the recommendations of Gurgel et al. (2012). Thresholds are assessed using conventional pure-tone air-conduction audiometric testing using narrowband noises or pure tones as signals. Hearing levels are measured relative to a large reference population; the difference between an individual's measured threshold and the reference threshold is expressed using the units dB HL. Positive numbers reflect poorer hearing relative to the reference population, and negative numbers reflect better hearing than the reference population. In the literature, hearing loss is typically attributed to noise exposure if the audiometric configuration is "notched," meaning that thresholds are poorer at 3, 4, or 6 kHz than at 1 and 2 kHz and 8 kHz. There are a variety of definitions of what constitutes a notched audiogram (for review, see Le Prell et al. 2011b). Two of the more common notch criteria are those of Coles et al. (2000) and Niskar et al. (2001),

requiring either a 10-dB or a 15-dB notch depth, respectively. Hearing loss due to noise is typically the most robust at these 3-, 4-, and 6-kHz frequencies because of the ear canal resonance at approximately 3 kHz and the half-octave shift in which hearing loss is expected at or above the exposure frequency (Ward et al. 2003). If drug benefit is assessed based on some reduction in the prevalence of notched configurations, then the definition of a notch will obviously affect the measured prevalence of audiometric notches in the audiograms from both treated and control populations.

Explicit criteria defining threshold shifts in noise-exposed workers, have been provided by a number of government agencies, including the Occupational Safety and Health Administration (OSHA), the National Institute on Occupational Safety and Health (NIOSH), and the Department of Defense (DoD). OSHA defines a *standard* threshold shift (STS) as "a change in hearing threshold relative to the baseline audiogram of an average of 10 dB or more at 2,000, 3,000, and 4,000 Hz in either ear" [OSHA 1983; Section 1910.95(g)(10)(i)], whereas NIOSH advocates a criterion for *significant* threshold shift (STS) with the recommended definition of change being "an increase of 15 dB in hearing threshold level (HTL) at 500, 1000, 2000, 3000, 4000, or 6000 Hz in either ear, as determined by two consecutive audiometric tests," with the second test required to reduce false-positive findings (NIOSH 1998; p. iv, see also pp. 43–50). The DoD defines STS as "a change in hearing threshold relative to the initial reference audiogram of an average of 10 dB or more at 2,000, 3,000, and 4,000 Hz, in either ear," and they also state, "A single frequency 15 dB shift at 1,000, 2,000, 3,000, or 4,000 Hz is considered an early warning flag with no requirements for follow-up testing or referrals, but with a requirement to counsel the patient and check hearing protection" (DoD Instruction 6055.12 2010). One potential strategy for evaluating otoprotective drug benefit is assessing whether it reduces the percentage of workers, soldiers, or other noise-exposed participants that meet the OSHA, NIOSH, or DoD criteria for an STS. In real-world trials, differential use of hearing protection devices (ear plugs or ear muffs) increases individual variability as it influences individual risk of STS. Campbell and Fox, in Chap. 6, similarly address the issue of how to monitor drug-induced ototoxic hearing loss in clinical trials. They describe ototoxicity criteria put forward by the American Speech-Language-Hearing Association (ASHA). However, just as the ASHA criteria were not designed with the intent to identify benefits of otoprotective agents, the OSHA, NIOSH, and DoD criteria may be relatively insensitive to drug-mediated benefits.

The potential use of criteria that define "compensable hearing loss" might be considered as an alternative, but this is even more problematic in that these criteria are intended to identify individuals who have suffered disabling auditory injury. Guidance from the Veterans Administration (VA) is provided in 38 CFR 3.385, which states, "For the purposes of applying the laws administered by VA, impaired hearing is considered a disability for VA purposes when the auditory threshold in any of the frequencies 500, 1000, 2000, 3000, 4000 Hz is 40 decibels hearing level (dB HL) or greater, the auditory thresholds for at least three of the frequencies 500, 1000, 2000, 3000, or 4000 Hz are 26 dB HL or greater, or speech recognition

scores using the Maryland CNC Test are less than 94 %." The use of speech tests is particularly interesting here, given guidance from the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS), which has recommended that word recognition scores be included in *all* clinical trials that assess auditory function (Gurgel et al. 2012). Interest and enthusiasm for speech, and speech-in-noise tasks in particular, appear to be increasing given suggestions that a history of noise exposure may underlie speech-in-noise discrimination difficulties (Kujawa and Liberman 2009; Lin et al. 2011; Makary et al. 2011), but it is not clear at this point what the most sensitive test might be (for detailed discussion, see Le Prell and Lobarinas 2015; Le Prell and Brungart, in press).

5.4.5.2 Guidance from the Department of Defense Hearing Center of Excellence

Recognizing the importance of these kinds of issues, the DoD Hearing Center of Excellence (HCE) has established a Working Group on Pharmaceutical Interventions for Hearing Loss (PIHL). A number of issues discussed in this chapter have been discussed previously in their newsletter series (http://hearing.health.mil/EducationAdvocacy/NewsLetters.aspx), and a series of articles has been prepared with authors from the DoD HCE partnering with academic and industry colleagues to provide a series of guidance documents. Several of these documents have been accepted for publication, with additional articles currently completing the final stages of the review process. These documents are intended to provide best practices and establish common procedures for preclinical and clinical investigation and will be a useful addition to the literature.

5.4.6 Phase 4 Studies: Postmarketing Surveillance Studies

Phase 4 studies are postmarketing surveillance studies, with the potential to expand on the initial label claims approved under the original NDA. These Phase 4 activities are largely outside the scope of this chapter, which is focused on early translational and clinical activities required to achieve of proof of concept in humans.

5.5 Human Clinical Studies in NIHL

Here, brief summaries regarding the development of a subset of the compounds being developed are offered, ending with a few common observations related to the future of these early and midstage exploratory studies.

5.5.1 N-acetylcysteine

N-acetylcysteine (NAC) is the most extensively investigated potentially otoprotective drug to date; its testing was facilitated by several features. First, NAC was already approved by the FDA for acetaminophen overdose and for inhalation as a mucolytic, with an FDA-approved dosing regimen unique to each of these two indications. Thus, there was substantial existing safety data in humans as well as efficacy for a different indication, which is different than developing an NCE for FIM application. Second, NAC received patent protection (Kopke et al. 2003), further facilitating commercial development. NAC was previously marketed as The Hearing Pill® by the American BioHealth Group (Somers 2007; Karlman 2012). In the absence of efficacy data, The Hearing Pill® was promoted as a dietary supplement, or a "nutraceutical," a category that cannot make claims of medical benefit because it was not evaluated by the FDA (Schachtman 2003).

NAC *was* assessed in several human clinical studies, although not in the marketed formulation of The Hearing Pill®. First, Kramer et al. (2006) documented TTS and temporary changes in OAEs in 31 normal-hearing subjects after a single music exposure at a recreational setting (nightclub), with NAC (900 mg) ingested as an effervescent tablet in water 30 min prior to entering a San Diego nightclub. Although no significant otoprotection was observed, the authors suggested that a significant difference in music exposure levels across the eight evenings of data collection (ranging from 92.5 to 102.8 L_{avg}) may have masked potential benefits of NAC. Two additional studies were completed using TTS models. Lin et al. (2010) assessed prevention of noise-induced TTS in 53 male workers at a steel manufacturing facility in Taiwan, reporting an average TTS at 3, 4, and 6 kHz of 2.77 dB after placebo and 2.45 dB after NAC. Although this small difference in TTS was reported to be statistically significant ($p = 0.03$), a 0.3-dB difference is not clinically relevant regardless of statistical reliability. Lindblad et al. (2011) tested NAC in a weapons training setting in which military subjects were exposed to impulse noise, but no reliable TTS was measured, making claims of potential otoprotective benefit impossible.

The methodological issues in these early studies (Kramer et al. 2006; Lin et al. 2010; Lindblad et al. 2011) highlight the importance of having a well-defined trial population and an adequately powered design. A fourth NAC study was more successful in adequately powering the active group against the placebo group. Kopke et al. (2015) assessed threshold shift in 566 normal-hearing participants treated with 900-mg NAC (effervescent tablet in water) or matching placebo (in water) three times daily, for a total of 2700 mg/day during the first 13 days of weapons training, followed by twice daily dosing for 3 days, for a total of 1800 mg/day. During the 16-day weapons training period, Marine recruits were exposed to M-16 rifle fire (325 rounds) and other non-rifle noise, including simulated explosions. Hearing thresholds were determined using 2–16 kHz tonal stimuli, measured before training and 10 days after training had stopped. The primary outcome (which is defined as part of the statistical analysis plan) was defined as the

incidence of a significant threshold shift (STS) including an increase of 20 dB or more at one frequency or 10 dB or more at two adjacent frequencies. There were no significant decreases for the left ear (NAC: 21 % vs. placebo: 19 %, $p = 0.7816$), although the group difference approached $p < 0.05$ for the right ear (NAC: 21 % vs. placebo: 27 %, $p = 0.0562$). Additional comparisons were conducted as secondary analyses; when STS was defined as an increase of 15 dB or more at one frequency or 10 dB or more at two adjacent frequencies, the rate of STS was reliably different for the ear corresponding to the trigger hand (NAC: 27 % vs. placebo: 35 %, $p = 0.0288$) (Kopke et al. 2015). The additional detail provided for this last study is included to highlight the difficulties of clinical trials in which only 19–35 % of the placebo group develop a hearing loss and, moreover, to illustrate the complexity of live fire exercises where the exposure may be asymmetric.

5.5.2 D-Methionine

According to the clinicaltrials.gov website, the study NCT01345474 is currently recruiting subjects from a population of drill sergeant instructor trainees ages 21–40 years at Fort Jackson, South Carolina. Subjects take twice daily oral D-methionine (D-Met) of up to 100 mg/kg/day for 18 days (starting 3 days before training, during 11 days of training, and continuing 4 days posttraining). This is a randomized, double-blind, placebo-controlled clinical trial. During the study, participants are exposed to M-16 fire during weapons training, with a 500-round minimum over an 11-day period. The primary outcome is pure-tone air-conduction thresholds measured 22 days after cessation of weapons training, including change from baseline as measured by absolute change and the frequency of STS. In addition, the study team is assessing tinnitus using questionnaires to assess changes in tinnitus loudness and annoyance.

D-Met has not been used in humans previously for the prevention of NIHL, although a variety of animal data support this indication. Translation to humans was facilitated by a Phase 1 safety study in which the pharmacokinetics of D-Met were assessed following oral administration of MRX-1024 (a formulation of D-Met) in normal volunteers (Hamstra et al. 2010). At that time, the patents protecting D-Met (Campbell 2001, 2008) were licensed by Molecular Therapeutics, Inc., which developed MRX-1024 for clinical studies. Testing in healthy volunteers was followed by Phase 1 testing in 25 patients receiving MRX-1024 concurrent with radiation therapy (RT) with or without weekly cisplatinum in an open-label study (Hamstra et al. 2010). Hamstra et al. (2010, p. 2666) report, "When administered concurrent with RT without chemotherapy, it was associated with a modest increase in grade 2 (two of six patients) and grade 3 (one of six patients) emesis. In those treated with MRX-1024 along with RT and weekly cisplatinum, there was no appreciable increase in emesis." After describing all study withdrawals due to nausea and emesis, the authors conclude, "Aside from nausea and emesis, there were no other significant toxicities observed related to MRX-1024." Development

later reverted back to Southern Illinois University School of Medicine. A new company, MetArmor, Inc., has recently been founded by Dr. Campbell to continue the clinical development of D-methionine as an otoprotective agent.

5.5.3 *Beta-Carotene, Vitamins C and E, and Magnesium*

Early data on prevention of NIHL using the combination of beta-carotene, vitamins C and E, and magnesium came from preclinical tests at the University of Michigan (Le Prell et al. 2007), and like the compounds described in Sects. 5.5.1 and 5.5.2, patent protection was sought before publication of preclinical data (Miller et al. 2011). This case study represents what can perhaps best be described as a hybrid development, as clinical trials were developed at academic institutions, funded by NIH, and completed with the help of industry patent licensees who formulated GMP supplies. This case study was initially introduced by Le Prell in Chap. 2, where the institutional review of NCT00808470 was described as encountering an "obstacle" in that University of Michigan leadership (the home of the parent NIH award NIH U01 DC008423) would not allow US studies evaluating the "nutraceutical" formulation to move forward without an IND. Under the requirements of an IND, the clinical trial materials were required to meet relevant pharmaceutical standards, including stability tests for all four active nutrient agents. Those tests are not currently required for dietary supplements marketed under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

The initial licensee of these patents, OtoMedicine, Inc., undertook the expensive process of formulation, manufacturing, and purity and stability analyses. OtoMedicine, Inc., was dissolved before the collection of all FDA-required documentation and the manufactured supplies could not be used in the planned studies. This was a significant setback with respect to time and resources. A new licensee for the University of Michigan patents, Hearing Health Sciences, Inc., was identified, and they developed a chewable tablet formulation. An IND application was filed with CMC data in hand, and the study was allowed in the fall of 2012 under IND 116027. Although this was different from the originally proposed 2008 start date in the 4-year NIH grant that funded the conduct of these studies, the NIH allowed the period over which funding was awarded to be extended through multiple no-cost extension periods, so that the trial could begin enrollment once clinical materials and IND approval were in hand. Since then, specific guidance on studies on the prevention of acquired hearing loss has indicated that such studies *always* need an IND before use in a clinical trial (E. Bastings, The FDA/IND Process and Recommendations, presented August 24, 2012, Baltimore, MD); thus, FDA guidance should be sought regarding "nutraceutical" agents when planning clinical trials.

5.6 Summary

Some 16 % of disabling hearing loss worldwide has been attributed to occupational noise (Nelson et al. 2005). The burden is reduced in developed countries, with some 9 % of adult-onset hearing loss in the United States attributed to noise exposure (Nelson et al. 2005). According to NIOSH, "Four million workers go to work each day in damaging noise. Ten million people in the U.S. have a noise-related hearing loss. Twenty-two million workers are exposed to potentially damaging noise each year" (http://www.cdc.gov/niosh/topics/noise/stats.html). Industrial noise is not the only source of damage; concerts, nightclubs, and sporting events have the potential to be quite loud. Power tools and other devices can be hazardously loud as well. A key concern is the worker who receives 100 % of the maximum daily noise exposure allowed by OSHA, then goes home and engages in loud recreational activity or uses loud equipment or machinery at home (for discussion, see Le Prell 2016).

Ruben (2000) raises concerns that subtle, "preclinical" deficits have the potential for increasing impact on the modern workforce, even in the absence of an STS. Strong communication skills are critical to many in the workforce. Negative consequences of accumulating hearing impairment, such as difficulty hearing normal communication, communicating over the telephone, or understanding speech in a noisy office setting, are already reflected in labor statistics in the form of decreased income (Ruben 2000). Communication difficulties result in underemployment, or even unemployment, and as the American labor force increasingly shifts from manual labor to service-related occupations *that critically depend on communication abilities,* communication disorders will continue to emerge as an increasingly important public health issue for the 21st century (Ruben 2000).

Hearing conservation is achieved through engineering controls (decreasing noise at its source), administrative controls (decreasing the amount of time spent in a noisy environment), and personal hearing protection devices (HPDs: earplugs and earmuffs). Without doubt, HPDs will continue to be important tools for hearing loss prevention, and they continue to improve, with electronic technology representing a major step forward for preserving situational awareness (Casali et al. 2009; Talcott et al. 2012). Nonetheless, the hearing conservation amendment was promulgated more than 30 years ago (OSHA 1983), and NIHL remains one of the top disabilities for the workforce. There is active debate as to whether the regulations are adequate (Dobie and Clark 2014, 2015; Morata et al. 2015; Suter 2015). Even if the noise limits are deemed sufficiently protective, compliance with HPD requirements is frequently inadequate based on poor uptake of education, failure to correctly use earplugs, failure to consistently use HPDs, and so forth. Regardless of one's opinion on the "best" workplace noise limits, it is clear that additional strategies for protecting hearing are urgently needed, including quieter devices, better HPDs, and improved educational interventions. Ethical drugs that successfully navigate the review and approval process for the purpose of hearing loss prevention will provide an additional new tool for those at risk when noise is unexpected or earplugs are

unavailable or impractical. To reach this point, continued efforts to move scientific investigations from the laboratory into the clinical test environment are urgently needed.

Compliance with Ethics Requirements

Eric Lynch is a Co-Founder of and the Chief Scientific Officer for Sound Pharmaceuticals, Inc.

Jonathan Kil is a Co-Founder of and the Chief Medical Officer for Sound Pharmaceuticals, Inc.

Colleen Le Prell was Co-Principal Investigator on clinical study SPI-1005-202 with Sponsor Sound Pharmaceuticals, Inc. under IND 068443. She is a co-inventor on patents assigned to the University of Michigan and the University of Florida.

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Chapter 6
Cisplatin-Induced Hearing Loss

Kathleen C.M. Campbell and Daniel J. Fox

Abstract For decades, cisplatin chemotherapy has significantly increased survival in numerous cancer patient populations. However, cisplatin treatment results in severe adverse side effects including nephrotoxicity, neurotoxicity, radiation-induced oral mucositis, ototoxicity, and permanent hearing loss. Protection from cisplatin's adverse side effects has therefore been a translational research focus for many years. This chapter discusses cisplatin's historical discovery, its clinical application, and cisplatin-induced ototoxicity mechanisms. The chapter then reviews current translational research to protect from cisplatin-induced hearing loss, including clinical behavioral and objective monitoring techniques; adult and pediatric grading scales implemented to measure and identify cisplatin-induced ototoxicity; and potential otoprotective mechanisms that are currently tested to prevent cisplatin-induced ototoxicity in animals and clinical trials. Finally, the chapter reviews potential clinical trial funding and the steps required by the FDA, including the extensive investigational new drug (IND) application, to test otoprotective agents for protection from cisplatin-induced hearing loss. At the chapter's end, readers should acquire general knowledge underlying cisplatin's intricate history and clinical cisplatin use and understand the steps required to design and perform translational otoprotection studies to prevent cisplatin-induced ototoxicity and permanent hearing loss.

Keywords Cisplatin history • Clinical monitoring • Food and Drug Administration • Funding sources • Grading scales • Investigational new drug • Mechanisms • Otoprotection trials • Ototoxicity • Ototoxic mechanisms

K.C.M. Campbell (✉) · D.J. Fox
Department of Medical Microbiology, Immunology, and Cell Biology,
Southern Illinois University School of Medicine, 801 N. Rutledge, Springfield,
IL 62794-9629, USA
e-mail: kcampbell@siumed.edu

D.J. Fox
e-mail: dfox@siumed.edu

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6.1 Introduction to Cisplatin Ototoxicity

Barnett Rosenberg's discovery of cisplatin as an antineoplastic agent historically impacted cancer patient survival. He found that the "inert" platinum-coated electrodes used during his electrophysiology studies actually created a precipitant, cisplatin, that prevented in vitro cell division (Rosenberg et al. 1965). Many years of research determined significant cisplatin-induced tumor size reductions and increased survivability in mice (Rosenberg et al. 1969). Essentially, Rosenberg's discovery transformed solid tumor cancer patient survival rates into an 80–90 % "cure" rate (Alderen et al. 2006).

Cisplatin is now one of the most successful clinical anticancer therapeutics used to treat solid tumors found in ovarian, cervical, testicular, bladder, lung, and head and neck cancers (Boulikas and Vougiouka 2004). However, cisplatin also results in severe cochleo-, nephro-, and neurotoxicities that induce permanent bilateral hearing loss, kidney failure, cognitive deficiencies, and radiation-induced oral mucositis (Lippman et al. 1973; Grunberg et al. 1989; Taguchi et al. 2005). Preventing cisplatin-induced damage without compromising its powerful influence on solid tumors has therefore been a major translational research focus for many years.

This chapter reviews current translational research to protect the inner ear from cisplatin-induced hearing loss. It discusses clinical behavioral and objective grading scales and monitoring techniques to measure and identify cisplatin-induced ototoxicity. The chapter also introduces potential otoprotective therapies that are currently being tested to prevent cisplatin-induced ototoxicity in animals and clinical trials. At the chapter's end, readers should have general knowledge underlying cisplatin's translational history, clinical cisplatin use, its impact on hearing, methods and procedures for cisplatin ototoxicity monitoring, grading of cisplatin ototoxic adverse events for clinical trials, and an introductory knowledge of otoprotective agents currently under development to prevent cisplatin-induced hearing loss, including the challenges encountered in the translational process.

6.2 Cisplatin-Induced Hearing Loss Mechanisms of Action and Incidence

Cisplatin HCl hydrolyzes in endogenous systems and enters cellular nuclei, where it binds to DNA with a high affinity to guanine (Sherman et al. 1985; Baik et al. 2003). Cisplatin-bound DNA influences DNA-binding proteins to either induce programmed cellular death or initiate cellular repair (Bierbach et al. 1999; McHugh et al. 2001). Cisplatin-induced cellular death generates excessive reactive oxygen species (ROS) via the NADPH-oxidase (NOX) pathway that overwhelm endogenous antioxidant pathways and damage cells (Itoh et al. 2011; Casares et al. 2012). Thus, while the DNA-binding molecular mechanisms render cisplatin an excellent

anticancer drug, the same mechanisms also can cause permanent damage to normal cells, particularly in the cochlea (Lippman et al. 1973). Inner ear pharmacokinetics and stress-induced pathways activated in the inner ear by cisplatin treatment have been well described (for recent review, see Laurell and Pierre 2015).

Cisplatin is the most ototoxic platinum-based chemotherapeutic agent (Moroso and Blair 1983). Hearing loss generally begins at the higher frequency regions as early as the first treatment cycle and gradually progresses into the midfrequencies with increased cumulative cisplatin dose (Kopelman et al. 1988). Children younger than 5 years of age are particularly prone to hearing loss onset compared to adolescents between 15 and 20 years of age (Li et al. 2004). Cisplatin-induced hearing loss is particularly detrimental to pediatric populations whose cognitive and speech development depends greatly on hearing perception (Knight et al. 2007).

Cisplatin-treated patients on high-dose protocols, such as in ovarian cancer, have significantly increased incidence (90–100 %) of hearing threshold shifts (Benedetti Panici et al. 1993). High-frequency hearing loss is first observed, but the hearing loss progresses into lower frequencies as a result of cumulative doses over a body surface area (BSA) of 100 mg/m^2 (Kopelman et al. 1988). At less than a BSA of 400 mg/m^2 cumulative dose, approximately 20–50 % of patients incur permanent hearing loss depending on the treated cancer type, which influences the cisplatin dosing regimen (Bokemeyer et al. 1998). Thus, hearing loss extent is strongly correlated to dose amount and duration of the cisplatin treatment.

6.3 Clinical Monitoring for Cisplatin-Induced Hearing Loss and New Drug Trials

For general clinical ototoxicity monitoring, the consensus guidelines of the American Speech-Language-Hearing Association (ASHA) (1994) and the 2009 position statement of the American Academy of Audiology (AAA) provide the most widely accepted guidances. However, those guidances are designed for early clinical detection of ototoxicity rather than determination or grading of adverse events in clinical trials. Furthermore, the guidances were not designed to determine if a pharmaceutical otoprotective agent reduces ototoxicity in clinical trials. To date, no formal or universally accepted guidelines are in place for reporting ototoxic adverse events in clinical trials or determining otoprotection. Currently, the US Food and Drug Administration (FDA) does not provide practice guidelines specifically for clinical trials in this area. However, a number of scales and approaches have been proposed and published (for a recent review, see Anderson and Campbell 2015). This section reviews some of the options available for both clinical care and clinical trials.

6.3.1 Audiological Monitoring Procedures

When monitoring cisplatin chemotherapy patients for ototoxicity, the monitoring objective for a particular patient must be considered. In all cases, a comprehensive baseline hearing assessment should be conducted to document current hearing status for a valid comparison to later hearing testing results. Approximately 15 % of American adults report impaired hearing (Blackwell et al. 2014). Thus, it is critical to know whether a patient has preexisting hearing loss. Without baseline testing, frequently the clinician cannot truly determine whether hearing *changed* during the course of treatment or the patient's perception of his or her hearing has changed.

For example, patients who are stressed, distracted, fatigued, experiencing malaise, in new listening environments, or listening to new speakers may report communication difficulty even if their auditory threshold has not changed. All of these situations are common in patients facing a potentially life-threatening illness, undergoing chemotherapy, and possibly experiencing concomitant radiation treatments. Furthermore, if the patients have preexistent hearing loss, a relatively small shift in hearing thresholds may have a disproportionate effect on their communication abilities relative to a patient experiencing the same degree of hearing threshold shift but with completely normal hearing at baseline. Cisplatin-treated patients with or without concomitant radiation to the head and/or neck may also experience a cognitive disorder commonly referred to as "chemobrain," which may impair their ability to process auditory information (Whitney et al. 2008). Thus, in clinical care, but particularly in clinical trials, relying on a patient's self-report of hearing loss to indicate ototoxicity will probably be both inaccurate and unreliable.

Consequently, baseline testing is essential to establish a clear relationship between hearing changes and any drug administration (Campbell and Durrant 1993; Campbell et al. 2000; Campbell 2004). The baseline evaluation also provides the opportunity for the audiologist to discuss the possibility of ototoxic hearing loss with the patient and family and assure them that they can be assisted if a hearing loss develops.

If the patient's chemotherapy can be modified, then the primary goal of ototoxicity monitoring is to identify ototoxicity in the very early stages, preferably while hearing loss is limited to the frequency ranges above 8 kHz, which are not critical for speech understanding in most listening situations. Cisplatin-induced hearing loss almost invariably starts in the highest frequencies and then later progresses into the conventional frequency range (0.25–8 kHz) (Fausti et al. 1984). Thus, early identification can potentially protect the patient's communicative abilities because hearing in the conventional frequency range is primarily responsible for speech understanding. Consequently, high-frequency audiometry is recommended in addition to all other measures if the chemotherapy regimen can potentially be altered. If high-frequency thresholds worsen, then the audiologist can notify the patient and physician so that other treatment options such as dose reduction, a different chemotherapeutic agent, or dosing schedule can be

considered. For clinical trials of an otoprotective agent, high-frequency audiometry is highly recommended to provide the most sensitive measure of otoprotection.

If the chemotherapy protocol cannot be altered even if ototoxicity occurs, then the priority for clinical care ototoxicity monitoring changes. When treatment cannot be safely altered, the goal of ototoxicity monitoring is to detect and monitor the progression of ototoxicity if it develops, help the patient and family understand the hearing loss, and develop communication strategies to accommodate it. The management strategies are similar to those for any other patient developing hearing loss. These strategies include counseling, including an explanation of the hearing loss, its impact on communication, and strategies to foster communication. Strategies may include counseling the family to provide better visual cues to the patient, reducing ambient noise in communication environments, preferential seating, stress reduction, and possible use of assistive devices or hearing aids.

If a patient is fitted with a hearing aid, special attention needs to be given to controlling the maximum power output of the hearing aid. The patient should also be counseled to avoid noise exposure during and in the months after cisplatin chemotherapy and to use hearing protectors whenever noise exposure is unavoidable. Noise exposure exacerbates cisplatin-induced ototoxicity during the course of chemotherapy and quite possibly for months or years after discontinuation (Bhattacharyya and Dayal 1984; Gratton et al. 1990). During the course of a clinical trial, noise exposure can confound results by introducing temporary or permanent threshold shifts that are unrelated to cisplatin per se or the investigational study drug. For clinical trials in cisplatin otoprotection, it is particularly important to question the subject about recent noise exposure just prior to each hearing test because noise exacerbates the risk of cisplatin-induced hearing loss, sometimes even years after cisplatin treatment is discontinued (Peleva et al. 2014). Thus, not only short-term but also long-term follow-up results for the clinical trials outcomes could be affected by noise exposures.

Whether for clinical care or for clinical trials, a team approach to ototoxicity monitoring is essential. Communications, procedures, and reporting for interactions between the physician, scheduling nurse, patient, and audiology clinic should be clarified in advance. Infection control and potential exposure to other patients in the audiology waiting area need to be addressed because these patients can be immunosuppressed. All audiologic testing should be conducted by experienced, licensed audiologists. The ototoxicity monitoring team must deliver fast, accurate, and flexible testing to this challenging test population because of their complicated schedules and chemotherapy-induced health issues. These patients may have difficulty attending testing sessions that test auditory stimuli at threshold level for long periods of time.

In addition, all audiologic test equipment must be calibrated at least once per year and must meet all American National Standards Institute (ANSI) or International Organization for Standardization (ISO) standards for audiologic testing. Similarly, the test environment must meet ANSI/ISO standards for ambient-noise levels. If speech testing is included, the speech signals will also need to be calibrated (ASHA

1987, 1988). For clinical trials, biannual calibrations are desirable to ensure that all measures can be accurately compared to baseline findings.

As recommended by the AAA Position Statement (2009), the baseline audiologic assessment should be comprehensive so as to identify other factors that could cause fluctuant hearing independent of the cisplatin (e.g., otitis media). A comprehensive baseline evaluation should include air conduction threshold testing in the conventional frequency range and in the high-frequency range. Bone conduction testing should be conducted at any frequency between 0.5 and 4 kHz in which air conduction thresholds are 15 dB HL (decibels hearing level) or greater to identify any conductive component in the measured hearing loss. Tympanometry is also needed at baseline to detect any middle ear abnormality. Speech reception threshold (SRT) testing and word recognition testing are generally not a part of subsequent monitoring used to determine if ototoxicity has occurred but are recommended at baseline so that a comparison is available if hearing loss later develops. Otoacoustic emissions (OAEs) may be included as an adjunct but are not recommended as a primary measure, as discussed in Sect. 6.3.1.9. Once a comprehensive baseline assessment is collected, the chemotherapy treatment protocol may be altered if early indication of ototoxicity is discovered.

After the baseline evaluation, ototoxicity monitoring generally includes only air conduction thresholds in each ear at the conventional frequency range and the high-frequency range if indicated. The thresholds obtained at each follow-up visit are compared against pretreatment baseline thresholds and not to the most recent follow-up evaluation. If the change from baseline meets the ASHA (1994) and AAA (2009) criteria for detection of ototoxicity, the patient then receives a full comprehensive audiologic assessment for comparison to baseline findings. These results are reported to the patient and physician.

The significant change criteria as defined by ASHA (1994) and AAA (2009) are any one of the following:

1. $\geq$ 20 dB change at any frequency,
2. $\geq$ 10 dB change at any two adjacent frequencies, or
3. loss of response at three consecutive frequencies where responses were obtained at baseline.

To be considered significant for ototoxicity, these changes must replicate 24 hours later with no indication of middle ear abnormality. Patients serve as their own controls for ototoxic change, which is computed relative to baseline measures. The methods for clinical ototoxicity monitoring and ototoxicity monitoring in clinical trials can be similar. However, in clinical trials, the protocols are more formalized, regimented, and tailored to the potentially ototoxic drug or otoprotective agent under study (Campbell et al. 2003).

For clinical trials, the ASHA criteria are frequently used as an early indication of possible ototoxicity. In that case, any patient with a threshold shift at the follow-up test meeting the ASHA change criteria is immediately scheduled for a full diagnostic evaluation to determine if the threshold shift is conductive (e.g., otitis media)

or sensorineural (possible ototoxic shift). If the full assessment confirms sensorineural and possibly ototoxic threshold shift, the degree of shift is then categorized according to an adverse event grading system. For cisplatin otoprotection clinical trials, the most common grading system used in the Cancer Therapy Evaluation Program (CTEP) is the Common Terminology Criteria for Adverse Events (CTCAE).

6.3.1.1 Behavioral Measures

The primary measure for ototoxicity monitoring in clinical care and generally in clinical trials is pure-tone air conduction threshold audiometry. When needed, bone conduction thresholds are also added to the test battery to clarify if a loss is sensorineural or conductive. The objective of these tests is to determine a patient's auditory sensitivity thresholds for pure-tone stimuli by air and bone conduction. Air conduction thresholds indicate hearing losses that are either conductive, sensorineural, or mixed (a combination of sensorineural and conductive hearing loss). An air–bone gap indicates conductive hearing loss components. Bone conduction threshold deficits reflect only the sensorineural component of the hearing loss. Air conduction and bone conduction thresholds are compared to determine the degree and type of hearing loss.

6.3.1.2 Bilateral Air Conduction Pure-Tone Threshold Audiometry

During air conduction threshold testing, the signal is generally delivered through earphones to each ear individually, with the subject responding by pushing a button or raising their hand when he or she hears the signal. The softest sound at which the subject responds 50 % of the time is considered threshold. Pure-tone threshold testing should utilize the modified Hughson–Westlake procedure (Carhart and Jerger 1959; ASHA 1987). Bilateral air conduction pure-tone threshold audiology is performed in the conventional (0.25–8 kHz) range prior to cisplatin administration.

Pure-tone air conduction testing should be conducted at 0.25, 0.5, 1, 2, 4, and 8 kHz and also at 3 and 6 kHz if more precision is needed as in clinical trials (e.g., for adverse event grading). The 10- to 16-kHz high-frequency range is recommended to test the earliest detection of cisplatin-induced ototoxicity or the efficacy of otoprotective agents because cisplatin-induced changes and otoprotection are represented tonotopically from high to low frequencies (Fausti et al. 1984; Campbell et al. 1996). The exact frequencies used for high-frequency audiometry can vary by the specific audiometer employed.

High-frequency audiometry can be problematic in certain patient populations because not all patients will have measurable hearing in the high-frequency range (Osterhammel 1980; Kujansuu et al. 1989); this is particularly problematic for the elderly (Stelmachowicz et al. 1989; Wiley et al. 1998). Despite these challenges,

extended high frequencies should be included as a primary or secondary outcome in cisplatin otoprotection clinical trials, with all patients who have measurable hearing at each frequency contributing shift data. Although otoprotection trials will typically focus on frequencies directly relevant for speech understanding, preventing the onset of hearing loss at the higher frequencies is clinically meaningful in that it provides proof the agent is bioavailable and effective in the ear and that it may prevent shift into the lower frequency ranges.

At the baseline visit, pure-tone air conduction testing is immediately repeated at 1 kHz and sometimes also at 2 kHz to determine if the subject or patient provides reliable responses. Responses are considered reliable if retest thresholds at both frequencies do not exceed ±5 dB of the previously obtained threshold response. This threshold reliability verification method for ototoxicity monitoring in clinical populations is based on Fausti et al. (1999) and Campbell et al. (2003); although the specific frequencies at which reliability was assessed differed across reports, the studies shared the conservative 5-dB criterion at two frequencies. Participant reliability is an important issue and the production of consistent detection responses is advisable for randomization.

6.3.1.3 Bone Conduction Threshold Testing

Bone conduction testing is measured by placing a calibrated vibrator that delivers the signal through the bone to the cochlea, bypassing the outer and middle ears. Common bone conductor placements are the mastoid and forehead. Bone conduction testing is assessed at 0.25, 0.5, 1, 2, 3, or 4 kHz if the air conduction threshold at that frequency is 15 dB HL or greater. Bone conduction threshold procedures are essentially the same as those used for air conduction threshold testing.

6.3.1.4 Pediatric Testing

Monitoring ototoxicity in pediatric patients generally requires special testing techniques if the child is behaviorally below expectations of a child 4–5 years of age. Children may need to be tested using play audiometry with two examiners or conditioned orientation response audiometry with a special pediatric audiometric test environment and toy reinforcements. If the child will not use earphones, sound field stimuli may be necessary.

Children receiving cisplatin can be particularly difficult to test if they have brain cancers. A speedy and experienced audiologist is necessary to obtain as much information as possible. Several studies have obtained excellent cisplatin ototoxicity monitoring data in children using a combination of techniques including air conduction thresholds in the conventional and high-frequency ranges and otoacoustic emissions as described in Sect. 6.3.1.9. However, the most sensitive

indicator of early ototoxic change in children is high-frequency audiometry (Knight et al. 2005, 2007).

6.3.1.5 Immittance Audiometry (Tympanometry)

Immittance audiometry, or tympanometry, is the measurement of sound reflection from the tympanic membrane as changes in air pressure occur. This procedure can be used to assess the outer and middle ear system including the Eustachian tube. Immittance audiometry does not measure ototoxicity directly but can help determine if outer or middle ear dysfunction is causing, or contributing to, hearing loss independent of any cisplatin effects. It is particularly valuable for cisplatin-treated patients because they are immunosuppressed, may be hospitalized, and are vulnerable to infections such as otitis media.

To measure tympanometry, a soft plastic probe is first inserted in the ear canal until an airtight seal is obtained. Then, a probe tone of about 226 Hz is presented into the ear canal while the air pressure of the external ear canal is altered from +200 to −400 dekapascals (daPa). The maximum compliance peak occurs when the ear canal and middle ear air pressures are equal, thus maximizing acoustic transmission through the middle ear.

The compliance peak indicates the pressure of the middle ear and implies the efficacy of Eustachian tube function. The height of the compliance peak reflects the mobility, or conversely, the stiffness of the tympanic membrane and middle ear. For clinical trials or to standardize procedures across sites, tympanometry screeners can provide fast, easy, and standardized measures with a simple "pass" or "fail" determination.

6.3.1.6 Speech Reception Threshold Testing

Speech reception threshold (SRT) is the softest intensity sound at which a subject repeats back spondee words (bisyllabic words with equal emphasis on both syllables) at least 50 % of the time. In some cases (e.g., very poor word recognition or very ill subject), a limited set of words may be used, typically six. Procedures are described in more detail in ASHA (1988).

Speech reception threshold testing is used as cross check for the reliability of pure-tone air conduction audiometry thresholds and includes checking for malingering. In addition, SRTs provide the basis for determining the sensation level for measuring word recognition, which is typically conducted at 25 or 40 dB above the SRT. Sensation level (SL) is the difference between the signal delivery level and the subject's threshold for that signal, i.e., a 25-dB SL word recognition test includes words presented at 25 dB above the SRT.

6.3.1.7 Word Recognition

The primary purpose of the word recognition test is to estimate the ability to understand and repeat single-syllable words presented at conversational or other suprathreshold levels. Word recognition word lists are phonetically balanced, meaning that they contain the phonemes of that language in the same frequency that those phonemes appear in that language.

Word recognition should be determined using recorded word lists so that speaker variables do not influence comparative results on subsequent testing. However, some children respond better to live voice. Frequently used sensation levels are 40 or 25 dB SL to increase the sensitivity of the test to hearing changes. If the recommended decibel SL is uncomfortably loud for a given patient (i.e., significant sensorineural hearing loss with recruitment), word recognition is then tested at the subject's most comfortable listening level. Sensation level is based on SRT so the level automatically adjusts if hearing loss develops during the course of the study as repeat SRTs are determined. Recorded 50-word lists should be employed unless the patient factors require live voice or half (25) word lists. However, to determine whether or not a significant change in word recognition has occurred, full 50-word lists are required to be used with standardized interpretation norms (Thornton and Raffin 1977).

6.3.1.8 Follow-up Procedures

Audiology reassessments are repeated at each follow-up visit. Follow-up visits are typically scheduled just before each round of chemotherapy and at a postdrug time point of 1–3 months. However, monitoring, particularly in children, is desirable for at least 5 years to check for progression. Comparisons of audiology assessments at these visits are made to the baseline assessment. Bone conduction thresholds, speech reception thresholds, and word recognition measures are generally repeated only if there is a significant threshold change (i.e., meeting ASHA criterion values) and the change is replicated within 24 h. If a change is detected, tympanometry testing to assess middle ear function is also repeated.

Word recognition scores are not generally used to determine if ototoxicity has occurred or if an otoprotective agent is effective. Rather, word recognition scores are used to help determine the impact of any hearing loss that does occur on communicative function and select the strategies to best help the patient.

6.3.1.9 Objective Measures

Otoacoustic emissions (OAEs) are signals generated by the cochlear outer hair cells and transmitted out through the middle ear system to a sensitive, low-noise recording microphone in the external auditory meatus. Several types of OAEs are found in humans, including spontaneous OAEs, sustained frequency OAEs

(SFOAEs), transient OAEs (TEOAEs), and distortion product OAEs (DPOAEs). However, only TEOAEs and DPOAEs are commonly used in audiologic clinical evaluations (for review, see Glattke and Robinette 2007).

TEOAEs and DPOAEs are evoked emissions, meaning that they occur in response to external stimuli, generally presented to the external auditory meatus. TEOAEs occur in response to transient signals, usually a broad-spectrum click, thus eliciting a broad-spectrum cochlear outer hair cell response. DPOAEs can be more frequency specific because they are elicited by two simultaneous tones of longer duration than the click used for TEOAEs. The primary tone is referred to as F_1, which is the lower frequency of the pair and the higher frequency is referred to as F_2. The tone pair elicits responses predominantly at the frequency $2(F_1 - F_2)$ but the responses are commonly listed according to the geometric mean (GM) frequency which is $(F_1 + F_2)/2$.

DPOAEs are more commonly used in ototoxicity monitoring than TEOAEs because they provide greater frequency response specificity and better sensitivity for the high-frequency region, which is most sensitive to ototoxic changes (Knight et al. 2005, 2007). In addition, DPOAE responses can often be recorded even in the presence of mild to moderate sensorineural hearing loss while TEOAEs are generally absent at any frequency region where sensorineural hearing loss exceeds approximately 30 dB HL (Lonsbury-Martin and Martin 1990; Martin et al. 1990; Probst et al. 1991).

OAE recording does have several advantages over pure-tone threshold testing because it requires no active responses from the patient and thus can be used even in very ill or even comatose patients. OAEs are quick and generally inexpensive and, although they require a quiet environment, they can be tested outside a sound booth. Both TEOAEs (Plinkert and Krober 1991; Stavroulaki et al. 1999) and DPOAEs (Mulheran and Degg 1997; Ress et al. 1999) generally change before air conduction thresholds in the conventional frequency range when ototoxicity occurs. DPOAEs generally show ototoxic change before TEOAEs (Lonsbury-Martin and Martin 2001). However, high-frequency audiometry usually provides even an earlier indication of ototoxic change than DPOAEs (Knight et al. 2005, 2007).

Although OAEs are classified as an objective measure, they are subject to several patient factors. Any patient noise or ambient noise may obscure the recording because OAEs are very low amplitude signals. Furthermore, any middle ear problem (e.g., otitis media) or ear canal blockage (e.g., cerumen) may obscure or preclude the recording because the signal must travel from the cochlea to the external auditory meatus for recording. Consequently, if a patient develops otitis media during the course of cisplatin administration, OAEs may not be a useful measure at that time. Although OAEs are not a true measure of hearing, preexistent hearing loss may preclude their recording, at least at the affected frequencies.

OAEs are an adjunct rather than a primary measure for monitoring ototoxicity. They may not reflect all changes in the auditory system secondary to cisplatin administration because they only measure cochlear outer hair cell function. Cisplatin damage to the auditory system includes multiple sites throughout the auditory system (Rybak et al. 2007), not only outer hair cell damage (Campbell

et al. 1996) but also damage to the stria vascularis (Meech et al. 1998) and auditory cortex (Gopal et al. 2012).

6.3.2 *Ototoxicity Definition and Grading Scales*

No universally accepted definition of ototoxicity exists. In addition to the ASHA (1994) and AAA (2009) criteria for early detection of ototoxicity, 15 grading scales have been developed, primarily for the purpose of grading adverse events in reports and clinical trials (for review, see Anderson and Campbell 2015). Readers may need to become familiar with them in evaluating the likely incidence and degree of hearing loss reported in previous clinical trials. Furthermore, some use more levels of ototoxicity grading that can lead to greater specificity or ability to distinguish between findings in various clinical trials groups. Some clinical trials use a four-level ototoxicity scale such as the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) versions 1.0, 2.0. 3.0, 4.0–4.03 and the Functional Hearing Loss Scale (Lewis et al. 2009; Nitz et al. 2013). Previous clinical trials have also used five-level ototoxicity scales such as the Brock (SIOP) scale (Khan et al. 1982; Brock et al. 1991) Finally, clinical trials have used seven- (Chang and Chinosornvatana 2010), eight- (Stöhr et al. 2005), and even nine-level scales such as the Muenster Scale (Schmidt et al. 2007). Some of these scales require baseline testing and others do not require baseline testing but only postdrug administration auditory testing, which can be a consideration in clinical trial design (Table 6.1).

Most, but not all, scales can be used in both pediatric and adult populations. Scales that do not require baseline hearing testing were commonly designed for pediatric populations because children are more likely to have normal hearing at baseline, although this will not always be true. Children may have preexistent sensorineural hearing loss, although much less commonly than adults, and they are

Table 6.1 Grading scales developed primarily to assess events in reports and clinical trials

Scale	Baseline testing
Khan et al. (1982)	Required
Brock et al. (1991)	Not required
CTEP: CTCAE versions 1 through 4.03	Required
Muenster Scale (Schmidt et al. 2007)	Required
Functional Hearing Loss Scale (Lewis et al. 2009)	Not required
Chang and Chinosornvatana (2010), Chang (2011)	Not required
SIOP Scale (Brock et al. 2012)	Not required
Nitz Scale (Nitz et al. 2013)	Required
WHO (1997)	Required
Stöhr et al. (2005)	Required

also more prone to conductive hearing loss, which can fluctuate during the course of chemotherapy. Baseline testing can assist in identifying and managing any conductive hearing loss that may influence the patient's hearing abilities during chemotherapy treatment. However, determination of ototoxic hearing loss is based on sensorineural hearing thresholds that are more easily monitored in the absence of a conductive hearing loss component.

For adults, scales for grading ototoxicity adverse events should always include a baseline audiologic assessment or the effect of the cisplatin cannot be easily parceled out from any preexistent sensorineural hearing loss. Furthermore, some scales were developed with a focus on cancer patients (e.g., CTEP: CTCAE scales) or even specifically for children receiving cisplatin (e.g., Brock scale, Chang scale, SIOP scale, Functional Hearing Loss Scale). The scales vary in many respects regarding the included frequencies, the hearing threshold criterion levels considered, and the number of grades, generally from four to nine classification levels, in the scale. Naturally, the variety of scales used over the years and even within the same time period in the literature renders comparisons across studies problematic. Agreement on a common scale would be a major advantage for comparing the efficacy of different drugs across otoprotection trials.

Some of the ototoxicity grading scales are widely used for cancer patients receiving cisplatin chemotherapy. The CTCAE 4.03 scale, issued June 14, 2010 (Table 6.2), has separate criteria for adults who are or are not enrolled in an ototoxicity monitoring program. Readers reviewing earlier studies will need to review

Table 6.2 CTCAE 4.03 adult grading scale

Grade	Parameters	
	Enrolled	Not enrolled
1	Adults enrolled in a Monitoring Program (on a 1-, 2-, 3-, 4-, 6-, and 8-kHz audiogram): Threshold shift of 15–25 dB averaged at two contiguous test frequencies in at least one ear	Adults not enrolled in a Monitoring Program: Subjective change in hearing in the absence of documented hearing loss
2	Adults enrolled in a Monitoring Program (on a 1-, 2-, 3-, 4-, 6-, and 8-kHz audiogram): Threshold shift of >25 dB averaged at two contiguous test frequencies in at least one ear	Adults not enrolled in a Monitoring Program: Hearing loss but hearing aid or intervention not indicated; limiting instrumental activities of daily living
3	Adults enrolled in a Monitoring Program (on a 1-, 2-, 3-, 4-, 6-, and 8-kHz audiogram): Threshold shift of >25 dB averaged at three contiguous test frequencies in at least one ear. Therapeutic intervention indicated	Adults not enrolled in a Monitoring Program: Hearing loss with hearing aid or intervention not indicated; limiting self-care activities of daily living
4	Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); nonserviceable hearing	Not specified for unenrolled

the specific version of CTCAE used in that study. Clinical researchers may use a much earlier version of CTCAE in their report compared to the publication because clinical trials may occur over a period of years and generally retain a consistent analysis method once initiated. The scales used may also vary by the primary location of the study, with studies outside the United States more likely to use WHO (1997), Stöhr et al. (2005), Muenster (Schmidt et al. 2007), or Nitz et al. (2013) scales.

6.3.2.1 Adult Grading Scales

One approach to ototoxicity monitoring in cisplatin clinical trials is to use the ASHA (1994) and AAA (2009) guidelines as a flag during the ototoxicity monitoring follow-up visits to trigger a full-scale audiologic assessment and follow-up and then use the CTCAE (Table 6.2) for the actual adverse event gradings. The CTCAE for the "unenrolled subjects" have disadvantages because they are based on highly subjective measures and they do not account for preexistent hearing loss. Not only may the subject's perception of hearing ability be subjective, but audiologists also vary in their criteria for when a hearing aid or other device/intervention is warranted. However, the CTCAE scales, preferably for subjects enrolled in a full prospective monitoring program, are among the most widely used for studies in adults.

6.3.2.2 Pediatric Grading Scales

A wide number of pediatric grading scales were originally developed for children receiving chemotherapy [e.g., Brock scale (Brock et al. 1991), Chang scale (Chang and Chinosornvatana 2010; Chang 2011), SIOP scale (Brock et al. 2012), Functional Hearing Loss Scale (Lewis et al. 2009), and CTCAE 4.03: pediatric scale (CTEP: CTCAE 2010)]. It should be noted that CTCAE 4.03 for pediatrics does require baseline assessment for the audiologic ototoxicity monitoring. Audiologists may vary regarding when they determine that a hearing aid, speech-language–related services, or a cochlear implant are indicated, which reduces the precision of ototoxicity classification for CTCAE grades 3 and 4. The pediatric CTCAE 4.03 scale is presented in Table 6.3.

A more objective scale is the SIOP Boston Scale (Brock et al. 2012). Although it does not require a baseline assessment and thus assumes normal hearing at baseline, this scale does employ conservative hearing loss criteria using 20 dB HL cutoffs. In the definition, ototoxicity is specifically based on sensorineural hearing level (SNHL) (Table 6.4).

Standardization and consensus on future ototoxicity monitoring procedures hopefully will be achieved to facilitate clinical studies and comparisons across studies. Until a universal scoring system is developed, the appropriate evaluation tool should be selected based on the study parameters.

Table 6.3 CTCAE 4.03 pediatric grading scale

Grade	Parameters (on a 1-, 2-, 3-, 4-, 6-, and 8-kHz audiogram)
1	Threshold shift of >20 dB at 8 kHz in at least one ear
2	Threshold shift of >20 dB at 4 kHz and above in at least one ear
3	Hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language–related services indicated
4	Audiologic indication for cochlear implant and additional speech-language–related services indicated

Table 6.4 SIOP Boston ototoxicity scale

Grade	Parameters
0	$\leq$ 20 dB HL at all frequencies
1	>20 dB HL (i.e., 25 dB HL or greater) SNHL above 4000 Hz (i.e., 6 or 8 kHz)
2	>20 dB HL SNHL at 4000 Hz and above
3	>20 dB HL SNHL at 2000 Hz or 3000 Hz and above
4	>40 dB HL (i.e., 45 dB HL or more) SNHL at 2000 Hz and above

6.4 Potential Otoprotective Agents

Currently, no drug is FDA approved to prevent or treat any form of hearing loss, including cisplatin-induced ototoxicity. However, a number of agents are under investigation for potential clinical prevention or possibly rescue from cisplatin-induced hearing loss. This section reviews only those agents in or approaching clinical trials. A number of additional agents are currently being investigated in the preclinical stage (for review, see Campbell and Le Prell 2012). Agents to reduce cisplatin-induced ototoxicity are being developed for either direct delivery to the cochlea through the tympanic membrane to the middle ear cavity or round window or systemic delivery by injection or oral ingestion. These methods of delivery closely follow those discussed in Chap. 5 by Lynch, Kil, and Le Prell for use in prevention of noise-induced hearing loss.

Local delivery advantageously avoids the risk of the otoprotective agent interfering with cisplatin's antitumor activity. Unfortunately, local delivery also requires either an injection through the tympanic membrane or a patent pressure equalization tube placed in the tympanic membrane to facilitate drug placement into the middle ear cavity. Some investigators are developing devices for chronic placement of round window drug delivery systems (Hoskison et al. 2013) and others are investigating magnetized nanoparticles for nonsurgical transtympanic delivery (Zou et al. 2012).

Additional considerations for local delivery of an otoprotective agent include otitis media, particularly in young children immunosuppressed by chemotherapy, loss of the protective agent by leakage through the Eustachian tube, and the

possibility that the drug delivered into the middle ear cavity will not effectively reach the round window because the presence of fluid may impede delivery. Local delivery also precludes any possibility that the protective agent could systemically protect against other types of cisplatin-induced toxicities such as nephrotoxicity, neurotoxicity, gastrointestinal toxicity, or "chemobrain." Systemic delivery, at least for some otoprotective agents, has the potential for protecting other organ systems in addition to hearing. For example, in preclinical studies, treatment with D-methionine has resulted in protection from weight loss (Campbell et al. 1996) and nephrotoxicity (Jones and Basinger 1989; Jones et al. 1991). However, the risk of antitumor interference must be carefully addressed both in preclinical, preferably in vivo, studies (e.g., Cloven et al. 2000) and carefully monitored in clinical studies.

Most, but not all, of the agents in or approaching clinical trials are antioxidants, not only because of efficacy but because of their known safety profiles. One of the agents studied the longest for protection from cisplatin-induced hearing loss is sodium thiosulfate (STS) (Otto et al. 1988; Neuwelt et al. 1996). STS is a cisplatin neutralizer (Jones et al. 1991; Church et al. 1995), and it therefore interferes with the antitumor effects that are necessary for cancer therapy. A current strategy to avoid STS tumor protection in both animal studies and clinical trials is to delay the STS administration by several hours after cisplatin dosing (Muldoon et al. 2000; Harned et al. 2008). Four clinical trials using STS as an otoprotective agent for cisplatin-induced ototoxicity are currently listed on clinicaltrials.gov. Two of the clinical trials use systemic STS (NCT00716976; NCT00652132) and two use local STS delivery (NCT01369641; NCT02281006) via eardrops or gel to the middle ear.

Amifostine has also been investigated in a number of clinical trials as a putative cisplatin otoprotective agent, but the preponderance of evidence including a meta-analysis of previous clinical trials (Duval and Daniel 2012) does not support its use as an otoprotective agent. The American Society of Clinical Oncology 2008 Clinical Practice Guideline Update Regarding Use of Chemotherapy and Radiation Therapy Protectants does not recommend amifostine as either an otoprotectant or neuroprotectant (Hensley et al. 2009).

Ebselen will be used in one active, but not yet recruiting, clinical trial to prevent cisplatin-induced hearing loss (NCT01451853). One Phase 1 safety trial was completed and published (Lynch and Kil 2005). In preclinical studies, ebselen did not interfere with cisplatin's antitumor action (Baldew et al. 1990; Lynch et al. 2005). For detailed discussion of the development of ebselen for prevention of noise-induced hearing loss, see Chap. 5 by Lynch, Kil, and Le Prell.

N-acetylcysteine (NAC) has been tested in several clinical trials for protection from permanent noise-induced hearing loss but without significant results (Kopke et al. 2015). Two studies have investigated NAC for cisplatin otoprotection with local delivery via transtympanic injections, using the opposite ear as a control. One study reported statistically significant otoprotection but only at 8 kHz (Riga et al. 2013), and the other did not find statistically significant otoprotection at any tested frequencies (Yoo et al. 2014).

D-Methionine (D-Met) is a promising otoprotective agent in Phase 3 clinical trials for protection from noise-induced hearing loss (NCT01345474). A number of

preclinical studies have demonstrated protection from cisplatin-induced hearing loss in animals using D-Met (Campbell et al. 1996, 1999; Korver et al. 2002). Data from tumor model studies do not suggest antitumor interference (Cloven et al. 2000). In a Phase 1 study, D-Met was safely administered to cisplatin-treated patients and notably reduced radiation-induced oral mucositis incidence (Hamstra et al. 2010). One Phase 2 clinical trial using oral D-Met did show statistically significant cisplatin otoprotection without antitumor interference (Campbell et al. 2009). Larger scale clinical trials are in the planning stages.

6.5 The Bench to Bedside Process

Translational research, taking a new drug from the laboratory through the clinical trial process and hopefully FDA approval, is frequently called "valley of death" research (Butler 2008). Translational research is usually both complicated and expensive, as it is necessary to ensure that any new clinical therapeutic is both safe and effective. The laboratory or clinical researcher wishing to become involved in this process will generally need to partner with a team of individuals skilled and experienced in the process. Some of the "valley of death" considerations for predicting success are reviewed in Coller and Califf (2009), including assessing if the new drug addresses a compelling health need with a strong rationale and a significant improvement over current therapies; assessing if the potential market and intellectual property protection provides a sufficient financial basis for the product to be cost effective; assessing the animal and human data for probable safety and efficacy; assessing the likelihood of adequate drug delivery at the intended target; and assessing the need for and likelihood of obtaining a suitable corporate partner and whether or not an acceptable pivotal clinical trial can be designed and completed. Many of these issues are reviewed in more detail in Chap. 2 by Le Prell.

For information regarding the types of information that must be prepared and gathered for the drug approval process, the FDA's website provides a wealth of information and contacts to help and inform individuals with a promising new drug that could have significant clinical impact (Food and Drug Administration 2015). For additional discussion of the FDA's role and recommended resources, see Chap. 5 by Lynch, Kil, and Le Prell and Chap. 8 by Staecker, Klickstein, and Brough.

One approach is for the new investigator to read the requirements for an investigational new drug (IND) application and then read the various FDA guidances regarding each required section. In addition, the FDA offers and recommends a pre-IND consultation and provides a list of contacts for the various drug development areas to assist the applicant through the Center for Drug Evaluation and Research (CDER).

Three types of IND applications may be filed, but for a new otoprotective agent for prevention of cisplatin-induced ototoxicity, the applicant will probably file an

investigator-initiated IND application that can be filed to study an unapproved drug or a drug that has been previously approved for a different indication.

As per the FDA website, the IND application must contain information in three broad areas:

1. Animal pharmacology and toxicology studies. These studies are generally performed in laboratories that meet good laboratory practices (GLP) standards. Usually they include at least two species, which are often rat and dog. The purpose of the preclinical data is to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experiences with the drug in humans (often foreign use). These data may also be used in the dose justification for the proposed clinical trial, although dose–response curves may also be needed.
2. Manufacturing information. This information specifies the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug. For clinical trials, the drugs should be formulated according to good manufacturing practices (GMP) standards in an approved facility.
3. Clinical protocols and investigator information. The IND application must provide detailed protocols for all proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks and whether they are designed to adequately obtain and analyze the information that is needed for that particular clinical trial. For example, a Phase 1 clinical trial will focus on human safety while a Phase 2 trial will include efficacy data. However, all clinical trials must include safety assessments. Also, information on the qualifications of clinical investigators is required to assess whether healthcare professionals are qualified to fulfill their clinical trial duties. Healthcare professionals include physicians who oversee the administration of the experimental compound and provide medical monitoring of side effects as well as audiologists who are responsible for directly measuring cisplatin otoprotection. Finally, the protocol must clearly specify the commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), to comply fully with all the investigational new drug regulations, and to maintain subject confidentiality and complete records.

After submitting the IND application, the sponsor must wait 30 calendar days before initiating any clinical trials. During these 30 days, the FDA reviews the IND application for safety to ensure that no research subject will be subjected to unreasonable risk.

While the above information describes the general areas, a new investigator will want to read further on considerations and terminology in pharmacokinetics and pharmacodynamics (see review, by Rey 2007) to understand the various considerations including the relationship to toxicity. Additional discussion of

pharmacokinetics, pharmacodynamics, and toxicity tests are provided in Chap. 5 by Lynch, Kil, and Le Prell.

The process is challenging and often expensive and labor intensive; however, it is designed to ensure that any approved drugs are both safe and effective.

6.6 Summary

In summary, cisplatin-induced ototoxicity remains a problematic clinical issue for both pediatric and adult patients. The basic mechanisms of cisplatin-induced ototoxicity and otoprotective agents remain highly active areas of research. Standardized guidelines do exist for clinical ototoxicity monitoring for these patients. Although no consensus guidelines exist for ototoxicity monitoring in clinical trials, the clinical monitoring guidelines can be adapted for them. For adverse event grading and reporting, a number of adverse event classification systems have been reported and are available for use. Some are more commonly used than others, but usage can vary by type and location of the clinical trial.

One of the most promising areas of research for cisplatin-induced hearing loss is the progression of protective agents through the preclinical and clinical stages. No otoprotective agent is currently FDA approved to prevent or treat cisplatin-induced hearing loss. Hopefully, one or more of these agents will be approved and available for clinical use in the not too distant future to reduce the incidence of ototoxicity in these patients.

Compliance with Ethics Requirements

Kathleen Campbell is the sole inventor on the patents for D-methionine. Her patents belong to her employer SIU School of Medicine. She is also the cofounder and Chief Scientific Officer for MetArmor, Inc. which has licensed her patents from SIU.

Dr. Daniel Fox is currently the Program Manager for MetArmor team, however he had no financial affiliations during the creation of this chapter.

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Chapter 7
Past, Present, and Future Pharmacological Therapies for Tinnitus

Brian L. Allman, Ashley L. Schormans, Marei Typlt, and Edward Lobarinas

Abstract Tinnitus, the perception of a sound that has no external acoustic source in the environment, is a challenging condition to manage clinically because its etiology, perceptual characteristics (e.g., pitch and loudness), and accompanying symptoms (e.g., insomnia, anxiety, and/or depression) vary greatly among patients. Despite the long history of tinnitus, its considerable prevalence, and economic burden, there currently exists no approved drug or widely accepted treatment. As such, previous pharmacological attempts to manage tinnitus have used drugs that are approved for other medical conditions in what is considered an "off-label" approach. Broadly, these drugs have included anesthetics, antidepressants, anxiolytics, anticonvulsants, glutamate-receptor antagonists, and muscle relaxants. This chapter provides readers who are new to the field an introduction to the specific off-label drugs that have been administered for tinnitus management as well as the associated experimental rationale, patient outcomes, and relevant animal research. Furthermore, the results and recommendations of systematic reviews are summarized. Finally, where possible, discussion on each drug concludes with the treatment recommendations of the American Academy of Otolaryngology—Head and Neck Surgery Foundation. Ultimately, the authors hope that readers gain an awareness of

B.L. Allman (✉) · A.L. Schormans · M. Typlt
Department of Anatomy and Cell Biology, Schulich School of Medicine & Dentistry, Western University, London, ON N6A 5C1, Canada
e-mail: brian.allman@schulich.uwo.ca

A.L. Schormans
e-mail: aschorma@uwo.ca

M. Typlt
e-mail: mtyplt@uwo.ca

E. Lobarinas
Callier Center for Communication Disorders, University of Texas at Dallas, 1966 Inwood Road, Dallas, TX 75235, USA
e-mail: edward.lobarinas@utdallas.edu

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the history of drug therapies for tinnitus as well as the reasoning for why a certain drug may not be currently recommended, whether it be its apparent inefficacy, potential for harm, or shortcomings in the associated experimental design of the clinical trials.

Keywords Anticonvulsants • Anxiolytics • Etiology • Glutamate-receptor antagonists • Laboratory animal models • Muscle relaxants • Off-label drug therapy • Prevalence • Tinnitus • Tricyclic antidepressants

7.1 Introduction

Tinnitus, derived from the Latin word *tinnire* ("to ring"), is a condition characterized by the perception of a sound with no corresponding external acoustic source. *Objective* tinnitus represents a rare form of the condition in which an individual (and perhaps an observer using a stethoscope) can hear a real sound that is generated by his or her own internal structures, such as blood vessels or musculature near the middle ear. These sounds can be pulsatile and synchronized with respiration or heartbeat or can be continuous such as in cases of venous hum. Conversely, *subjective* tinnitus is a much more common condition that describes a phantom sensation that can be heard only by the afflicted individual. Often, subjective tinnitus is perceived as a ringing or buzzing in one or both ears. Objective and subjective forms of tinnitus are not mutually exclusive, as some individuals have described experiencing both types of auditory sensations.

As described in the following sections, subjective tinnitus, henceforth referred to only as "tinnitus," is a challenging condition to manage clinically because its etiology, perceptual characteristics (e.g., pitch and loudness), and accompanying symptoms (e.g., insomnia, anxiety, and/or depression) vary greatly among patients. Ultimately, translational research on tinnitus is focused on identifying its neural basis as well as finding safe and effective treatment strategies, as both of these goals remain elusive. To this end, researchers have developed laboratory animal models capable of screening treatment strategies in hopes of translating these findings into improved therapies for tinnitus sufferers.

Moving beyond anecdotal reports, several clinical trials have been conducted to determine the efficacy of various drugs at suppressing tinnitus. However, because there currently exists no approved drug treatment for tinnitus, these previous pharmacological attempts to manage tinnitus have used drugs that are approved for other medical conditions in what is considered an "off-label" approach. It has been estimated that more than four million off-label prescriptions are written for tinnitus each year in the United States and Europe (Vio and Holme 2005), and there are likely even more supplements sold commercially without a prescription. Off-label drugs requiring a prescription have included anesthetics, antidepressants, anxiolytics, anticonvulsants, glutamate-receptor antagonists, and muscle relaxants.

This chapter provides an introduction to the specific off-label drugs that have been investigated for tinnitus management as well as the associated experimental rationale, patient outcomes, and relevant animal research. In addition to providing an update to previous comprehensive articles on the pharmacotherapy of tinnitus (Salvi et al. 2009; Langguth and Elgoyhen 2012), this chapter also summarizes the results and recommendations of available articles from the Cochrane Database of Systematic Reviews, as these review articles are recognized as providing an in-depth critique of the primary research devoted to evidence-based healthcare (http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html). Finally, where possible, the discussion on each drug concludes with recommendations from the American Academy of Otolaryngology–Head and Neck Surgery Foundation, which published an exhaustive, evidence-based Clinical Practice Guideline for the evaluation and treatment of tinnitus (Tunkel et al. 2014).

As outlined in Sect. 7.4, most of the clinical trials examining off-label drugs have failed to provide compelling evidence that tinnitus can be routinely managed with pharmacotherapy in the majority of patients. It is important to note, however, that a considerable degree of the uncertainty regarding the efficacy of these various drugs likely can be attributed to methodological limitations in the clinical trials themselves (e.g., randomization or inadequate placebo controls). Thus, this chapter provides the reasoning for why a certain drug may not be currently recommended, whether because of its apparent inefficacy, potential for harm, or shortcomings in the associated experimental design of the clinical trials, as these collective reasons have contributed to the difficulty in translating drug therapies for tinnitus into evidence-based practice (Weaver 2014).

7.1.1 Tinnitus Prevalence

A large proportion of adults will experience tinnitus at some point in their life, albeit perhaps only for a short time and likely as a consequence of exposure to loud noise or transient vascular changes. However, in approximately 10 % of the general population (Heller 2003), tinnitus is a chronic condition that can lead to difficulty concentrating, insomnia, and, in some cases, severe forms of anxiety and depression, all of which can negatively affect quality of life (Erlandsson and Hallberg 2000). According to data derived from the 2011–2012 National Health and Nutrition Examination Survey (NHANES), conducted by the US Centers for Disease Control and Prevention, it is estimated that approximately 20 million Americans experience chronic tinnitus, with 2 million people suffering from extreme and debilitating cases (https://www.ata.org/understanding-facts). Other analyses of NHANES data (1994–2004), which is based on a sample of 14,178 completed surveys, estimate that approximately 50 million American adults have experienced some form of tinnitus, with 16 million experiencing frequent tinnitus within the past year (Shargorodsky et al. 2010). Similar rates of tinnitus prevalence and disturbance ($\sim$5–16 % of population, with $\sim$1–4 % disabled) have been

reported in European (Axelsson and Ringdahl 1989; McCormack et al. 2014), African (Khedr et al. 2010), Asian (Xu et al. 2011; Jalessi et al. 2013), and South American (Oiticica and Bittar 2015) countries, making tinnitus a global concern.

7.1.2 Tinnitus Diagnosis and Measurement

A comprehensive tinnitus diagnosis should involve a multidisciplinary approach because tinnitus can be a symptom of various underlying pathologies (e.g., hearing loss, neurovasculature abnormalities, head/neck trauma, retrocochlear pathology, etc.) and it can be accompanied by several different comorbidities (e.g., anxiety, depression, and/or insomnia) (Langguth et al. 2013). Although it is beyond the scope of the present chapter to provide a detailed description of the recommended diagnostic procedures, it is worth introducing the stepwise decision-tree approach for clinical management of tinnitus that has been proposed from the Tinnitus Research Initiative (TRI)—a leading, nonprofit foundation dedicated to supporting collaborative research to improve the understanding of the pathophysiology of tinnitus as well as the development of effective treatments. Ultimately, the TRI recommends that the basic diagnostic steps include a case history, clinical ear examination, audiologic testing, and assessment of tinnitus severity (Langguth et al. 2013).

Regarding the measurement of tinnitus, there are two important components: perception and reaction (Tunkel et al. 2014). Tinnitus perception refers to the acoustic aspects of the phenomenon, such as its loudness, pitch, and temporal features. These can be, and often are, assessed with psychoacoustic measures, including matches to real acoustic stimuli (Henry et al. 2014). In contrast, the patient's reaction to his or her tinnitus encompasses the person's emotional well-being and is reflected in subjective measures of how bothersome his or her tinnitus is (i.e., its severity), measures usually derived from in-depth interviews or questionnaires (Shi et al. 2014). Several questionnaires are available for assessing the severity and effects of tinnitus. These include the Tinnitus Handicap Questionnaire (Kuk et al. 1990); the Tinnitus Reaction Questionnaire (Wilson et al. 1991); the Tinnitus Handicap Inventory (Newman et al. 1996), which is the most commonly used questionnaire in the United Kingdom (Baguley et al. 2013); and more recently, the Tinnitus Functional Index (Meikle et al. 2012; Henry et al. 2015).

Because the psychoacoustic measurements of tinnitus do not fully explain the subjective "feelings" or emotional toll of its severity (Meikle et al. 1984; Folmer et al. 1999), clinicians are encouraged to include measures of both the patient's perception and reaction to his or her tinnitus in a comprehensive evaluation (Langguth et al. 2011). The use of a validated tinnitus questionnaire is important in providing a baseline for assessing the efficacy of treatment in clinical trials related to the subjective elements of tinnitus (Tunkel et al. 2014). That said, given the number of questionnaires available, it can be difficult to compare across studies if

each clinical trial evaluates the treatment outcome using a different, albeit validated, questionnaire. Also important to consider when evaluating the potential efficacy of putative treatments is the potential for placebo effects to confound the interpretation (Duckert and Rees 1984).

7.1.3 Tinnitus Etiology

Tinnitus is a difficult condition to manage clinically because its perceptual characteristics, accompanying symptoms, and etiology vary considerably among patients. For example, tinnitus is often comorbid with other conditions such as noise- or age-related hearing loss, hyperacusis, head/neck injury or age-related issues, temporomandibular joint disorders, neurovascular complications, or insult to the auditory nerve (e.g., via microvasculature compression or vestibular schwannoma) (Langguth et al. 2013). Further contributing to the heterogeneity of tinnitus and its associated symptoms is the finding that approximately 40 % of patients report that there was "no related onset factor" associated with their tinnitus (for review, see Elgoyhen and Langguth 2010).

It is commonly acknowledged that hearing impairment and increasing age are significant risk factors for tinnitus (Ahmad and Seidman 2004). Furthermore, a study among American adults reported that a history of loud leisure-time, firearm, or occupational noise exposure is also associated with increased odds of experiencing tinnitus (Shargorodsky et al. 2010). As exposure to loud noise is a pervasive hazard for military personnel (Grantham 2012), it is well established that servicemen and servicewomen find themselves at increased risk for tinnitus (Theodoroff et al. 2015). Among returning veterans from conflicts in Iraq and Afghanistan, 49 % of personnel exposed to blast trauma developed tinnitus (Cave et al. 2007).

In further considering the relationship between hearing loss and tinnitus, a retrospective observational study on 286 tinnitus patients found that the tinnitus pitch was in the same range and correlated significantly with the frequency of the maximum hearing loss (Schecklmann et al. 2012). That said, an abnormal audiogram is not always detected in tinnitus patients (Langguth et al. 2013), particularly if the pure tones used are within the conventional range of audiometric testing (125–8,000 Hz). Several studies have confirmed, however, that when the hearing thresholds of these tinnitus patients are assessed above 8,000 Hz, hearing impairments are indeed revealed and the pitch of the tinnitus is near or at the region of these higher frequencies (for review, see Henry et al. 2014), findings that further support the role of hearing loss in tinnitus etiology.

In addition to hearing loss, symptoms of depression are also commonly reported in patients who seek medical attention for their tinnitus. It remains challenging, however, to accurately estimate the prevalence of depression in patients with tinnitus from the general population because of research selection bias. Patients recruited for studies are often those who are actively, and sometimes aggressively, seeking treatment for their tinnitus and its associated symptoms (e.g., depression,

anxiety, and/or insomnia). This self-selection bias may lead to an overestimation of prevalence of depression among individuals with tinnitus. Despite variability in the rates of depression documented in the literature (14–80 %; Langguth et al. 2011), several studies report a positive correlation between depression and tinnitus-related severity and annoyance (for review, see Pinto et al. 2014). From these findings, an important clinical question emerges: Is there directionality to this comorbidity of tinnitus and depression? For example, are patients with depression more vulnerable to developing tinnitus? Or is depression simply a reflection of a learned distress response brought on by tinnitus? In a comprehensive review of the literature, Langguth and colleagues (2011) proposed that the comorbidity of tinnitus and depression does not likely occur by chance nor does depression simply manifest as a reaction to one's tinnitus. Instead, they contend that tinnitus and depression are pathophysiologically interrelated because the two disorders share similar alterations in neurotransmitter systems, and imaging studies have revealed overlap of brain circuits that are activated in both tinnitus and depression (see Sect. 7.3 for the putative mechanisms of tinnitus). That said, the extent to which there may be interrelation will need to be thoroughly evaluated given that the majority of individuals with depression do not have tinnitus. In addition, there are many individuals with tinnitus who are not being treated for depression by a healthcare provider. Thus, it is possible that those subjects who actively seek treatment are suffering from both tinnitus and depression, but their symptoms, although related, do not share a common pathway. It is reasonable, however, to consider that tinnitus can exacerbate and/or lead to depression and that depression can make coping with tinnitus more difficult or render individuals more susceptible to tinnitus distress.

Anxiety, another psychological condition, has also been identified as a significant risk factor for tinnitus severity (for review, see Langguth et al. 2011). For example, in a study of patients deemed to be at high risk for severe or disabling tinnitus (via the Tinnitus Severity Questionnaire), it was estimated that approximately 50 % had a concurrent anxiety disorder (Zöger et al. 2006). Subjects included in this study had pure-tone averages better than 50 dB hearing level (HL) in their worse-hearing ear (Zöger et al. 2006). Additional studies have identified a relationship between tinnitus distress and *anxiety sensitivity*, whereby anxious patients misattribute the bodily sensations of their tinnitus as a sign of a potentially harmful underlying condition that serves to heighten their anxiety (Hesser and Andersson 2009; Gül et al. 2015). Given the comorbidity of anxiety and tinnitus, it is not surprising that the intensity of a patient's tinnitus can be exacerbated by stressful events (Hébert and Lupien 2009). Moreover, a large-scale epidemiological study reported a linear association between the presence of tinnitus and the magnitude of long-term stress (Hasson et al. 2011). It is worth noting, however, that such human correlational studies are unable to distinguish cause and effect, such as whether tinnitus increases stress levels, if stress causes tinnitus, or if both are related to some third unmeasured factor (Mazurek et al. 2012; Canlon et al. 2013).

7.1.4 Economic Burden of Tinnitus

According to a 2013 report, tinnitus and hearing loss have emerged as the top two service-related disabilities for which American veterans received compensation from the US Department of Veterans Affairs (2014). Consequently, the financial cost associated with tinnitus compensation for the military has soared, totaling $300 million for the 2010 fiscal year under the major disability only for hearing loss category and $920 million overall individual claims (Department of Veterans Affairs Compensation Benefits Report FY 2010). It is important to note, however, that the economic burden of tinnitus-related disability is likely not restricted to military agencies, as it has been estimated that approximately 1 % of the general population suffers from debilitating tinnitus (McCombe et al. 2001) that can impair their workplace productivity and earning potential (Henry et al. 2005). For example, based on a large cohort study, patients with tinnitus have a greater than a threefold increased risk of going on to receive a disability pension compared to individuals who went on sick leave for a non-otology/audiology diagnosis (Friberg et al. 2012).

7.2 Laboratory Animal Models of Tinnitus

Over the past approximately 25 years, a number of laboratory animal models have been developed to investigate the pathophysiology of tinnitus, with the vast majority using rodents (e.g., rats, mice, and hamsters). It is important to note that before assessing any changes in cochlear function or brain activity that may underlie tinnitus, it was necessary that researchers first overcome the challenge of developing behavioral tests that were capable of determining whether or not animals were actually experiencing tinnitus. Jastreboff and colleagues (1988) were the first to establish an animal model of tinnitus in the rat. Subsequently, a variety of behavioral paradigms have been developed to screen rats and other laboratory animals for noise- and drug-induced tinnitus (for review, see Heffner and Heffner 2012; Stolzberg et al. 2012; Hayes et al. 2014). In general, the majority of the initial behavioral paradigms involved training an animal to perform a distinct behavior when sound was present in its environment and a different behavior during quiet conditions. Then, following a noise or drug exposure, if the animal mistakenly behaved during quiet conditions as though it was "hearing" an acoustic stimulus, the researchers concluded that the animal was experiencing tinnitus. There are a number of inherent challenges in developing these models in that the conditions under which animals are trained to respond or withhold responding are absent of acoustic stimuli. Then, presumably, when the animal no longer perceives quiet because of tinnitus, it behaves as if there were a real sound in the background. Ultimately, based on these behavioral paradigms, it is now well established that, similar to humans, excessive exposure to loud noise or ototoxic drugs (e.g., sodium

salicylate, the active component of aspirin) can induce tinnitus in laboratory animals.

To date, one of the most commonly used behavioral tools to screen animals for noise-induced tinnitus has been the gap prepulse inhibition of the acoustic startle (GPIAS) paradigm. The technique was developed by Turner and colleagues (2006) and was based, in part, on earlier work by Ison and colleagues (Ison 1982; Ison et al. 2002). In contrast to the aforementioned behavioral tests that involved training animals before inducing tinnitus, the GPIAS paradigm does not require overt training, as it is based on an animal's reflexive motoric response (a "flinch") to a loud sound. The amplitude of this reflexive acoustic startle response can be modified by presenting an audible acoustic cue before the onset of a startling stimulus. In the GPIAS paradigm, the cue is a silent gap in a continuous background noise. Alternatively, acoustic cues such as tones and noise bursts in quiet presented prior to a startling stimulus can also modify the acoustic startle reflex amplitude. A key feature of the GPIAS paradigm is the consistent finding that if an animal is able to detect a brief silent gap in a background sound before the loud startle stimulus, its acoustic startle amplitude will be attenuated or abolished (i.e., it "flinches" less in response to the loud sound). Supporters of the GPIAS paradigm suggest that if the animal's tinnitus pitch is qualitatively similar to the background sound, then it should be unable to detect the silent gap, and consequently, its acoustic startle amplitude will not be suppressed or will be suppressed to a lesser degree. This difference is important because changes in startle amplitudes after "tinnitus" induction could result from generalized changes across all trials or the results of trial averages that include trials in which animals detected the cue and trials in which the animals completely failed to detect the cue.

It should also be noted that the notion of tinnitus "filling in" the silent gap has been seriously challenged in human (Fournier and Hébert 2013; Boyen et al. 2015) and laboratory animal studies (Hickox and Liberman 2014; Radziwon et al. 2015). Moreover, a study on rats identified an additional caveat of the GPIAS paradigm: it is susceptible to "false positives" for tinnitus following hearing loss (Lobarinas et al. 2013). To illustrate this point, a temporary and reversible unilateral, conductive hearing loss was produced in rats by plugging one ear with a silicone elastomer. When tested under the GPIAS, paradigm animals showed behaviors consistent with "tinnitus" as evidenced by a lack of difference between the trials that contained a gap, relative to trials with no gap (i.e., it appeared that the animals could not detect the gap). However, on closer inspection, the presence of the earplug had significantly reduced the response to the loud acoustic startle stimulus under both cued and uncued trials. If the startling stimulus no longer produced a startle response, there was nothing from which to inhibit and thus a lack of difference. It did not matter whether the trial was cued or not as the animals no longer exhibited a robust startle response. When the same earplugged animals were tested under the same gap or no-gap conditions but with a startle response induced with a tactile stimulus (i.e., a 10–12 PSI airpuff to the back of the neck), the animals readily detected the gap cue prior to the air puff and showed robust inhibition. These results highlight some of the challenges associated with developing animal models and the

need to both build robust evidence and critically evaluate existing evidence. Clearly, a failure to accurately screen animals for the presence/absence of tinnitus is a significant and persistent concern for researchers who intend to subsequently investigate its pathophysiology or possible drug therapies for translational research aims.

In addition to the challenges of accurately screening laboratory animals for tinnitus (for review, see Heffner and Heffner 2012; Eggermont 2013), it is important to note that current models were designed to assess the perception of tinnitus. In contrast, the emotional and/or cognitive effects of tinnitus have not been explored in animals. This could be viewed as either an advantage or a disadvantage. If the goal is to determine whether a particular therapy reduces the actual sound of tinnitus, then the current animal models may be an attractive tool to determine efficacy. However, if tinnitus is defined by the negative psychological reaction experienced by patients who are unable to habituate to the sound of tinnitus, then animal models would be of limited use. These different viewpoints also significantly affect efforts at studying tinnitus, as efficacy may be defined by a reduction or elimination of the tinnitus sound or by a reduction in the psychological reaction to tinnitus.

Despite the aforementioned challenges, there are still significant and distinct benefits of using laboratory animal models for translational tinnitus research. For example, animal models allow researchers to (1) precisely control how tinnitus is induced; (2) invasively record neural activity from various brain regions using microelectrodes; and (3) safely evaluate the efficacy of novel treatments for reducing the tinnitus percept. In Sect. 7.4, we present the outcomes of various animal studies that have either screened drugs that had already been administered to humans for tinnitus (e.g., memantine and cyclobenzaprine) or drugs that have yet to be tested in clinical trials for tinnitus (e.g., retigabine).

7.3 Putative Mechanisms of Tinnitus

At present, the mechanisms underlying tinnitus continue to remain elusive. It is unlikely that the signal for tinnitus simply originates in the cochlea and travels to the brain via the auditory nerve because, although some patients' tinnitus improved after their auditory nerve had been surgically transected, other patients experienced persistent (or worsened) tinnitus following surgery (House and Brackman 1981). These data suggest that some forms of tinnitus are generated centrally or perpetuated even in the absence of a connection to the cochlea (Eggermont et al. 2012). Further support of a central generator for some forms of tinnitus has emerged from several neuroimaging studies (Melcher 2012). These studies show that brain activity is enhanced in auditory and nonauditory areas in patients with tinnitus relative to control subjects without tinnitus (for review, see Adjamian et al. 2009;

Lanting et al. 2009). Ultimately, it has been suggested that although tinnitus may indeed be triggered by cochlear damage, tinnitus can be perpetuated by the subsequent plastic changes that occur in the central auditory system independent of the periphery (Henry et al. 2014).

Based on several decades of research using both invasive neural recordings in laboratory animals as well as noninvasive recordings and neuroimaging techniques in humans, a variety of central mechanisms of tinnitus have been proposed (see Eggermont et al. 2012). In a comprehensive review, Henry et al. (2014) outlined these putative tinnitus mechanisms within a framework of various neural models, including (1) dorsal cochlear nucleus hyperactivity, (2) tonotopic reorganization, (3) central gain, (4) neural synchrony, and (5) network models. The dorsal cochlear nucleus (DCN) hyperactivity model of tinnitus suggests that hearing impairment causes a loss of inhibition in this early relay nucleus, leading to an increase in spontaneous neural activity that ascends along subsequent structures in the central auditory system and ultimately manifests as tinnitus (Kaltenbach et al. 2005; Dehmel et al. 2012). Tonotopic map reorganization occurs at each relay nucleus throughout the central auditory system as a consequence of the sensory deafferentation caused by the hearing loss. There is speculation that this reorganization, typically characterized by an expansion of the representation of frequencies spared after cochlear damage, results in the phantom perception of tinnitus (Rauschecker 1999). The central gain model of tinnitus proposes that following the reduction in sensory input from the cochlea, structures in the central auditory system become hyperactive owing to homeostatic mechanisms that are triggered to preserve neural sensitivity but do so at the expense of also amplifying "neural noise" (i.e., tinnitus) (Noreña 2011). Based on results from electro- and magnetoencephalography in humans, neural synchrony models refer to the aberrant cortical oscillatory activity that is believed to arise from hyperpolarization of the thalamus following sensory deafferentation (Llinas et al. 1999; De Ridder et al. 2015). These changes in the thalamus result in a synchronized, bursting pattern of activity of neurons that project to the cortex, which ultimately causes abnormally synchronized cortical activity believed to contribute to the tinnitus percept (Llinas et al. 1999; De Ridder et al. 2015). Finally, network models of tinnitus are founded on neuroimaging data that reveal that more than one brain region demonstrates aberrant activity or morphology in patients with tinnitus (Leaver et al. 2011; Elgoyhen et al. 2012). For example, frontal, temporal, and parietal cortical areas have been implicated in the perception of tinnitus, whereas tinnitus distress appears to be associated with synchronized activity in the subcallosal anterior cingulate cortex, the insula, parahippocampal area, and amygdala (Langguth et al. 2011). Overall, it should be noted that the proposed neural models of tinnitus may not be mutually exclusive. For example, a loss of inhibition early in the auditory pathway or "central gain" due to homeostatic mechanisms may ultimately manifest as changes in large-scale network activity.

7.4 Off-Label Approach to Pharmacotherapy for Tinnitus

Despite the long history of tinnitus suffering and its considerable prevalence and economic burden, there is currently no FDA-approved drug for the treatment of tinnitus. Previous pharmacological attempts to manage tinnitus have instead used drugs approved for other medical conditions. Broadly, these off-label drugs have included anesthetics, antidepressants, anxiolytics, anticonvulsants, glutamate-receptor antagonists, and muscle relaxants.

Other attempts have used various dietary supplements for the treatment of tinnitus. Many of these "supplements" carry disclaimers such as, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" (US Food and Drug Administration 2015). Such statements are included because, under the Dietary Supplement Health and Education Act of 1994 (DSHEA) and current FDA regulations, these formulations are considered food and thus exempt from the rigorous labeling and testing standards applied to drugs. Because of the lack of scientific support for the use of dietary supplements (Tunkel et al. 2014), this chapter provides an overview of the off-label prescription drugs that have been examined in clinical trials as well as the scientific rationale underlying their use and the associated patient outcomes.

7.4.1 Anesthetics

Bárnáy (1935) inadvertently found that tinnitus could be suppressed with intravenous administration of the anesthetic procaine, which is commonly known as Novocain. Similar promising findings were reported over the next several decades (for review, see Melding et al. 1978). In the early 1980s, a series of clinical trials investigated the effect of intravenous administration of the voltage-gated sodium channel blocker lidocaine on tinnitus. As summarized and critiqued by Bauer and Perring (2008), these studies monitored the effect of intravenous lidocaine on tinnitus (versus a saline placebo control) 5–30 min postinfusion using a within-subjects design and found that lidocaine reduced the loudness, pitch, and annoyance of tinnitus in the majority of subjects. However, these effects were transient, and 9–32 % of subjects included in the various studies reported that their tinnitus *worsened* after lidocaine. Furthermore, the study design was compromised because most subjects experienced side effects (e.g., imbalance and speech disorders) to the lidocaine, preventing them from remaining blind to the treatment.

It has long been known that the inclusion of appropriate placebo controls is important in clinical trials that seek to evaluate drug therapies for tinnitus. Duckert and Rees (1984) suggested to patients who had previously participated in a lidocaine study that they were to again receive an injection of lidocaine but instead were unknowingly administered saline. The placebo effect influenced 40 % of subjects,

as they reported a change in their tinnitus following the placebo (saline) injection. These findings reach far beyond the evaluation of the proposed efficacy of lidocaine and serve as a cautionary note that the effectiveness of drug therapies for tinnitus may be subject to strong bias by the placebo effect.

Studies have also sought to elucidate the mechanism(s) by which intravenous lidocaine suppresses tinnitus. For example, Kalcioglu et al. (2005) investigated whether the effect of lidocaine on tinnitus suppression was due to its effect on altering otoacoustic emissions in the cochlea. Ultimately, having found similar changes in distortion product otoacoustic emission (DPOAE) measures in subjects whose tinnitus lessened with lidocaine treatment versus those whose did not, the authors concluded that lidocaine-induced suppression of tinnitus was not likely due to altered DPOAEs. Using positron emission tomography, Reyes et al. (2002) measured regional cerebral blood flow (rCBF) before and after lidocaine infusion and found that there was reduction in rCBF (and presumably neural activity) in the auditory cortex of patients who experienced a decrease in tinnitus loudness, findings that were consistent with the authors' hypothesis that tinnitus originates in the central auditory pathway rather than the periphery. It is important to note, however, that these conclusions cannot rule out potential peripheral effects of lidocaine on auditory nerve fibers, synapses, or inner hair cells.

With respect to efficacy, the potential usefulness of intravenous lidocaine as a treatment for tinnitus is strongly diminished by its unwanted side effects, transient nature, increase in tinnitus among some participants, and impractical intravenous route of delivery outside a clinical setting. Despite these limitations, because a significant proportion (40–82 %) of subjects in the studies summarized by Bauer and Perring (2008) reported a reduction of tinnitus following intravenous lidocaine administration, these findings have been put forth in general support of the contention that tinnitus may indeed be treated with pharmacotherapy (Langguth and Elgoyhen 2012). Perhaps future studies will be able to offset the clear drawbacks of intravenous lidocaine administration while preserving its promising effects at silencing tinnitus.

7.4.2 Tricyclic Antidepressants

If, as suggested, tinnitus and depression share similar pathophysiology (Langguth et al. 2011), it is reasonable to ponder whether the drugs that effectively treat depressive symptoms may also be effective at managing tinnitus loudness and/or severity. To date, a variety of tricyclic antidepressants have been evaluated in clinical trials to treat tinnitus, including trimipramine, nortriptyline, and amitriptyline. In a double-blind crossover trial versus placebo, trimipramine was found to be ineffective at reducing tinnitus disability owing to a lack of statistically significant results coupled with a large placebo effect (Mihail et al. 1988). Sullivan et al. (1993) found that nortriptyline showed a nonstatistically significant trend to decrease functional disability and tinnitus loudness in a 12-week, double-blind,

randomized controlled trial that included subjects with either major depression or depressive symptoms. The effectiveness of amitriptyline (10 mg; 3 times/day) was evaluated in a 10-week, randomized, open-label, placebo-controlled trial (Podoshin et al. 1995) and a 6-week, randomized, parallel, placebo-controlled single-blind study (50 mg/day for first week; 100 mg/day for 5 weeks) (Bayar et al. 2001). According to Podoshin and colleagues (1995), the majority of patients reported no improvement in tinnitus with amitriptyline treatment, whereas Bayar et al. (2001) found that a higher dose of amitriptyline resulted in a significant reduction in the subjective rating of tinnitus and its loudness as well as a reduction in tinnitus by the end of the study in 95 % of the patients (compared to 12 % of the placebo group).

Baldo et al. (2012) published a Cochrane Review on the effectiveness of antidepressants for tinnitus treatment and provided a comprehensive critique of the aforementioned studies and their outcomes. It is worth noting that Baldo and colleagues excluded additional studies that administered antidepressants because of issues such as high participant dropout rate (Zöger et al. 2006; Holgers et al. 2011), lack of randomization (Sullivan et al. 1989), or failure to include a placebo control (Roberts et al. 2011). Considering the primary outcome measure to be a change in tinnitus disability, Baldo et al. (2012) concluded that the four randomized controlled trials investigating tricyclic antidepressants yielded only a slight improvement, and thus there was insufficient evidence in support of antidepressant therapy for tinnitus.

Ultimately, the clinical practice guideline published by the American Academy of Otolaryngology–Head and Neck Surgery Foundation does not recommend antidepressants for treating tinnitus (Tunkel et al. 2014). That said, given the possibility that tinnitus patients who have sought medical attention may also have depressive symptoms, it has been suggested that a multidisciplinary diagnostic approach be used. A team approach involving collaboration between audiologists, otolaryngologists, and mental health professionals is strongly recommended for patients with severe tinnitus as well as those with histories suggestive of comorbidity with anxiety or depression (Pinto et al. 2014).

7.4.3 Benzodiazepines

Based on the proposed relationship between stress and tinnitus, researchers have sought to determine the efficacy of anxiolytic (antianxiety) drugs on tinnitus and its associated symptoms. Several clinical trials for tinnitus have been conducted using benzodiazepines, a class of psychoactive drugs with anxiolytic (as well as anticonvulsant and sedative) properties. Benzodiazepines act as positive allosteric modulators of γ-aminobutyric acid ($GABA_A$) receptors, thereby enhancing GABA-mediated inhibition. In addition to their anxiolytic effects, it has been suggested that benzodiazepines could suppress tinnitus by increasing inhibitory neurotransmission in the central auditory system, thereby offsetting the

hyperexcitability that has been implicated in tinnitus pathophysiology (Jufas and Wood 2015). In further support of the possible therapeutic potential of benzodiazepines, an imaging study found that patients with tinnitus have a reduction in benzodiazepine-binding sites in the medial temporal cortex, as assessed with single-photon emission computed tomography and a benzodiazepine radioligand (Shulman et al. 2000).

In a systematic review, Jufas and Wood (2015) considered the strength of the evidence for benzodiazepine use in tinnitus management and weighed that against the associated risks. The authors summarized and critiqued six studies (outlined below) investigating various benzodiazepines, including diazepam (Valium), alprazolam (Xanax), and clonazepam. Collectively, these studies used a variety of outcome measures, such as audiometry, visual analogue scales, the Tinnitus Handicap Inventory, and an assessment of tinnitus loudness, to determine the efficacy of the drug therapy.

Diazepam is mainly used to treat anxiety and insomnia. Studies conducted in the early 1980s found that diazepam was ineffective at managing tinnitus in a double-blind crossover trial (Kay 1981), as well as in a single-blind comparison of participants (Lechtenberg and Shulman 1984).

Alprazolam significantly reduced tinnitus loudness in a 12-week, double-blind, placebo-controlled study where the dosage was adjusted (0.5–1.5 mg/day) for each participant (Johnson et al. 1993). Although the majority of participants improved, this study has been challenged because of its individualized dosing regimen and lack of inclusion of a validated tinnitus questionnaire as an outcome measure (Salvi et al. 2009). It appears that these concerns are warranted, as Jalali and colleagues (2009) reported that alprazolam (1.5 mg/day) did not significantly improve the Tinnitus Handicap Inventory score or tinnitus loudness in a randomized, triple-blind, cross-over, placebo-controlled trial. Ultimately, the conflicting results between these two studies could partly arise from differences in the patient populations. Because Jalali and colleagues (2009) excluded tinnitus patients with depressive or anxiety disorders, it is possible that the beneficial effect on tinnitus loudness observed by Johnson et al. (1993) was due to alprazolam's general anxiolytic properties on patients in their study rather than its direct effect on tinnitus pathophysiology (Jufas and Wood 2015).

Of the benzodiazepines used in clinical trials, clonazepam, which has a long plasma half-life of 20–40 h, has shown the most favorable results in reducing tinnitus. For example, in a randomized, single-blind comparison study using clonazepam, 18 of the 26 tinnitus patients experienced reduction in tinnitus volume, with more than half of these patients reporting a better than 50 % improvement in tinnitus volume using a patient assessment rating scale (1–5) (Lechtenberg and Shulman 1984). A follow-up study found that clonazepam reduced tinnitus annoyance and intensity in a randomized, single-blind, placebo-controlled trial (Bahmad et al. 2006). Similarly, Han et al. (2012) conducted a randomized, open-label, crossover comparison study and reported that 3 weeks of clonazepam significantly reduced tinnitus annoyance and loudness as well as scores on the Tinnitus Handicap Inventory.

When considering benzodiazepines for tinnitus management, it is important to be mindful of potential confounds in the aforementioned clinical trials as well as the likelihood of adverse side effects. For example, Jufas and Wood (2015) cautioned that, despite the evidence supporting the efficacy of clonazepam in three studies, none of them adequately described sufficient participant blinding to the treatment, and this may have resulted in an overestimation of the positive effects reported by the participants. It is difficult to keep participants blinded to the experimental conditions because benzodiazepines have a considerable side effect profile, including sedation, memory impairment, and slurring of speech. Benzodiazepines also carry a risk of drug dependency. Of the benzodiazepines discussed previously, alprazolam is perhaps of greatest concern because its relatively short plasma half-life (12–15 h) makes it difficult for patients to withdraw from use (Wolf and Griffiths 1991). Finally, there are reports that tinnitus can *emerge* after discontinuation of long-term use of benzodiazepines (Busto et al. 1986, 1988; Ashton 1991). Based on the results available and the potential for adverse effects, previous review articles (e.g., Langguth and Elgoyhen 2012; Jufas and Wood 2015) as well as the published Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014) have cautioned against the use of anxiolytics, such as benzodiazepines, for the treatment of tinnitus.

7.4.4 Anticonvulsants

The use of anticonvulsants is not restricted to epileptic conditions, as this class of drugs has been prescribed for various psychiatric disorders and pain syndromes (Langguth and Elgoyhen 2012). The two most commonly used anticonvulsants in clinical trials for tinnitus management have been carbamazepine and gabapentin. Carbamazepine, which is structurally similar to tricyclic antidepressants, effectively inhibits high-frequency neuronal firing by binding to voltage-gated sodium channels and stabilizing the sodium inactivation state so that fewer channels can subsequently open (Ambrósio et al. 2002). At present, the mechanism(s) underlying gabapentin's actions as an antiepileptic and antinociceptive drug is not completely understood. It has been suggested that its actions may be mediated by multiple cellular effects, which likely involve blockage of voltage-gated calcium channels (Sills 2006). Ultimately, the use of anticonvulsants in clinical trials for tinnitus management has been rationalized based on their actions in reducing the neuronal hyperexcitability proposed to underlie tinnitus.

In the late 1970s, it was reported that the subset of tinnitus patients who benefitted from intravenous lidocaine also responded positively to carbamazepine (Shea and Harell 1978; Melding and Goodey 1979). As a follow-up to these studies, Donaldson (1981) conducted a randomized, crossover trial comparing the effect of carbamazepine versus placebo. Unlike the studies in which 600–1,000 mg/day of carbamazepine was effective in approximately half of the patients tested (for review, see Salvi et al. 2009), the lower dose used in the study by Donaldson (1981)

(200 mg/day) resulted in a nonsignificant effect on tinnitus. Using a higher dose (450 mg/day) in a randomized, double-blind trial, Hulshof and Vermeij (1985) found that carbamazepine actually *worsened* tinnitus compared to placebo (albeit nonsignificantly), and the majority of patients experienced side effects such as dizziness, nausea, and headache. Finally, 300–600 mg/day of carbamazepine did not show a significant benefit in tinnitus patients as assessed with visual analog scale and Tinnitus Severity Index in a randomized, double-blind clinical trial of patients with nonpulsatile tinnitus (Gerami et al. 2012). Despite these equivocal results, carbamazepine has been reported to be effective at managing *pulsatile* tinnitus (Rahko and Hakkinen 1979; Mardini 1987), a rare form of tinnitus related to auditory nerve vascular compression in which the phantom sensation is described as sounding like clicking or a typewriter (i.e., "typewriter tinnitus"; Levine 2006).

In a series of randomized, double-blind, placebo-controlled trials, the anticonvulsant gabapentin was found to be no more effective than placebo at improving scores on the Tinnitus Handicap Inventory (Piccirillo et al. 2007; Witsell et al. 2007) or Tinnitus Severity Index (Dehkordi et al. 2011). Similarly, Bakhshaee et al. (2008) found no significant difference in the Tinnitus Severity Index or loudness perception between gabapentin and placebo in a double-blind crossover trial. In an attempt to determine the efficacy of gabapentin on different subpopulations of tinnitus patients as well as find an optimum dose for each patient, Bauer et al. (2015) conducted a double-blind crossover trial. This trial specifically segregated patients whose tinnitus was attributed to high-level sound exposure and included entry and washout placebo phases that bracketed escalating (800, 1,800, and 2,400 mg) and decreasing drug dose (900 mg) series for 3–4 weeks. Consistent with the earlier studies, Bauer et al. (2015) confirmed the limited efficacy of gabapentin in decreasing the loudness and impact of tinnitus.

Similar to the aforementioned carbamazepine clinical trials where efficacy was reported to differ with various daily dosage regimens, Zheng et al. (2008) used an animal model and found that carbamazepine at 15 mg/kg but not at lower or higher doses could reduce salicylate-induced tinnitus in rats that were assessed with a conditioned lick suppression paradigm. In contrast to the aforementioned human studies, Bauer and Brozoski (2006) found that gabapentin was effective at reversibly attenuating tinnitus in noise-exposed rats using a psychophysical procedure based on each animal's auditory discrimination ability. In fact, Bauer and colleagues (2015) acknowledged that it was the promising findings from their earlier animal work that directly informed their decision to investigate the effect of gabapentin in humans with noise-induced tinnitus. In the clinical trial, because the objective, psychometric assessment of tinnitus loudness paralleled the subjective, questionnaire-based measures of loudness, the authors suggested that gabapentin primarily impacts the "sensory" features of tinnitus. Perhaps the positive effects of both carbamazepine and gabapentin observed in animal studies relate to the fact that the behavioral paradigms assess whether or not an animal perceives a (phantom) sound, and as such, the "sensory" nature of tinnitus is measured without the secondary features commonly reported in humans, such as the attentional and emotional reaction to tinnitus. Consequently, even if the intensity of the tinnitus is

reduced, it may not be sufficient to reduce the reaction to any residual tinnitus. Alternatively, if the tinnitus signal is abolished, as some animal data suggest, there should no longer be any reaction as the phantom sound is no longer present. The discrepancies between the animal and human data highlight significant challenges and the need for the systematic steps of the translational research process.

In addition to carbamazepine and gabapentin, animal studies that focused on potential peripheral effects have investigated the anticonvulsant retigabine on tinnitus and cochlear function. Retigabine is an unconventional anticonvulsant that exerts its effects through voltage-gated potassium channels. More specifically, retigabine acts as an activator of neuronal KCNQ/Kv7 potassium channels, which on opening cause hyperpolarization, thereby lessening neuronal excitability. Retigabine was found to prevent the reduction in the compound action potential (CAP) that occurs following salicylate administration in rats, findings that the authors suggested could protect against salicylate-induced or other forms of tinnitus (Sheppard et al. 2015). Similarly, noise-exposed mice that were injected with retigabine (starting 30 min after noise exposure and continuing for 5 days) were less likely to develop tinnitus than saline-injected mice that received the same noise exposure (Li et al. 2013). It was reasoned that retigabine prevented tinnitus by offsetting the neuronal hyperexcitability and reduction of KCNQ activity that occurs in the dorsal cochlear nucleus following noise exposure and CAP suppression (Li et al. 2013). In a follow-up study from the same laboratory (Kalappa et al. 2015), the novel KCNQ-channel activator SF0034 was found to be a more potent and less toxic anticonvulsant than retigabine in rodents, which also appeared to prevent noise-induced tinnitus in mice. It is worth noting that in both studies (Li et al. 2013; Kalappa et al. 2015), the noise-exposed mice were screened for tinnitus using the gap prepulse inhibition of the acoustic startle (GPIAS) paradigm. Because the GPIAS paradigm has been challenged as a screening tool for tinnitus (see Sect. 7.2 for details), the promising therapeutic effects of KCNQ-channel activators would be strengthened by additional studies that screened for tinnitus in drug-treated animals using paradigms that rely on carefully designed, behaviorally conditioned responses that can control for the confounding effects of hearing loss. That said, the study by Li et al. (2013) has provided important first steps in understanding potassium-channel pathologies following noise exposure and may one day lead to novel pharmacotherapy for tinnitus patients (Kaltenbach 2013).

In 2011, Hoekstra et al. published a Cochrane Review evaluating the effectiveness of anticonvulsants in tinnitus patients. After excluding several studies from consideration due to such factors as lack of randomization or use of only a single dose of a given drug, seven clinical trials (encompassing 453 patients) were reviewed. Based on a meta-analysis, it was concluded that anticonvulsants showed only a small effect of doubtful clinical significance in the treatment of tinnitus, and 18 % of patients experienced side effects. Consequently, according to the Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014), anticonvulsants are not presently recommended for treating tinnitus, as they failed to show a preponderance of benefit over harm.

7.4.5 Glutamate-Receptor Antagonists

As an alternative to administering drugs aimed at enhancing GABAergic inhibition in tinnitus patients, clinical trials have also attempted to dampen tinnitus-related hyperexcitability by antagonizing glutamatergic (excitatory) neurotransmission. To this end, a variety of glutamate-receptor antagonists have been used, including memantine, neramexane, caroverine, acamprosate, and AM-101. To date, a Cochrane Review has not summarized and critiqued the previous clinical trials of glutamate-receptor antagonists, and the Clinical Guideline of Tinnitus (Tunkel et al. 2014) provides only limited commentary on acamprosate as a treatment option for tinnitus (see below).

Memantine acts as a glutamatergic antagonist by blocking *N*-methyl-D-aspartate (NMDA) channels once they have already opened rather than competing to bind at the actual glutamate-receptor site (Johnson and Kotermanski 2006). Memantine has been proposed as a putative therapeutic agent for tinnitus of cochlear origin because it is known to suppress the excitotoxicity mediated by NMDA receptors on cochlear hair cells (Oestreicher et al. 1998). Using a conditioned lick suppression paradigm in rats, Lobarinas et al. (2006) found that a low dose of memantine (3 mg/kg) failed to completely suppress tinnitus induced by sodium salicylate. However, when this same laboratory increased the dose of memantine (up to 5 mg/kg) and tested animals using the GPIAS paradigm, memantine appeared to suppress salicylate-induced tinnitus (Ralli et al. 2014). Furthermore, Zheng et al. (2012a) found that memantine treatment at the higher dose (5 mg/kg) reduced the proportion of rats that showed behavioral evidence of noise-induced tinnitus using a conditioned lick suppression model (Zheng et al. 2012a).

To date, only one clinical trial has investigated the effect of memantine on tinnitus. In a randomized, double-blind crossover design, 90 days of treatment with memantine did not improve scores on the Tinnitus Handicap Inventory beyond that of the placebo condition, and 9 % of patients experienced side effects (Figueiredo et al. 2008). Suckfüll et al. (2011) performed a double-blind clinical trial to investigate the effect of neramexane, a compound related to memantine that acts as a noncompetitive NMDA antagonist as well as a nicotinic acetylcholine-receptor antagonist, on patients with moderate to severe tinnitus. The various neramexane treatment groups (25, 50, and 75 mg/day) as well as the placebo group all showed trends for improvements in the scores reported for the Tinnitus Handicap Inventory questionnaire (THI-12) at the 16-week study end point, but the results did not reach statistical significance. At 4 weeks after the end of treatment, however, there was a significant improvement in THI-12 scores in the 50 mg/day group compared to the placebo group (Suckfüll et al. 2011). Additional clinical trials investigating the efficacy, safety, and tolerability of neramexane were completed (NCT00405886; NCT00955799) or terminated (NCT00827008) from 2006 to 2012, but it does not appear that any results have been made available as of this writing (https://clinicaltrials.gov/).

Caroverine, in addition to acting as a noncompetitive NMDA antagonist and a competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor antagonist, is a calcium channel blocker and antioxidant. Beginning in the late 1990s, a series of clinical trials investigated the efficacy of caroverine on tinnitus. These were conducted based on the rationale that tinnitus of cochlear origin occurs due to excessive glutamate neurotransmission in inner hair cells. In a placebo-controlled single-blind study, a single intravenous injection of caroverine immediately reduced both the subjective rating and psychoacoustic measurement of tinnitus in 63 % of patients in the treatment but not in the placebo control group (Denk et al. 1997). However, a separate study that used the same patient selection and treatment conditions as the protocol of Denk et al. (1997) did not find a positive effect of caroverine administration (Domeisen et al. 1998). Finally, in a proof-of-concept study, when caroverine was applied noninvasively as a 1 % topical solution to the tympanic membrane of the affected ear, 57 % of patients reported an improvement in tinnitus severity (Ehrenberger 2005).

Acamprosate, a drug approved to aid in the withdrawal of alcohol dependency, has been investigated in clinical trials for tinnitus management based on its putative actions as both a glutamate antagonist and positive allosteric modulator of GABA. In a double-blind study, 87 % of patients treated with acamprosate for 90 days reported tinnitus relief compared to 44 % of patients in the placebo group (Azevedo and Figueiredo 2007). Furthermore, a randomized, double-blind, placebo-controlled crossover trial found that there was a significant improvement in both objective measures (psychoacoustic matching of tinnitus loudness) as well as subjective measures of tinnitus (visual analog scale of tinnitus loudness and quality of life questionnaires), with more than 90 % of subjects reporting improvement in their tinnitus (Sharma et al. 2012). Moreover, these positive effects seemed to persist when the acamprosate group discontinued their treatment and crossed over to the placebo phase for an additional 45 days (Sharma et al. 2012). Despite acknowledging these seemingly favorable results, the Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014) does not recommend acamprosate treatment because of insufficient evidence of its efficacy.

Systemic administration of NMDA antagonists can cause considerable undesirable side effects, which ultimately restricts the dosing that can be administered to patients with tinnitus. As reviewed by Meyer (2013), local drug delivery via intratympanic membrane injections can be used to increase the drug concentration in the inner ear while limiting the side effects associated with systemic administration (see Chap. 5 by Lynch, Kil, and Le Prell for additional discussion). In 2011, Muehlmeier et al. evaluated the safety and local tolerance of intratympanic delivery of the noncompetitive NMDA antagonist AM-101 as a therapy for patients who have had tinnitus for less than 3 months. In a randomized, double-blind, placebo-controlled, Phase 1/2a study, they reported that intratympanic AM-101 was well tolerated by study participants (n = 16) irrespective of the administered dose, and there was some preliminary evidence of its efficacy at managing tinnitus. Based on these results, a follow-up Phase 2 clinical trial was conducted on 248 patients

(van de Heyning et al. 2014). Intratympanic administration of AM-101 resulted in a statistically significant, dose-dependent improvement in the subjective measures of tinnitus loudness, annoyance, and sleep difficulties in patients with acute acoustic trauma- or otitis media-triggered tinnitus; however, there was no overall treatment benefit on the objective measure of minimum masking level of the patients' tinnitus, suggesting that whereas patients were less distressed, the tinnitus sound itself remained unchanged (van de Heyning et al. 2014). In support for AM-101 as a potential treatment for acute noise exposure, a study on rats found that local administration of AM-101 in the cochlea reduced the level of noise-induced trauma to the inner hair cells and lessened the decline of signal transmission in the auditory nerve (Bing et al. 2015). At the time of publication of this chapter, subjects were being recruited to participate in Phase 3 clinical trials to investigate the efficacy of AM-101 to treat acute tinnitus that started as the result of an injury to the inner ear or otitis media (NCT01803646) as well as to test the safety and local tolerance of repeated treatment cycles of AM-101 (NCT01934010; NCT02040207). According to information on the NIH-sponsored website (https://clinicaltrials.gov/), final data collection from these studies is estimated to be completed in 2016.

7.4.6 Muscle Relaxants

The efficacy of muscle relaxants such as baclofen and cyclobenzaprine to treat tinnitus has been assessed in clinical trials as well as in animal studies. Baclofen is a derivative of GABA that acts as an agonist of the $GABA_B$ receptor. Although baclofen was found to reverse the noise-induced hyperexcitability of neurons in the rat inferior colliculus in a dose-dependent manner (Szczepaniak and Møller 1996), a double-blind placebo-controlled study found that 3 weeks of baclofen administration (10 mg orally twice daily for 1 week, 20 mg orally twice daily for the second week, and 30 mg orally twice daily for the third week) was no more effective than a placebo in ameliorating tinnitus in patients, as it failed to show any clinical or statistical advantage over the placebo for both subjective and objective measures of tinnitus (Westerberg et al. 1996). However, this study was challenged based on the inclusion of subjects with different types of tinnitus, which may have rendered the study underpowered (Møller 1997) and because a less effective form of baclofen containing both the L- and D-isomers was administered to patients (Smith et al. 2012). In rats, when the more potent form of baclofen (L-isomer) was administered in the days *immediately following* noise exposure, the animals still went on to develop tinnitus (Zheng et al. 2014). In contrast, in a different group of rats that had *already* screened positive for noise-induced tinnitus, the administration of L-baclofen was found to reduce their tinnitus (Zheng et al. 2012b). Finally, to further complicate the actions of baclofen on tinnitus, case reports have been published in which baclofen was found to *induce* severe tinnitus in patients who were taking the medication for alcohol dependence (Auffret et al. 2014). One must be cautious

when interpreting these case reports, however, because additional medications may have confounded the relationship between baclofen and tinnitus in these patients.

In a 12-week, open-label pilot study, the centrally acting muscle relaxant cyclobenzaprine was found to significantly reduce tinnitus severity as assessed by scores on the Tinnitus Handicap Inventory (Coelho et al. 2012). A separate pilot study found that cyclobenzaprine positively affected both the distress and intensity of tinnitus in a subset of patients; 25 % of patients responded with a 55 % reduction in tinnitus distress, whereas 24 % of patients responded with a 53 % reduction in tinnitus intensity (Vanneste et al. 2012). Consistent with the effects of cyclobenzaprine on tinnitus intensity, a study using the GPIAS paradigm found that rats with noise-induced tinnitus showed a reduction in behavior consistent with tinnitus following cyclobenzaprine treatment (Lobarinas et al. 2015). At present, the pharmacological actions of cyclobenzaprine are not completely understood. As suggested previously (Lobarinas et al. 2015), perhaps cyclobenzaprine exerts its seemingly positive effects on tinnitus by acting as an attenuator of phantom pain or as a modulator of attentional mechanisms via its effects on the locus coeruleus, a brainstem region associated with awareness, arousal, and attention. Based on the promising findings in the open-label pilot studies, it was suggested that a randomized, double-blind, placebo-controlled clinical trial was warranted to evaluate the efficacy of cyclobenzaprine as a treatment for tinnitus (Coelho et al. 2012; Vanneste et al. 2012). At the time of publication of this chapter, no clinical trial was yet underway according to an NIH-sponsored website (https://clinicaltrials.gov/).

7.5 Methodological Considerations

Collectively, the preceding sections reveal the considerable challenges associated with translating drug therapies for tinnitus management. For example, it can be difficult to even interpret the seemingly equivocal results of many of the aforementioned clinical trials owing to experimental insufficiencies and/or inconsistencies across studies. Ultimately, these methodological shortcomings contribute to the general lack of support for drug therapies in tinnitus management (Weaver 2014).

In the coming years, it is expected that there will continue to be an increase in the number of investigations devoted to uncovering the neural basis of tinnitus as well as in studies seeking to determine the efficacy of novel or off-label drugs. Moving forward, researchers using animal models are encouraged to scrutinize the validity and reliability of their chosen model for screening animals for tinnitus-like behavior, as failure to do so could confound the assessment of the efficacy of novel drugs for tinnitus treatment. When testing novel or off-label drugs in tinnitus patients, it is clear that future clinical trials should strive to avoid the methodological shortcomings of the studies discussed in this chapter, such as inadequate placebo controls or participant blinding. To that end, Jufas and Wood (2015) acknowledged that successful participant blinding can be achieved if the placebos

used in clinical trials share similar side-effect profiles to the drug under investigation.

In a much-needed call to attention, Landgrebe et al. (2012) have proposed an international standard regarding the methodological aspects of clinical trials for tinnitus. Importantly, the authors have identified several critical aspects of trial design that should be considered in future studies, some of which include (1) limiting the heterogeneity of included participants so as to reduce the variability in the findings (e.g., including/excluding tinnitus patients who also suffer from insomnia, anxiety, and/or depression); (2) using validated subjective and objective outcome measures to comprehensively assess the auditory features of the tinnitus percept, emotional features such as distress and attentional features like awareness; and (3) adjusting the treatment duration and the follow-up period to accurately assess the putative efficacy of the therapy (Landgrebe et al. 2012).

7.6 Potential Alternatives to Drug Treatment for Tinnitus

In addition to drug treatment, a variety of alternative strategies have been attempted for the clinical management of tinnitus, including sound therapy, cognitive behavioral therapy, and repetitive transcranial magnetic stimulation (rTMS). A brief outline of each of these therapies is included in Sects. 7.6.1–7.6.3. For more information, interested readers are encouraged to consult with comprehensive reviews that summarize and critique the effectiveness of sound therapy (Hobson et al. 2012), TRT (Phillips and McFerran 2010), cognitive behavioral therapy (Martinez-Devesa et al. 2010), and rTMS (Meng et al. 2011) for the clinical management of tinnitus.

7.6.1 Sound Therapy

Sound therapy for tinnitus generally refers to the use of sound generators, hearing aids, or combined devices to partially or completely mask tinnitus, with the aim of reducing the patient's awareness and/or associated reactions. Licensed audiologists who have undergone specialized training usually perform these therapies. One such approach, Tinnitus Retraining Therapy (TRT), developed by Pawel Jastreboff, combines counseling with maskers, when needed, as part of a comprehensive treatment strategy (Jastreboff and Hazell 2004). The masking is set to the "mixing" point so that patients can still hear the tinnitus, but it is mixed with competing background noise. This strategy facilitates adaptation as opposed to simply covering up the tinnitus transiently, while the counseling focuses on reducing tinnitus reaction. Another sound therapy approach was developed by Neuromonics™ Inc., a device that was the first of its kind to be approved by the US Food and Drug Administration (FDA). Whereas TRT focuses on counseling with sound generation

providing a supportive role, Neuromonics™ is centered on extensive use of a customized sound generator under the guidance of a healthcare provider.

7.6.2 Cognitive Behavioral Therapy

Beyond TRT and Neuromonics™, more formal psychological treatment for tinnitus can be provided by a mental health professional. One of the most widely used strategies is cognitive behavioral therapy. This approach seeks to manage the suffering associated with tinnitus by training patients to restructure their negative thoughts, enhance coping strategies, and encourage them to face situations that may initially exacerbate their negative feelings to promote habituation. This form of therapy can sometimes reduce the reaction to tinnitus even when the acoustic percept shows no significant change (Martinez-Devesa et al. 2010).

7.6.3 Repetitive Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is an experimental tool for stimulating cortical neurons via brief magnetic pulses delivered to the scalp, with the goal of interfering with the tinnitus-related neural activity (Langguth et al. 2012). This form of treatment requires physician oversight and has been applied to central disorders such as migraine and stroke. Repetitive transcranial magnetic stimulation (rTMS) was approved as a treatment for major depression by the FDA in the United States in 2008 for patients unresponsive to antidepressant pharmacotherapy. Although rTMS has been successful in a subset of tinnitus patients, the associated costs and specialized facilities have limited its widespread use.

7.7 Summary

Given that tinnitus etiology, as well as its perceptual characteristics and associated symptoms, can vary considerably among patients, perhaps it is not surprising that no single drug has been widely accepted as being effective at either quieting tinnitus or eliminating its distress. Although some drugs have shown promising effects in a subset of patients (e.g., carbamazepine for “typewriter tinnitus” or AM-101 for acute noise-induced tinnitus), there is limited support from the aforementioned clinical trials and Cochrane Reviews that any specific off-label drugs are capable of fully treating tinnitus. Ultimately, based on the systematic reviews and acknowledgment of the methodological concerns of several of the clinical trials, the Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014) stated that clinicians should not *routinely* recommend antidepressants, anxiolytics, anticonvulsants, or

intratympanic medications for the primary goal of treating persistent, bothersome tinnitus. That said, it is acknowledged that their recommendation to avoid the routine use of medications for tinnitus does not apply to those patients with comorbid disorders, such as depression, anxiety, or seizure disorder, in which such drugs could be indicated and useful (Tunkel et al. 2014).

In the future, it is expected that validated animal models will continue to serve a crucial role in uncovering the neural basis of tinnitus as well as providing opportunities to screen novel therapies for tinnitus suppression. As discussed earlier, translating these findings from animal studies to the improved treatment for tinnitus patients will ultimately require the collaboration of scientists, audiologists, otolaryngologists, and mental health professionals to fully address the worldwide problem of tinnitus.

Compliance with Ethics Requirements

Brian L. Allman declares that he has no conflict of interest.

Ashley L. Schormans declares that she has no conflict of interest.

Marei Typlt declares that she has no conflict of interest.

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Chapter 8
Developing a Molecular Therapeutic for Hearing Loss

Hinrich Staecker, Lloyd Klickstein, and Douglas E. Brough

Abstract The last 30 years have seen an explosion in our understanding of the molecular basis of hearing loss. The pathways underlying the development of the ear as well as the numerous molecular components that make hearing work have been extensively explored. So far, this has not translated into the development of new types of therapeutics for hearing loss, which is actually the most common neurodegenerative disease in humans. A significant portion of our scientific focus in hearing research has been on understanding the pathways that control the genesis of auditory and vestibular hair cells in an effort to apply this in patients. This chapter reviews some of the key discoveries in patterning of the neurosensory epithelium of the inner ear and discusses the factors that go into transforming that information into a potential drug that is testable in human subjects.

Keywords Drug development • Gene therapy • Hair cell regeneration • Hearing loss

H. Staecker (✉)
Department of Otolaryngology–Head and Neck Surgery, University of Kansas School of Medicine, Rainbow Blvd., MS 3010, Kansas City, KS 66160, USA
e-mail: hstaecker@kumc.edu

L. Klickstein
Novartis Institutes for Biomedical Research, 220 Massachusetts Ave., Cambridge, MA 02139, USA
e-mail: Lloyd.klickstein@novartis.com

D.E. Brough
GenVec Inc., 910 Clopper Rd., Gaithersburg, MD 20878, USA
e-mail: dbrough@genvec.com

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8.1 Introduction to Hair Cell Regeneration

The discovery that birds had the ability to regenerate sensory hair cells launched the field of hair cell regeneration research (Cotanche 1987; Cruz et al. 1987). Our understanding of mammalian hair cell biology has always been that these cells were terminally differentiated and that loss of these cells resulted in a permanent loss of hearing (Ruben 1967). Hearing loss is the most common neurodegenerative disease in humans, and loss of balance sensation is more poorly quantified but probably equally common. The number of people with hearing loss worldwide has been steadily increasing over recent years, reaching almost 49 million people in the United States alone (Cotanche and Kaiser 2010). A recent report from the World Health Organization predicts that more than a billion individuals are at risk for noise-induced hearing loss (http://goo.gl/HmCD6Z/). According to the National Institute on Deafness and Other Communication Disorders (NIDCD) 2010 statistics, approximately 17 % of the American adult population experiences hearing loss and 3 out of every 1,000 children are born deaf. The prevalence of hearing loss increases with age, as about 47 % of adults older than 75 years old have hearing impairment (http://goo.gl/W3kvFa).

Although hearing loss may not be life threatening, it can greatly influence a person's quality of life, and it can have a significant financial impact on the individual and society (Jung and Bhattacharyya 2012). Current treatments of hearing loss, including hearing aids and cochlear implants, are beneficial, but they are far from perfect. In addition, hearing aids suffer from poor acceptance and have only a 40 % penetrance into populations that may need them. Given the prevalence of hearing loss and the very poor penetration of hearing aids and other assistive listening devices, other approaches are urgently needed. Therefore, a primary goal of the scientific community over the last 25 years has been to understand the process of hair cell development in avian and mammalian systems in the hope of manipulating genes involved in the development process for clinical benefit (i.e., restoring auditory function by inducing the development of new hair cells) (see, e.g., Salvi et al. 2008).

8.2 Early Mammalian Experiments

A key feature of avian hair cell regeneration is that there is both a mitotic event resulting in replacement of hair cells and supporting cells as well as replacement of hair cells via nonmitotic transdifferentiation of existing supporting cells into hair cells (for review, see Oesterle and Stone 2008). Mammalian systems were initially thought to lack both the mitotic and differentiation components that allow the replacement of hair cells. Several early tissue culture experiments demonstrated that the mammalian vestibular and auditory neuroepithelia had at least a limited capacity to regenerate (Forge et al. 1993; Warchol et al. 1993). This occurs through a process

of transdifferentiation during which supporting cells turn into hair cells. No mitosis was seen to occur in mammalian tissue, therefore theoretically limiting the amount of regenerative capacity of a tissue (Zine and de Ribaupierre 1998). As many common causes of hearing loss, such as sound trauma, aging, and exposure to ototoxins, involve at least some degree of hair cell loss, regeneration of hair cells has remained a favorite target for translational research in the inner ear and research has focused on the molecular basis of hair cell replacement.

8.2.1 Genes/Proteins Involved in Hair Cell Genesis

Significant progress has been made in defining the developmental pathways that lead to the generation of hair cells. The sensory epithelium of the inner ear consists of a mosaic of hair cells and supporting cells organized so that each sensory cell is in contact only with supporting cells. Both supporting cells and hair cells derive from a common progenitor cell (Puligilla and Kelley 2009). Differentiation of these progenitors into hair cells is controlled by the helix-loop-helix transcription factor *atonal* (*Atoh1*), referred to as *Math1* in the mouse and *Hath1* in humans. Supporting cells contacting hair cells are prevented from differentiating into hair cells through expression of *Hes1* or *Hes5*, which inhibits *Atoh1*. *Hes* expression is modulated through signaling by the notch delta system (Table 8.1) (Kopecky and Fritzsch 2011). Modulation of any of the members of this signaling cascade has the potential to alter the fate of portions of the neuroepithelium, resulting in the production of new hair cells.

Expression of *Atoh1* during development follows a basal-to-apical gradient, in parallel to the pattern of cell cycle exit described by Ruben (1967). As initial experiments indicated that lack of production of new hair cells was a key difference between mammalian systems and spontaneously regenerating systems, the role of cell cycle control in hair cell regeneration has also been evaluated. At least two different cell cycle control molecules have been shown to be able modulate the production of hair cells (Lowenheim et al. 1999; Rocha-Sanchez et al. 2011). To use this information in the development of a potential therapeutic for inner ear disease, several key elements have to be addressed. A clear target disease state in which hair cell loss is a major factor must be selected, a specific molecular pathway that can be safely modified must be identified, and a strategy for effective delivery of the therapeutic product must be developed. Finally, the design of the treatment has to meet regulatory requirements. Given these criteria, there is a series of genes that can potentially be targeted either through overexpression or through inhibition in an attempt to modulate mammalian hair cell regeneration (see Table 8.1).

Probably the most studied approach to regenerating hair cells is induction of forced differentiation of supporting cells through the delivery of the *atonal* gene. At present, a wide variety of different models have been used to demonstrate that transfection of *Atoh1* into damaged inner ear tissue can induce production of hair cells (Kawamoto et al. 2003; Shou et al. 2003). Later studies demonstrated a

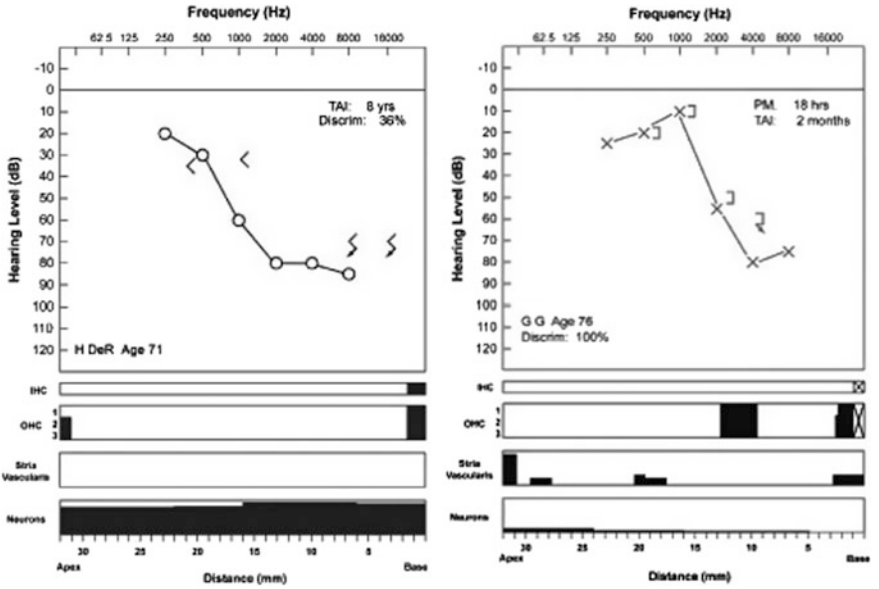

Fig. 8.1 As demonstrated in these cytococleograms from *Schuknecht's Pathology of the Ear*, there is not necessarily a match between hair cell loss and the audiogram (Schuknecht 1993). These two audiograms have similar patterns but one has predominantly neuronal loss and the other has predominantly hair cell loss. Only the second patient would be a candidate for a hair cell regeneration trial. Otoacoustic emissions (OAEs) could potentially be used to identify patients with hair cell loss, but for initial clinical trials, patients' hearing loss will probably be too severe to allow OAE testing. When hearing loss exceeds 40 dB, OAEs are likely to be absent. (Adapted from Joe Adams and Saumil Merchant, *Disorders of intoxication*, and Joseph Nadol, *Disorders of aging*. In *Schuknecht's Pathology of the Ear*, 3rd ed. Used with permission from PMPH-USA, Ltd., Shelton, CT)

Table 8.1 Potential targets/pathways that can be manipulated to induce hair cell regeneration

Gene	Type	Modulation needed	Pros/cons
Cyclin D	Cell cycle regulator	Increase	Proapoptotic
Rb	Pocket protein	Inhibit	Proapoptotic
p27kip	CKI	Inhibit	May be limited to neonatal period
p19ink4D	CKI	Inhibit	May be limited to IHC, utricle
Notch	Modulation of *atoh1*	Inhibit	May be target for pharmacologic agents
Hes/Hey	Notch signaling	Inhibit	Potential for RNAi
Atoh	Transcription factor	Inhibit	Limited effect

functional recovery of hearing and balance after *Atoh1* gene therapy (Izumikawa et al. 2005; Staecker et al. 2007). Inhibition of notch signaling, which can be accomplished by pharmacologic agents, has also been shown to have the potential for functional recovery of hair cells after damage (Batts et al. 2009; Mizutari et al. 2013). A potential significant advantage of using notch inhibitors is that there are multiple known pharmacologic agents that interfere with notch signaling. This would obviate the need for developing a more complex molecular therapeutic agent. This is balanced by the potential toxicity of some notch inhibitors. Downstream signaling from notch through inhibition of *Hes1* and *Hes5* could potentially also be used to induce regeneration of hair cells (Zine and de Ribaupierre 1998). This approach would need a molecular strategy with the delivery of siRNA to inhibit *Hes* expression (Jung et al. 2013).

8.3 Why Hair Cell Regeneration as a Target?

Hearing loss or dizziness are symptoms rather than diseases, so step one of developing a therapeutic is recognizing that no single treatment is going to address all types of hearing loss or balance disorders. We therefore have to start the process by picking a disease process for which we have a diagnostic test and for which a human clinical trial is potentially feasible. A significant advantage of picking hair cell regeneration as a target for drug development is that there is a long history of developmental biology research as a basis to pick drug targets, and this supports the construction of models that allow a clear development of the relationship between dose of drug and outcome, such as relating vector particle number to total number of recovered hair cells. Incorrect choice of disease process would likely make a successful clinical trial impossible. For example, for many disease processes, there is no clear understanding of the mechanism by which hearing losses are caused. Even though there is well-known hair cell loss in late Ménière's disease, the exact mechanism of low-frequency fluctuating hearing loss remains unexplained. Therefore, approaching this patient base with a regeneration therapy is unlikely to work.

An important factor that should not be overlooked is the availability of human temporal bone pathology specimens for studying the explicit underlying pathology of the potentially targeted diseases. There are several national temporal bone libraries that are supported by the National Institutes of Health–National Institute on Deafness and Other Communication Disorders (NIH–NIDCD). Consultation with this invaluable resource allows at least a histologic evaluation of many disease processes, although in many cases, the specimens are obtained years after the active disease process has ended. Therefore, when targeting a disease for which to develop a treatment, a histologically characterized human disease for which there is an animal model to carry out the drug development process should be selected.

8.4 Ethical and Practical Considerations in Defining a Therapeutic Target

When designing a pharmacologic or molecular intervention for hearing loss, it is important to keep in mind that current cochlear implantation devices provide tremendous benefit to the patient in terms of hearing rehabilitation. The outcomes with the planned pharmaceutical or molecular intervention should be expected to be better than the least significant cochlear implant outcomes. Alternatively, new interventions should target an area such as vestibular hair cell regeneration for which a cochlear implant equivalent is not yet available. A potential counterpoint is that trial of a regenerative therapy in a patient with bilateral severe-to-profound hearing loss does not preclude later cochlear implantation, whereas testing a novel therapeutic in an already implanted ear is difficult. Patients with bilateral vestibular hypofunction would also be a potential target, especially those suffering from aminoglycoside ototoxicity (Staecker et al. 2011). These patients, however, often have normal hearing and would thus be at risk for potential side effects.

8.4.1 The Challenge of the Inner Ear

The great challenge of inner ear disease is that most clinically available testing protocols do not allow precise identification of the underlying pathology of the inner ear. As seen in Fig. 8.1, there can be two patients with high-frequency hearing loss but they can have very different patterns of loss of hair cells, neurons, and cells in the stria vascularis. This additionally does not even begin to discuss the possibility of synaptic disorders or underlying molecular basis for inner ear dysfunction. Potential diseases for which a molecular therapeutic might be considered include loss of hearing and balance clearly related to hair cell damage. Molecular therapies have already been studied in animal models after aminoglycoside injury and noise trauma. Other diseases for which molecular therapies might be considered include adult-onset progressive hearing loss in which replacement of a defective gene or inhibition of a pathologic dominant gene could be attempted as well as diseases in which a preventative approach may be considered (sound trauma). A large portion of congenital genetic hearing loss could not be addressed, as in utero gene delivery could not be launched from a clinical trial standpoint. Postnatal treatment of congenital hearing loss may be difficult because there is often degeneration of the organ of Corti beyond a molecular pathology alone (Jun et al. 2000). Presbycusis, probably the largest target of all, is challenging because it consists of a mix of hair cell, stria vascularis, and spiral ganglion disorders and would require very long term trials to show efficacy.

8.4.2 What Is Your Model Disease?

Assuming that hair cell loss is selected as the target, several key concerns that have been seen in animal models of hair cell loss must be addressed. Many of the rodent models that have been used in ototoxicity models demonstrate a rapid loss of spiral ganglion neurons after damage to the organ of Corti (Harrison et al. 1991). This process also occurs in larger animal models such as cats, although at a lower rate (Leake et al. 2008). Obviously, hair cell regeneration is useless if there is no neural connection between the cochlea and the brainstem. Cochlear implant studies and studies of human temporal bones suggest that unlike rodents, humans maintain a fairly robust spiral ganglion population in most hearing-related pathologies (Linthicum and Fayad 2009). Hair cell regeneration experiments in animals also suggest that the presence of new hair cells can induce neuronal migration, lending at least some confidence that if hair cells are restored, they can attract an existing spiral ganglion population (Kawamoto et al. 2003).

Interestingly, the effect of spiral ganglion population survival on successful hearing is not entirely understood. In cochlear implantation studies, there are some links between spiral ganglion survival and auditory outcomes (Seyyedi et al. 2014). As different diseases are associated with different spiral ganglion populations, the development of animal models and eventual choice of human clinical trial populations can be refined to reflect the ideal potential outcomes of the trials. Therefore, choosing a patient who, based on existing temporal bone pathology data, may have significant neuronal degeneration could negatively impact trial outcomes. In addition, when planning for a clinical application, the human life span, onset of deafness, and duration of deafness must be considered. Again, from cochlear implantation research, there are clear indications that central auditory system changes occur if the brain does not receive sound information before 3 years of age or if a patient is profoundly hearing impaired for longer than 20 years (Ching et al. 2013; Mosnier et al. 2014).

In hair cell regeneration in particular, there is a reliance on the conversion of supporting cells into hair cells through transdifferentiation. In theory, it is possible to deplete the inner ear of supporting cells, which would result in a nonfunctional ear. Quantitative analysis of the human vestibular system suggests that supporting cells are present in a 5:1 ratio to hair cells whereas rodents have a lower ratio (Severinsen et al. 2010). Within the cochlea, there are several potential cell types that can potentially transdifferentiate into hair cells, although the supply of cells would be more limited than in the vestibular system. Experiments tracking the production of supernumerary hair cells suggest that the source of supernumerary hair cells is the lesser epithelial ridge (Bodson et al. 2010). An alternate strategy that is being evaluated is to induce endogenous stem cells to produce new hair cells (Martinez-Monedero et al. 2007).

Another concerning observation raised in the review of animal models used for regeneration studies is that after damage, the cochlea loses its three-dimensional structure to form a “flat” epithelium (Izumikawa et al. 2008). This flat epithelium

has some of the characteristics of supporting cells but does not regenerate when transfected with *atonal* (Oesterle and Campbell 2009). When looking at human temporal bone specimens, in the bulk of specimens examined, it appears that there is a robust surviving supporting cell population that retains near-normal anatomic relationships within the damaged organ of Corti (Linthicum and Fayad 2009). This observation influences the design of our animal models. What often differentiates human temporal bone pathology in patients with ototoxicity from observed pathology in animal models of ototoxicity is that hair cell loss is not as complete in humans. The most likely explanation for this is that that the goal in human therapy, when patients require treatment with ototoxic drugs for life-saving purposes, is to limit the side effects on the ear, whereas animal models are designed to provide complete and repeatable damage to the inner ear. This is a situation that does not occur in the clinical setting. It needs to be kept in mind for models used in translational research. Ideally, for a hair cell regeneration study, a rodent model that has partial loss of hair cells is needed, but the partial loss must be reproducible across subjects for the model to be useful and for experiments to be adequately powered.

8.5 Delivery Options to the Inner Ear

Once a potential drug to develop for hair cell regeneration has been identified and selected for further investigation, a methodology for effectively delivering the drug to the inner ear is needed. Systemic therapy for inner ear disease is in general not desirable. Because a molecular therapeutic agent may not cross the blood–brain barrier and systemically delivered drugs can potentially affect nontarget organ systems, a local therapy is preferred for treating diseases of the inner ear. Multiple strategies have been devised for delivering drugs either transtympanically or directly into the inner ear fluid (Staecker and Rodgers 2013). Recent studies that look at modulators of notch inhibition demonstrate some evidence that when these drugs are delivered using intratympanic delivery and direct delivery to the inner ear, they may be able to induce hair cell regeneration (Mizutari et al. 2013). Modulation of transdifferentiation via *atonal* delivery requires delivery of the gene to the supporting cells via gene therapy. Past studies have shown poor penetration of vectors when applied to the round window membrane, suggesting that direct access to the inner ear would be needed.

A variety of human surgeries exist that could potentially be adapted to inner ear gene delivery. Surgeons have been routinely opening the inner ear via the stapes footplate and have a long track record of safely operating on the stapes. To date, no drugs have been injected through the stapes footplate in humans, but animal experiments suggest that this would be feasible (Praetorius et al. 2003). An alternate route for delivery of drugs into the perilymph space is injection through the round window membrane. Guinea pig experiments have demonstrated that a cannula

hooked up to an osmotic pump can deliver a wide variety of substances into the perilymph via this approach (Brown et al. 1993). Recent advances in cochlear implantation have demonstrated that a flexible electrode can be inserted into the scala tympani without loss of hearing (Kiefer et al. 2004). Based on the calculated volume of a cochlear implant electrode and fluid displaced by the insertion of the electrode, it is reasonable to predict that displacement of that volume of fluid within the perilymph would be tolerated during drug injections as well.

When planning human studies, the volume of drug adequate to achieve a therapeutic effect might be predicted from kinetic data and drug diffusion models derived from animal models (Plontke and Zenner 2002). The rodent cochlea has a significantly smaller volume than the human cochlea, and it is not clear if direct scaling for a rodent model to the human can be calculated (http://oto2.wustl.edu/cochlea/) (Thorne et al. 1999). Other groups that have been working on transtympanic delivery have approached this by doing pharmacokinetics using a sheep model (Wang et al. 2011). Sheep have a slightly larger cochlea and use of sheep as subjects avoids some of the cost and ethical dilemmas in developing primate experiments.

A potential problem in delivery through the round window membrane is the proximity of the cochlear aqueduct. The cochlear aqueduct opens in the basal turn of the scala tympani next to the round window. The patency of the cochlear aqueduct in humans is variable. At least in younger patients, it is frequently open, raising the possibility of distribution of the injected drugs into the cerebrospinal fluid (CSF) space (Marchbanks and Reid 1990; Shuto et al. 2011). Animal experiments have suggested that regeneration induced by *atonal* gene therapy may be more efficiently induced when the vector is injected into the scala media (Husseman and Raphael 2009). A transcochlear approach to the scala media in humans would be very difficult to develop. The scala media is, however, accessible via the endolymphatic sac. Raphael and colleagues have demonstrated the ability to deliver viral vector into guinea pig cochleas through this approach (Yamasoba et al. 1999). In humans, molecules such as gadolinium have been injected into the endolymphatic sac and have been seen to be distributed throughout the scala media without loss of hearing (Mandala et al. 2010). Theoretically, the human inner ear could also be accessed via the semicircular canals, as has been shown in mice and rats.

When picking a surgical approach for delivering a completely novel therapeutic that in and of itself carries some theoretical risk, the complexity of the surgery and risk of the surgery should be minimized. The safest access to the round window membrane would require a mastoidectomy and facial recess with subsequent removal of the tectum to see the round window. The round window potentially could be accessed via the transcanal approach, but one would need development of the angled needle to puncture the round window membrane in a controlled fashion. The stapes footplate, on the other hand, is easily accessible via the transtympanic/transcanal approach and can be fenestrated with a laser. Drug can

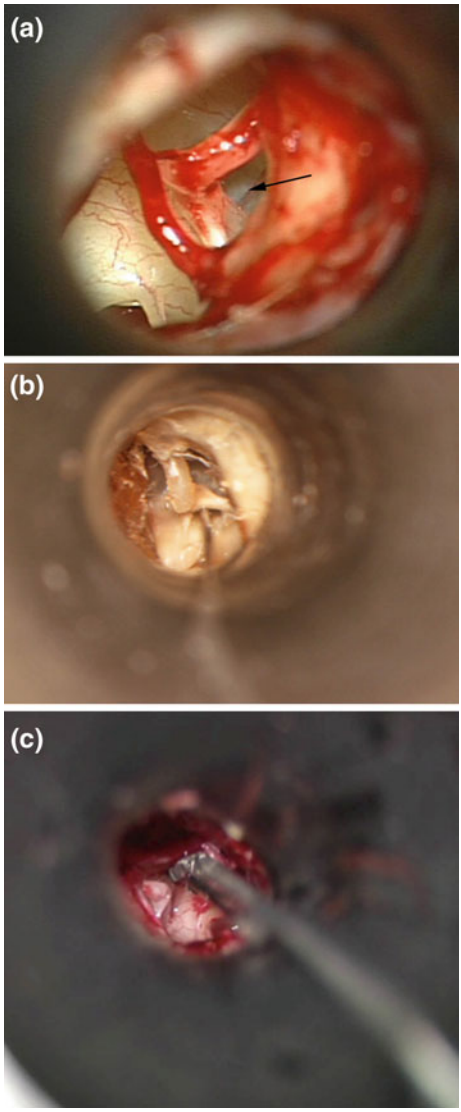

Fig. 8.2 Delivery options for perilymph-based delivery in humans. Looking down the ear canal after lifting the ear drum, both the round window and stapes footplate (*arrow*) can be accessed (**a**). Potential advantages of the stapes approach include the ability to have a direct view onto the footplate without bone removal and an oval window that allows one to rest a delivery catheter (**b**). For initial trials, the delivery catheter can be held in place with a cup forceps to allow completion of infusion. Delivery of *atonal*-expressing vector in a human patient via a custom delivery catheter resting in a 0.25-mm stapedotomy (**c**)

then be injected into the perilymphatic space (see Fig. 8.2). Besides total volume injected, more rapid speed of injection may also negatively affect the inner ear. Some cochlear implant studies suggest that slower insertion speeds result in better hearing preservation (Rajan et al. 2013). Development of an injection device for inner ear drug delivery should take that into account by limiting the speed of injection into the inner ear through the use of a micropump.

8.6 Developing an Animal Model

Hair cell regeneration research has used multiple different model systems. Avian models have the advantage of spontaneous regeneration, and newer vertebrate models such as *Danio rerio* (zebrafish) have been useful for understanding the underlying biology of the regeneration process. For translation and large-scale drug testing, rodent models are probably most appropriate because these are more commonly used in pharmacokinetic and toxicity studies. A model that can be translated into the preclinical environment for animal safety testing and then used for FDA submission is helpful. One potential problem with using rodents for hair regeneration research, however, is their relative lack of response to the aminoglycosides that are typically used to ablate the hair cells in the cochlea. The doses used in rodents are frequently much higher than those used in humans, given the goal of ablating the auditory epithelium. Several protocols have been developed for ablation of the auditory system in mice; however, development of a mouse model in which hearing loss is restricted to the higher frequencies to more accurately model human high-frequency hearing loss is significantly more complex given problems inducing a repeatable high-frequency hearing loss (Jansen et al. 2013). Similarly, in the balance system, it is fairly straightforward to ablate all vestibular hair cells completely but more complex to develop a mechanism of injuries that repeatedly partially injures the neural epithelium (Schlecker et al. 2011).

An adult mouse utricle tissue culture model has been useful for testing vectors for vestibular hair cell regeneration (see Fig. 8.3). It has the advantage of using

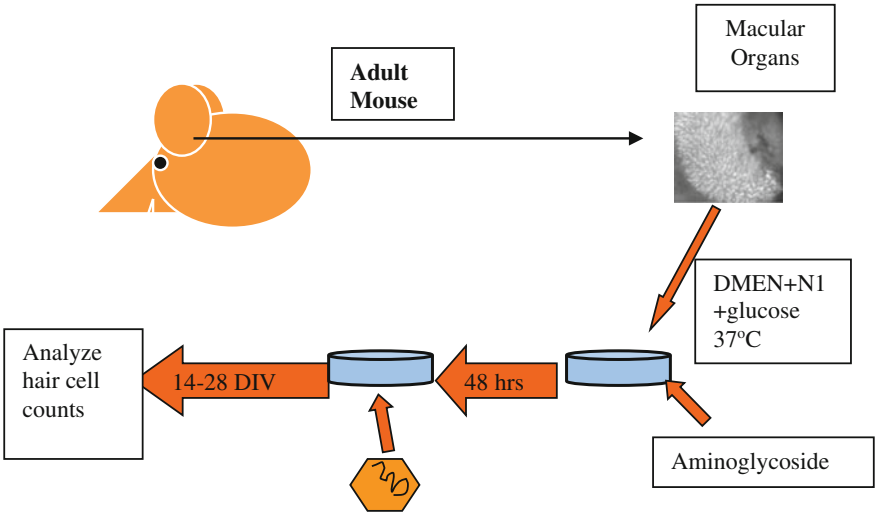

Fig. 8.3 Model of mouse utricle to evaluate constructs. The vestibular end organs can be harvested from an adult animal and maintained in vitro for long time periods. Constructs demonstrating good efficacy in vitro can then be developed in an in vivo setting

adult rather than neonatal tissue, it can be maintained in the trope for a prolonged time, and it is easy to quantify cell survival. Profound hearing loss can be induced in mice via a combination of aminoglycoside and diuretic drugs (Taylor et al. 2008). For induction of complete vestibular loss, neomycin can be injected through the round window of the mouse. This reliably induces greater than 90 % loss of vestibular hair cells and is a useful model for testing proof of concept of a new vector construct.

Use of the toxic nitrile, 3,3′-iminodipropionitrile (IDPN) has been demonstrated to induce vestibular hair cell injury in a number of different models (Crofton et al. 1994). For delivery of the vector, a number of different approaches to the inner ear, including stapedotomy and round window injection, can be used. The easiest access point to the inner ear of the mouse is the posterior semicircular canal, which can be accessed on the side of the skull. Use of this delivery point minimizes anesthesia time and allows high throughput for large-scale studies in which surgery must be performed on large numbers of mice. In the rat, the semicircular canals are less easily accessed and are deeper in the bone; however, using the facial nerve as a landmark, the canal can be accessed similarly to the mouse (Gassner et al. 2012). For many large contract research organizations (CROs), the rat is the preferred animal for toxicology studies (for additional discussion of toxicology studies, see Chap. 5 by Lynch, Kil, and Le Prell). Therefore, it is useful to be able to deliver drugs within both mouse and rat models. The additional advantage of rodent models is having a very well characterized genome, allowing a variety of different experiments. Outcomes can be determined through hearing testing, evaluation of balance, and histologic measures. Indeed, all of the outcomes that may be of interest in humans, such as threshold sensitivity, otoacoustic emission integrity, tinnitus, and so forth, can be assessed. All are needed for preclinical evaluation of drug toxicity and efficacy.

8.7 Gene Therapy Basics and Modeling a Vector System

Most of the research on gene delivery and the auditory system has focused on either adenovector-based or adeno-associated vector-based delivery systems. The utility of different vector systems has been extensively reviewed (Kawamoto et al. 2001). For the ear in particular, an important consideration is that during the manufacturing process, the vector must be produced at a sufficient particle concentration that delivery of an effective dose of vector into the inner ear will not cause any hydraulic trauma. For inner ear delivery in particular, adenovector delivery systems are ideal because they have a long track record of human use and have been used in the neuroepithelium of the eye. Additionally, for applications such as hair cell regeneration where transcription factor activity is needed only for a brief period of time, adenovectors provide an ideal vehicle because they are transcriptionally silenced within several weeks of delivery, thus limiting expression of the transgene to a short

What is your target disease?

- Hearing loss with known hair cell loss

How do you get your vector to the right place?

- Local delivery into perilymph

How do you control the amount and location of gene transcription?

- Tissue-specific Promoters and control of promoter strength

How do you ensure safety?

- Control vector dose and volume

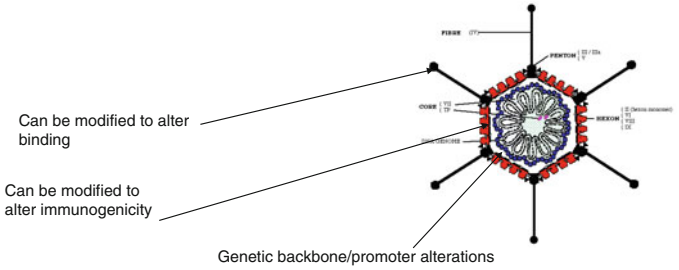

Fig. 8.4 Several points have to be considered when designing a vector for delivery of a molecular therapeutic for hearing loss. Careful construction of a tissue-specific promoter-driven construct that is synthesized to produce the highest possible titer per volume of active particles allows low infusion volumes in the inner ear

time period. For treatment of genetic diseases, long-acting vectors such as adeno-associated vectors would be needed.

Within the design of the vector itself, several design elements are included to ensure safety. For nononcolytic gene therapy, vectors have to be designed to be replication deficient. This can be accomplished through deletion of key vector genome components and generation of vector in a specially modified cell line. Essentially, a gene therapy-based drug needs to be treated like any other pharmaceutical and defined in terms of dose–response relationships. Because the cochlea is a low-volume space, we want to optimize vector delivery by delivering vector only to supporting cells. This can be achieved by either altering the binding properties of the vector or using a promoter that is supporting cell specific. Combining these two traits optimizes the sensitivity and specificity of the molecular drug (see Fig. 8.4).

Early studies evaluated the effect of promoters on expression of transgenes in inner ear tissue as well as evaluating the effect of promoter strength on hair cell regeneration (Praetorius et al. 2010). It is clear that very different patterns of expression can be achieved that may or may not be appropriate for expression of *Atoh1* and hair cell regeneration. For delivery of *atonal*, efficacy of hair cell production was inversely related to promoter strength. Potentially different vector systems could be developed that may more specifically target populations of cells within the inner ear (Staecker et al. 2014). Alternate serotype adenovectors might have the additional benefit of inducing a less robust immune response in the inner ear. Finally, there are also techniques for modifying vectors to bind to specific

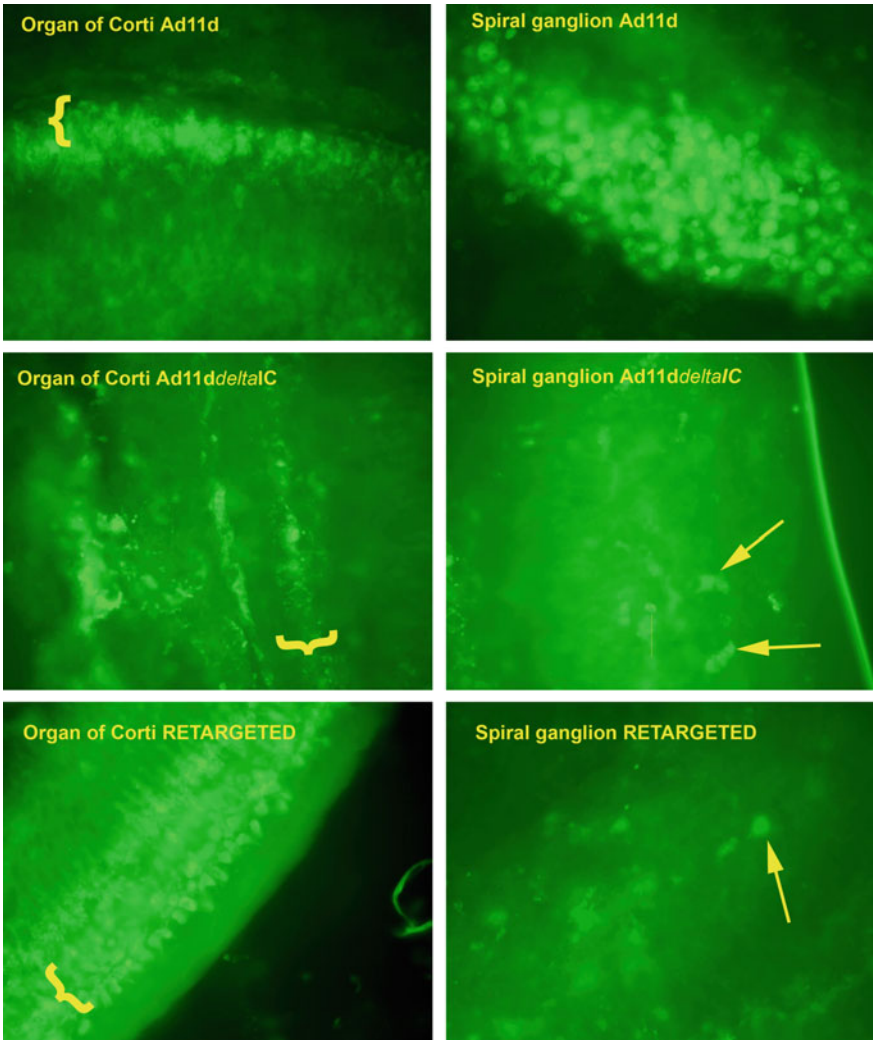

Fig. 8.5 Ad5 vectors can be retargeted to alternative binding patterns. Expression of green fluorescent protein (GFP) in neonatal organ of inner ear cultures is shown for the organ of Corti (*left*) and the spiral ganglion (*right*). Native vector (*upper panels*) expresses in the spiral ganglion and underneath the hair cells. Binding ablated vector (*center panels*) shows little expression of GFP. Vector targeted to bind endothelial growth factor (EGF) receptor appears mostly in the organ of Corti with spiral ganglion GFP expression ablated

epitopes within a tissue. As seen in Fig. 8.5, an adenovector-expressing green fluorescent protein (GFP) has been conjugated to an antibody that binds the vector and epidermal growth factor (EGF) receptor. Delivery to the mouse organ of Corti cultures results in altered distribution of vector-induced gene expression. Although

this technique is promising in terms of targeting, it would result in a drug production process that has significant regulatory hurdles. In terms of translation of therapy, we opted to use an adenovirus Ad5 capsid-based vector due to its extensive track record in human studies (Wei 2005). This was combined with a vector manufacturing process that allowed production of very high titer wild-type free vector. For moving studies forward into the preclinical arena, the transgene for human *atonal* delivery was *Hath1* driven by the human glial fibrillary acidic protein promoter to produce a vector that expressed *Hath1* only in supporting cells.

8.8 Manufacturing Issues That Must Be Considered

Once the lead molecule had been designed and tested for efficacy, preparations need to be made to move the project into the preclinical phase. This means production of a batch of vector produced under good manufacturing practice (GMP). GMP guidelines are overseen by the US Food and Drug Administration (FDA) and are described in the Food Drug and Cosmetic act (21 S 351). Additional steps that need to be evaluated in the process are development of an assay for measuring potency of the drug (i.e., ability to produce *Hath1* protein), verification of the absence of wild-type vector, and validation of assays to determine vector particle number per unit volume. The stability of the gene medicine product also needs to be validated. All of this information is contained in the initial investigational new drug (IND) application. The FDA offers an overview on this topic on its website (http://goo.gl/W1Fcpe).

8.9 Preclinical Studies

At this point in development, the lead molecule has to be tested in an animal model. Pharmakokinetics/biodistribution and toxicology have to be carried out under good laboratory practice (GLP). This is a system of conducting preclinical experiments that will support an IND application, and requirements are outlined by the FDA under a series of GLP regulations (21 CFR 58). In brief, the regulations provide guidance on the organization of personnel conducting the experiments, quality assurance, facility issues, standard operating procedures, and conduction of the study as well as archiving of the reports and results. Before undertaking preclinical studies, it is advisable to meet with the FDA's Center for Biologics Evaluation and Research (CBER), which oversees gene therapy trials. For development of an inner ear-based therapy, several hurdles need to be addressed. The correct animal model has to be chosen, target organs for evaluation of toxicity need to be identified, and duration of the experiment and outcomes measures have to be determined. The study has to evaluate the formulation and delivery method that are proposed for an eventual clinical study.

For biodistribution studies, tissues are examined by a quantitative polymerase chain reaction for vector sequences at hours to 6 months after delivery in a rat model. For the purposes of the IND applications, it is not necessary to perform these experiments in a disease model and generally 10 animals per group are acceptable. The rat was chosen for hearing toxicology experiments because prior studies demonstrated that Ad5 capsid vectors could be delivered in this model (Gassner et al. 2012). For biodistribution studies, a sensitivity of <100 vector copies/μg DNA is considered standard for assay development. The tissue panel for an ear study would include the injected and contralateral ear, draining lymph nodes, brain, heart, lung, liver, kidney, spleen, blood, and ovaries/testes. If focused on a short-acting transcription factor delivered by a nonintegrating vector, long-term (>6 month) studies are not necessarily required by the FDA during the preclinical phase. The corollaries to these studies are toxicology studies in which dose ranging is used to determine a locally toxic dose (induction of hearing loss) in a naïve animal and histopathology is used to examine all of the organs listed previously for local damage. These types of studies are best performed by a CRO with expertise in GLP studies. For inner ear studies, there are not many organizations that are set up to do the hearing testing and inner ear histology; thus, collaborative efforts including a researcher experienced in the inner ear are typically needed. This information is put together with a proof of concept model in which the GMP lead molecule is tested for efficacy in a disease model.

8.10 Design of a Hair Cell Regeneration Clinical Trial

Phase 1 clinical trials focus primarily on safety. At present, multiple studies are looking at delivery to the middle ear, but delivery of a molecular therapeutic would require injection into the perilymph or intralabyrinthine (IL) delivery. This kind of therapy is a completely novel form of delivery that has never been tested in humans and therefore needs a safety readout that is separate from analysis of the drug effects. Patients who are recruited for this trial should have enough residual function to measure any detrimental effects of either the delivery process or the drug itself on hearing or balance. This introduces the obvious risk that patients may lose their remaining hearing if the drug delivery process does induce damage; thus, the ideal subjects for initial studies will have some residual hearing in both ears such that the study participant has remaining hearing in one ear if adverse events do occur. During the Institutional Review Board (IRB) process, one of the elements of interest is complete and transparent disclosure of risks associated with participation in research, including clinical trials. If a placebo control is part of the experimental design, the IRB may pay special attention to the ethics of performing an invasive surgical sham procedure (Niemansburg et al. 2015).

Picking the correct dose of the therapeutic is an important component of trial design. Animal studies suggest that there is a minimal effective dose for functional recovery after delivery of *atonal* even though an increase in hair cell number can be

seen with a lower dose of vector (Staecker et al. 2014). This suggests that there is a minimal dose of vector required for efficacy. For vector-based therapeutics, there is a maximum concentration of vector that can be manufactured. Dosage of the *atonal*-containing vector can therefore be controlled by diluting concentrated stock or varying the volume of vector infused into the inner ear. For a clinical trial, the dose of vector is based on the effective dose derived from animal models scaled up to the volume of the inner ear of a human. A variety of normative data for the relative size of the inner ear among models is available (for reviews across species, see Thorne et al. 1999). In a trial, achieving the optimal dosing is best accomplished by starting with an estimated low but effective dose and performing a dose escalation experiment as lower doses are confirmed safe. Additional factors that need to be addressed are the development of a delivery device suitable for injecting microliter volumes into the inner ear over a several-minute time frame. These devices would additionally need to be evaluated for compatibility with the drug of interest; that is, binding to the vector is necessary.

The selection of patients for the clinical trial is critical. Having talked to many patient groups, the authors of this chapter found a lack of appreciation of the complexity of hearing loss. Just because a sensorineural hearing loss is present, it does not necessarily mean it is due to loss of sensory hair cells. Moving forward then requires identification of patient populations where there is some degree of certainty that hair cell loss is the etiology of their hearing loss. This is best accomplished by identifying patients based on disease process, such as aminoglycoside exposure or noise trauma. Gene therapy trials in general have required longer follow-up than standard pharmacologic trials; thus, participants must be willing to continue their follow-up participation for extended periods. Consultation with the regulatory authorities is required for optimizing the design of the trial.

8.11 Funding

A variety of funding mechanisms are available for translational research projects. The NIDCD has offered a series of requests for applications (RFAs) focused on translational research. Translational research at academic institutions is thus perhaps most frequently funded through this dedicated R01 mechanism. When academic research leads to potential new drug technologies, pharmaceutical companies can license those technologies and seek additional funding for drug development. Additional mechanisms such as Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs provide grants that fund proof of concept Phase 1 studies as well as larger rollouts in the Phase 2 part of the grant. Unlike traditional research grants that most academics are familiar with (i.e., R01, R03, R21), a small business entity must provide the primary oversight and the principal investigator must be an employee of the business. Clinical development can occur within academic institutions, however, and the U01 clinical trial cooperative agreement is used by the NIH to fund clinical investigations. Finally,

academics can remain actively engaged in clinical research when business entities choose to provide contract funding for clinical or translational activities at an academic institution. Ownership of intellectual property and publication rights need to be carefully negotiated in these latter situations. Although the preceding mechanisms are available, it should be noted that the preclinical animal experiments needed for regulatory filing and the clinical trial itself are generally speaking outside the funding capacity of granting agencies and typically require a corporate partner. For discussion of the development of D-methionine within an academic institution through grant funding mechanisms, see Chap. 6 by Campbell and Fox.

8.12 Conclusion

Hair cell regeneration has been a leading focus of hearing research for the last 30 years. During that time, we have identified key pathways in multiple genes that have the potential to generate hair cells. Ultimately, translation of this information to human studies requires identification of a clinical need and design of a stable lead molecule that is safe and has verifiable dose–response characteristics as well as being able to be manufactured on an industrial scale. The movement of the *atonal* gene from discovery to lead molecule development, preclinical testing, and finally human clinical trials hopefully represents the first of many molecular therapeutics for hearing loss that move from bench to bedside. The outcomes and safety studies as well as experience from moving *atonal* into a human population will facilitate the development of a wide variety of other therapeutics that are currently being tested in animal models.

Compliance with Ethics Requirements

Douglas E. Brough is an employee of GenVec Inc.

Lloyd Klickstein is a stockholder of Novartis and an employee of Novartis Institutes for BioMedical Research.

Hinrich Staecker is on the surgical advisory board of MedEl GmbH and is a consultant for Auris Medical.

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Chapter 9
Photons in the Ear

Xiaodong Tan, Nan Xia, and Claus-Peter Richter

Abstract Among neural prostheses, cochlear implants (CIs) are considered the most successful devices. To date, they have benefited more than 324,000 patients with severe-to-profound hearing loss. CIs directly stimulate the auditory nerve and restore some hearing. Despite the great success of the devices, the outcomes in performance are variable. CI users often have difficulties in speech recognition in challenging listening environments and their perception of music is limited. It has been argued that performance correlates with the number of independent channels, which can be used to transmit information to the brain. While physical properties of the tissue result in a wide spread of the electrical current in contemporary devices and limit the number of independent channels, other modes of stimulation may provide an opportunity to increase spatial selectivity of neural stimulation and thus increase the number of independent channels for information transfer. An improvement in performance of the implant users is expected. This chapter provides an overview of the opportunities and the contemporary challenges of neural stimulation with light regarding auditory prostheses.

X. Tan · N. Xia · C.-P. Richter
Department of Otolaryngology, Northwestern University,
303 E. Chicago Ave., Chicago, IL 60611, USA
e-mail: xiaodong.tan@northwestern.edu

N. Xia
Key Laboratory of Biorheological Science and Technology,
Bioengineering College, Chongqing University, Chongqing 400044, China
e-mail: loojourney@yahoo.com

C.-P. Richter (✉)
Department of Biomedical Engineering, Northwestern University,
2145 Sheridan Road, Evanston, IL 60208, USA
e-mail: cri529@northwestern.edu

C.-P. Richter
Department of Communication Sciences and Disorders, The Hugh Knowles Center,
Northwestern University, 2240 Campus Drive, Evanston, IL 60208, USA

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9.1 Introduction

Today, cochlear implants (CIs) have restored some hearing in more than 324,000 individuals with severe-to-profound deafness (NIDCD Information Clearinghouse 2015). Among neural prostheses, CIs are considered the most successful devices. The average cochlear implant user can understand running speech under quiet listening conditions. The scores in standard speech recognition tests for many of the patients are higher than 50 % and can reach close to 100 % (Wilson and Dorman 2008; Amoodi et al. 2012; Friedmann et al. 2015). Despite the unparalleled success of auditory prostheses, CI users are still challenged in noisy listening environments and they have little music appreciation (Rubinstein 2004; Limb 2006). Improving cochlear implants means overcoming existing constraints (Limb and Roy 2014). Although *biological constraints* are difficult or not possible to overcome, *technical constraints* of cochlear implant devices can be addressed. Biological constraints include all changes of the neural system that resulted in deafness. Technical constraints describe the device limitation when compared to the normal auditory system.

9.1.1 Biological Constraints

Sensorineural hearing loss is associated with degenerative neurobiological and physiological changes in the auditory periphery and the central pathway (for a review, see Shepherd and Hardie 2001). These changes cannot be reversed by technology and thus become the biological constraints for hearing restoration with CIs. The most common and almost inevitable change is the degeneration and death of spiral ganglion neurons (SGNs). Without the synaptic innervation with hair cells, the dendrites tend to demyelinate and shrink, which eventually results in SGN death. The significantly reduced number of SGNs is one limiting factor for direct electrical stimulation and hearing restoration.

The neuronal loss is typically nonuniform and results in “holes” of neurons along the cochlea (Shannon et al. 2002). The nonuniform loss of neurons will distort the frequency representation along the spiral ganglion. Imperfect or distorted frequency perception is particularly unfavorable for speech recognition in noisy listening environments and for music appreciation (Zeng et al. 2014). Nevertheless, the good news is that studies on the maintenance and regeneration of SGN neurites are underway (Mukherjea et al. 2015). Prospective new drugs, which can stimulate the growth of the neural fibers of SGNs are expected to help overcome this barrier in the future (see, for example, Chap. 8 by Staecker, Klickstein, and Brough).

Following cochlear damage, connections in the auditory brainstem and midbrain appear to remain intact. Nevertheless, morphological and physiological changes along the auditory pathway must occur and likely contribute to the limited fidelity of CIs (Ryugo et al. 1997; Redd et al. 2000; Tirko and Ryugo 2012). Morphological changes include a decrease in the size of neurons, number of afferent inputs, and size and density of synapses (Saada et al. 1996; Redd et al. 2002; Baker et al. 2010). Physiological changes in response properties such as prolonged delay times, elevated threshold, desynchronization, altered firing patterns, and increased levels of adaptation were also reported, which could occur either immediately or over the long term after hair cell loss (Hartmann et al. 1984; van den Honert and Stypulkowski 1984). These physiological changes are especially adverse to the temporal resolution of the auditory system, which also influences the performance of CI users. Along the auditory pathway, spatial activation increased after hearing loss, and a loss of inhibitory influences was described. At the cortex, spatially larger cortical activation was seen with positron emission tomography (Wong et al. 1999; Naito et al. 2000; Limb et al. 2010). Although these changes could mean a plastic reorganization and more intense use of remaining auditory networks (Truy et al. 1995; Naito et al. 2000; Green et al. 2008), they also indicated a reduced spatial resolution and number of independent channels.

9.1.2 Technical Constraints

The hearing range for a normal-hearing individual is between 0.02 and 20 kHz (~10 octaves) with a resolution as low as 0.1 octave and a loudness range of 0–120 dB with a resolution as low as 1–2 dB. This is achieved by 3000–3500 inner hair cells and about three times more outer hair cells, which provide more than 30 independent perceptual channels (Shannon et al. 2004; Shannon 2005). In contrast to normal-hearing individuals, CI users' "hearing range" is between 0.4 and 8 kHz (~4.5 octaves) with a loudness range of 6–30 dB and about 20 discernible levels.

CI users have a largely reduced number of independent channels. The limitation lies not only in the number of physical contacts, which at present is up to 22 channels, but also in the number of channels that can be used to simultaneously process auditory information. Current spread and physical proximity of the channels often make the signals from adjacent channels indiscernible, so that there are typically only four to eight independent channels available to CI users (Fishman et al. 1997; Reiss et al. 2012; Snel-Bongers et al. 2012). Hence, the frequency fidelity is drastically reduced. Furthermore, during the implantation, the insertion depth of the electrode arrays varies. This results in an uncertainty of the electrode placement (Firszt et al. 2007; Snel-Bongers et al. 2012). Short insertion of the electrode into the cochlea may impede the ability to stimulate the apical section of the spiral ganglion, which accounts for the largely reduced perception below 0.4 kHz. Although adjustable to a certain degree, imprecise frequency representation of the electrode results in poorer performance of CI users (Baskent and

Shannon 2005). Other factors that affect encoding of acoustic information include the ability of the auditory nerve to generate action potentials in a given phase (phase locking). Phase lock in the pristine cochlea is up to 5 kHz, while it decreases to less than 0.3 kHz in CI users. Compared to the biological constraints, technical constraints might be easier to solve, and studies on new methods of stimulation and new CI designs are underway.

9.2 Photons as Alternative Stimulation in CIs

The goal for neuroprostheses is to restore neural function of a healthy system. Despite novel and better prostheses designs and better clinical implementation of the neuroprostheses, there are several challenges that neurostimulation faces (for a review, see Grill et al. 2009). In particular, the spread of current in the tissue makes spatial selective stimulation difficult or energy inefficient. Novel stimulation strategies and stimulation modalities are explored to overcome those technical constraints. As an alternative to electrical stimulation, methods to control neural activity by light have been explored recently. It has been argued that optical methods could improve spatial selectivity and increase the fidelity of neural prostheses. Stimulation of the neurons is spatially selective and does not require direct contact between the electrode and the neural structure. Therefore, for cochlear prostheses, neural stimulation with light may constitute a novel way to increase the selectivity of the stimulation and the number of independent channels, which can be used to encode the acoustic information. Optical methods include *optogenetics* (Hernandez et al. 2014; Jeschke and Moser 2015), *optoacoustics* (Wenzel et al. 2009; Zhang et al. 2009; Schultz et al. 2012b), and *infrared neural stimulation* (Izzo et al. 2006). Each of the methods has its own merits and challenges.

9.2.1 Optogenetics

It has been demonstrated that neurons can be made sensitive to irradiation with visible light by expressing an ion channel, channel rhodopsins (ChR), in their cell membrane (Boyden et al. 2005). To explore optical stimulation with blue light in the cochlea, transgenic mice were engineered to express ChR2 in the somata, dendrites, and axons of SGNs but not in cochlear hair cells. Auditory responses could be evoked in those mice by using a blue light source (Hernandez et al. 2014). Selectivity of the optical stimulation was demonstrated by masking the response to the optical stimulus with an acoustic stimulus and by determining spatial tuning curves obtained from neural activity recorded from the inferior colliculus during optical stimulation. The stimulation threshold was 2 $\mu J/mm^2$, with a dynamic range for the responses of more than 20 dB (Moser et al. 2013; Hernandez et al. 2014; Jeschke and Moser 2015). The minimal latency for the response was 3.1 ms. The

width of the spatial tuning curves was 475 ± 65.5 μm for optogenetic stimulation, which was smaller when compared to the width of the spatial tuning curves obtained during acoustic pure-tone stimulation (666.7 ± 95.7 μm) or monopolar electrical stimulation (828.6 ± 101.7 μm). In addition to using transgenic animals, the authors also crossed the *Thy1.2*-driven *ChR2* transgene with $Oto^{Pga/Pga}$ mice to express ChR2 in their SGNs to mimic a model to rescue from early onset of genetic deafness. The channel was also expressed in SGNs using a viral vector. At present, efficient and cell-specific expression of the optogenetic tool has been observed for adenovirus carrier (AAV2) (for a review, see Richter and Tan 2014; Jeschke and Moser 2015; Moser 2015). After transfection, neural responses could be evoked by direct irradiation of the neurons up to 60 Hz, the current limit of their stimulation setup (Hernandez et al. 2014).

The optogenetic tool was not only tested in the cochlea. ChR2 was also transiently expressed in guinea pig and rat brainstems via a single injection of adeno-associated virus vector carrying the target gene. After a survival period of 2–3 weeks, a broad pattern of expression of the channel was observed in the cochlear nucleus 2–3 weeks after the injection (Acker et al. 2011). Neural responses showed a broad pattern of excitation in the central nucleus of the inferior colliculus (ICC) similar to electric stimulation (Darrow et al. 2013b) or to an acoustic click (Darrow et al. 2013a).

The potential of optogenetics for the auditory system lies in its known mechanism, while the challenges lie in the dynamics of the channels. Typically, ChR2 can be used to generate action potentials at a rate of about 70 Hz (Hernandez et al. 2014). This is slower than the neural activity in the normal auditory system. Tissue will significantly scatter light in the visible wavelength range and selective stimulation will require the light source in close proximity to the target structure (for a review, see, e.g., Richter and Tan 2014). Another challenge for optogenetics as a tool in prostheses used in humans lies in the requirement to introduce exogenous genes. Although not established as a routine treatment in clinical practice, gene therapy is currently being explored in humans. Many reviews and opinion papers have recently been published on this topic (Liu et al. 2003; Pezzoli et al. 2012; Cox et al. 2015), and it has also been addressed in Chap. 8 by Staecker, Klickstein, and Brough.

9.2.2 Optoacoustics

Optoacoustics describes a photothermal effect that results from the absorption of photons by the target structure. After the absorption, the photon energy is converted into heat, leading to rapid heating of the irradiated volume. The resulting thermoelastic expansion will propagate as a wave with a measurable pressure. The pressure is particularly large if the pulse duration is shorter than the propagation time for a stress wave from the irradiated volume. In a simplified view, for pulse durations shorter than 1 μs, the condition has been described as stress confined

(Tuchin 2000; Niemz 2004; Welch and van Gemert 2012). Recently, it has been reported that for pulse durations that are orders of magnitude longer than 1 μs, audible stress waves can be generated (Teudt et al. 2011; Schultz et al. 2012a, b). It has been suggested that light-induced pressure waves can be used to mechanically stimulate the cochlea (Wenzel et al. 2009; Zhang et al. 2009; Schultz et al. 2012b). Laser-induced pressure waves vibrate the basilar membrane and stimulate inner and outer hair cells. The inner hair cells are required to transform the acoustic signal into action potentials on the auditory nerve. Since the acoustic signal is similar to an acoustic click, it is counterintuitive that the stimulation results in a selective stimulation of the cochlea. Nevertheless, it has been demonstrated that infrared laser pulses generate a focused pressure wave in front of the optical fiber (Fridberger and Ren 2006; Teudt et al. 2011).

Wenzel et al. (2009) used a laser that emits green light (the crystal used as a lasing medium in this laser is a neodymium-doped yttrium aluminum garnet or short Nd:YAG laser, $\lambda = 532$ nm, $\tau_p = 10$ ns, $f = 10$ Hz, $Q = 0$–23 J/pulse) to stimulate the cochlea of guinea pigs. They were able to evoke auditory brainstem responses in hearing animals. The response could not be evoked in deaf animals. For radiation wavelengths in the near infrared, the responses correlated with the water absorption for the photons. Furthermore, a positive correlation for responses in the cochlea to optical stimulation occurred at $\lambda = 600$–800 nm, the absorption coefficient of hemoglobin (Schultz et al. 2012b).

The important message from the experiments is that all stimuli at radiation wavelengths in the infrared will heat the target volume and will generate stress relaxation waves. Consequently, when the technique is considered for scientific applications or for prosthetics, the issues of thermal damage and stress-related effects must be addressed. For sensorineural hearing loss, optoacoustic effects will be inefficient because of the missing hair cells, and therefore this is unlikely to become a major player in development of improvements in auditory prosthesis.

9.2.3 Infrared Neural Stimulation of the Cochlea

Infrared neural stimulation (INS) of the cochlea has been studied in gerbil, mouse, guinea pig, and cat. Experiments were conducted in normal-hearing, acutely deafened, and chronically deaf animals. Typically, animals are rendered acutely deaf by the direct injection of neomycin into scala tympani (Schultz et al. 2012b; Thompson et al. 2015; Young et al. 2015). To render animals chronically deaf, either neomycin is injected into the middle ear (Richter et al. 2008; Young et al. 2015) or an intraperitoneal injection of kanamycin followed by an intravenous injection of a diuretic drug such as furosemide is used (Thompson et al. 2015). The rigorousness of the drug use determines the degree of cochlear damage. In animals with some remaining hearing, cochlear function was lost in the cochlear base, while cochlear function was compromised only in the cochlear apex. Typically, responses

to pure tones were absent at high frequencies (above 16 kHz) and elevated at low frequencies (below 16 kHz).

In gerbils, an infrared laser (the crystal used as a lasing medium in this laser was a holmium-doped yttrium aluminum garnet or short Ho:YAG laser, $\lambda = 2.12$ µm, $\tau_p = 250$ µs, $f = 2$ Hz, $Q = 0$–127 µJ/pulse) was used to stimulate the auditory nerve (Izzo et al. 2006). The laser was coupled to a 200-µm-diameter optical fiber, which was placed in front of the cochlear round window. The optical beam was directed toward the SGNs. Compound action potentials (CAPs) were evoked in response to the laser pulses. Note, responses could be evoked in hearing and in deaf animals missing all hair cells (Fig. 3 in Izzo et al. 2006). An increase in radiation energy induced a monotonic increase in the evoked response. Input–output curves are variable across animals. Differences are likely caused by the physiological state of each cochlea and differences in optical fiber placement. In acutely deafened and in chronically deaf gerbils, thresholds for optically evoked CAPs were not significantly elevated for short pulse durations (Richter et al. 2008). Experiments were also conducted with different infrared diode lasers from Aculight (the laser medium is formed by a p–n junction of a semiconductor diode similar to that found in a light-emitting diode; $\lambda = 1844$–1940 nm, $\tau_p = 5$ µs–1 ms; $f = 2$–1000 Hz) to characterize the patterns of the CAPs (Izzo et al. 2007b, 2008). Moreover, the responses of single auditory nerve fibers were recorded during optical stimulation. The recordings from low-spontaneous-rate neurons showed on average a firing efficiency of approximately 40 % at 200-Hz laser stimulation rate (Littlefield et al. 2008).

Spatial selective stimulation of the auditory nerve with infrared radiation was demonstrated in three series of experiments in the cochlea: (1) immunohistochemical staining for c-Fos (Izzo et al. 2007a), (2) tone-on-light masking (Matic et al. 2011), and (3) recording of neural responses in the inferior colliculus and constructing corresponding spatial tuning curves (Fig. 9.1) (Richter et al. 2011). The transiently expressed transcription factor c-Fos was used to stain activated nerve cells and to identify the spatial area of the cochlea that was stimulated with a Ho:YAG laser ($\lambda = 2.12$ µm, $\tau_p = 350$ µs, $f = 2$ Hz, $H = 60$ mJ/cm^2), which was coupled to a 100-µm optical fiber. Immunohistochemical staining for c-Fos in the cochlea showed a small area of optical stimulation, which occurred directly opposite to the optical fiber (Izzo et al. 2007b). This pattern of c-Fos staining is in contrast to that after electrical stimulation. Electrical stimulation leads to a large, more spatially extended population of labeled, activated neurons.

Spatial selectivity has also been determined with tone-on-light masking (Matic et al. 2011). Laser pulses with fixed optical parameters were delivered with a 200-µm optical fiber and were presented simultaneously with an acoustic tone. The tone was variable in frequency and level. Tone-on-light masking in gerbils revealed tuning curves with best frequencies between 5.3 and 11.2 kHz. The width of the tone-on-light tuning curves was similar to the width of tone-on-tone tuning curves.

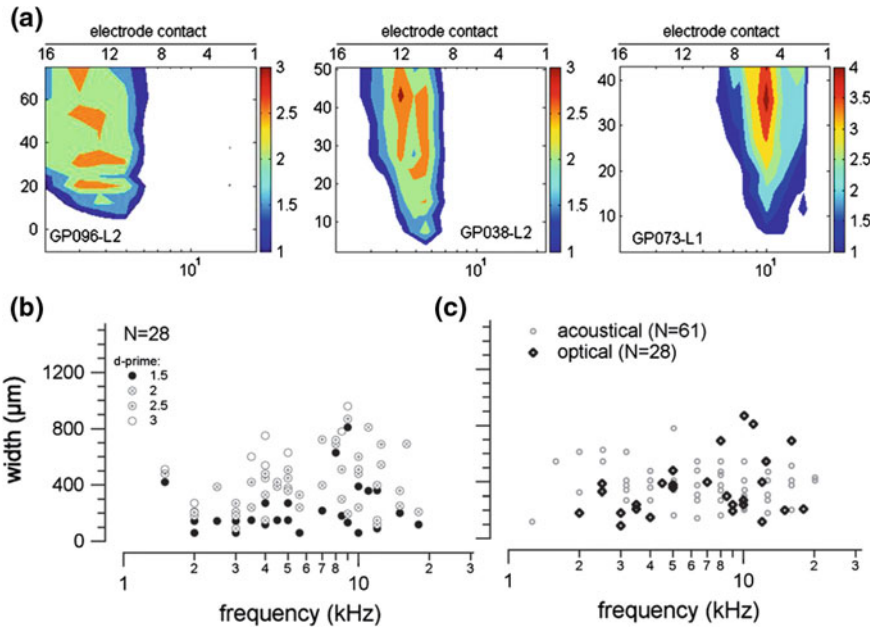

Fig. 9.1 Examples of activity plots from the central nucleus of the inferior colliculus (ICC) in response to INS in cochlea. Each contour has been taken from a different animal. *Color bars* provide the cumulative d' values (**a**). (**b**, **c**) Characteristics of optically and acoustically evoked spatial tuning curves (STCs). STC widths for d' values between 1.5 and 3 at steps of 0.5. The width of the STCs increased with d' values (**b**). STC widths for optical (*diamonds*) and acoustical (*circles*) stimuli at a $d = 2$ are presented (**c**). On average, the widths for optical stimulation were 357 ± 206 µm and 383 ± 131 µm for pure-tone stimulation. Differences were statistically significant ($p < 0.05$). (Modified from Richter et al. 2011, Figs. 6 and 7)

The results indicate that the spatial area of INS in the gerbil cochlea is similar to the cochlear area excited by a low-level acoustic tone, showing promising results for future use of INS in implantable cochlear prostheses (Matic et al. 2011).

The spatial selectivity of INS in the acutely damaged cochlea of guinea pigs was determined from neural activity recorded in the ICC during INS (Fig. 9.1). Results obtained with INS were compared to stimulation with acoustic tone pips in normal-hearing animals. For the measurements, the radiation was delivered via a 200-µm-diameter optical fiber, which was inserted through a cochleostomy into scala tympani of the basal cochlear turn. ICC responses were recorded in response to cochlear INS using a multichannel penetrating electrode array. Spatial tuning curves were constructed from the responses. The majority of ICC spatial tuning curves indicated that the spread of activation evoked by optical stimuli is comparable to that produced by acoustic tone pips.

9.2.4 Stimulation of the Vestibular Nerve

At present, the first prostheses to stimulate the vestibular nerve have been tested (Della Santina et al. 2010; Golub et al. 2014; Phillips et al. 2015). The devices use electrical current for neural stimulation and aim to reduce imbalance and disorientation caused by vestibular dysfunction. Like cochlear implants, vestibular prostheses suffer from current spread in the tissue. As a result, unintended stimulation of semicircular canal(s) occurs. As for the cochlea, INS had been explored as a novel method for stimulation of the vestibular system. Harris et al. (2009) irradiated the vestibular nerve with infrared light (wavelength λ = 1840 nm, pulse length τ_p = 10 μs–1 ms, and radiant power of 200 mW). They evoked neural responses from the eighth nerve at a location where vestibular and auditory fibers were present. While direct irradiation of the ampullae produced an evoked potential at the maximum radiation energy obtained from the diode laser, no eye movements resulted from the stimulation, suggesting that no vestibulo-ocular reflex was activated.

In a subsequent study, Rajguru et al. (2010a, b) showed that INS can activate vestibular hair cells. Initial experiments were conducted in toadfish, *Opsanus tau.* Afferents of the horizontal semicircular canal showed inhibitory and excitatory responses evoked by irradiating the neuroepithelium, which houses the sensory hair cells. Some afferents reduced their average activity during irradiation, while others increased their activity. In addition to the well-defined excitatory or inhibitory behavior of the recorded neural units, a smaller subset of afferents displayed a mixed response composed of an onset inhibitory response followed by an excitatory phase with tonic stimulation. Primary semicircular canal afferents in the toadfish are known to receive convergent inhibitory [γ-aminobutyric acid (GABA)] and excitatory (glutamate) synaptic input from hair cells (Holstein et al. 2004a, b). Data from those studies indicated that afferents receiving glutamatergic inputs may increase their discharge rate with INS. This is consistent with depolarization of hair cells and increased tonic release of glutamate. On the other hand, afferents that synapse on combinations of glutamatergic and GABAergic hair cells were observed to reduce their discharge rate with INS.

The results obtained in the fish have been recently confirmed in the chinchilla (Boutros et al. 2013). Because these single-unit responses included a mix of large excitatory, inhibitory, and mixed responses from canal afferents, it is unclear whether infrared stimulation can evoke significant vestibulo-ocular reflex (VOR) eye movement responses. Initial results of INS in the chinchilla vestibular system (using the following laser parameters: λ = 1870 nm, τ_p = 200–350 μs, f = 200–400 Hz) included the demonstration of eye movements during IR stimulation in two out of four chinchillas (Boutros et al. 2013).

For the vestibular system, it remains to be demonstrated that INS is spatially selective. Furthermore, it has not been demonstrated that stimulation of afferent nerve fibers from individual canals can be achieved once they have collected in the nerve trunk.

9.2.5 Challenges and Progress on Optical Stimulation in Cochlea

Implementing optical methods has its own challenges. Although the results from various animal models show that the auditory nerve can be stimulated with light after the neurons are sensitized with an optogenetic tool or cochleas with residual hearing are stimulated with infrared radiation, it is not completely clear how a prosthesis based on light can be realized in the near future and whether it will improve contemporary technology.

The parameter space for the optical source has to fulfill the following requirements to be suitable for use in the auditory system. First of all, the light sources cannot be large devices because they will be inserted into the cochlea. They should be able to deliver light pulses at least at 200 Hz with precise temporal control of the pulse delivery and radiant power. Light sources are typically small lasers or micro-light-emitting diodes (μLEDs). For optogenetic applications, light sources with sharp spectral tuning at the activation wavelength of the optogenetic tool are required because microbial opsin-derived tools can be deactivated by light of wavelengths near the activation wavelength (Berndt et al. 2009). Second, the ratio of number of photons emitted to the number of electrons passing though the light source (external quantum efficiency) must be high. Electrons not converted to photons contribute to heating of the cochlea, with the possibility of damages from the temperature increase.

For a comparison, electrical stimulation requires about 10 times less energy per pulse to evoke an action potential than optogenetic approaches have reported (Hernandez et al. 2014) and about 100 times less than INS would require (Richter and Tan 2014). It has to be shown that the potential increase in the number of perceptual channels in an optical implant outweighs the additional energy required for stimulation.

Progress on implantable optical prostheses in cochlea has been made. Today, a single-channel and a three-channel light delivery and stimulation control system has been developed by Lockheed Martin Aculight (Bothell, WA) for the cat cochlea. It is a wireless, battery-powered unit (<200 g) for chronic stimulation studies in large-animal models (i.e., cat). Three individually controllable lasers are housed in the smaller package, which can be carried in a backpack. Real-time control of all laser parameters, including power (0–250 mW), repetition rate (0–300 Hz), pulse width (50 μs–1 ms), and wavelength (1.85–1.87 μm), has been achieved. All data (stimulation inputs and recorded outputs) are time stamped, sorted, saved, and easily accessible from a graphical user interface. In a recent modification, a breakaway interface connector allows for attachment/detachment of various optical fiber-based implantable light delivery systems with up to three channels with <1 % variability in optical transmission (Xia et al. 2015).

Other options to deliver the light include optical fibers or waveguides. While optical fibers may be suitable for a low-density prosthesis application, optical fibers are not suitable for prostheses that encode more dense information, such as cochlear

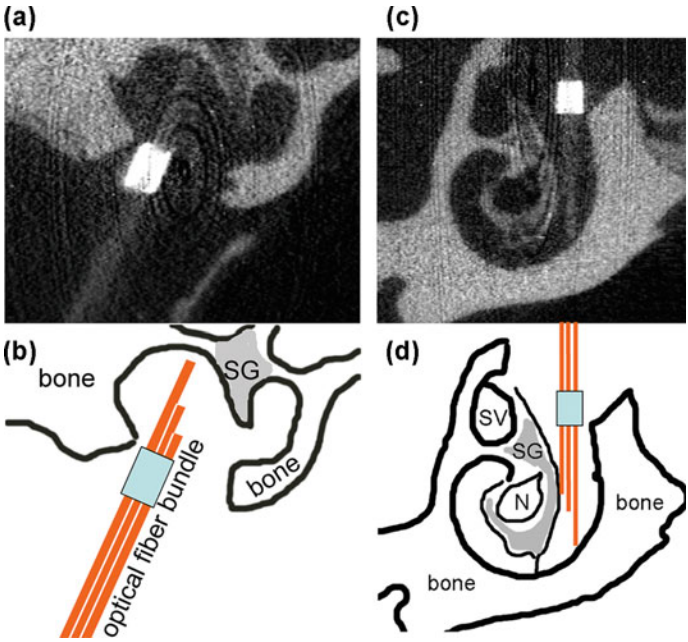

Fig. 9.2 Micro computed tomography (microCT) images of two examples showing a three-channel light delivery system inserted into a cat cochlea (**a**, **b**). Sketches of the above microCT images showing the sites of irradiation. SV, scala vestibuli; SG, spiral ganglion; N, neurons (**c**, **d**)

implants and visual prostheses. In cochlear applications, optical fibers face another challenge. They are stiff and the bending radius is not large enough to safely place the fibers along the cochlea. The fibers may break during the insertion or they damage cochlear tissue (Balster et al. 2014). Even though a single optical fiber was chronically implanted into a cat cochlea for chronic stimulation (Matic et al. 2013), the multichannel optical fiber bundles, which are used to irradiate neurons along one-half of the basal turn, are unlikely a solution for a chronically implanted light delivery system (Fig. 9.2).

In addition to the type of optical source used, the placement of the source has implications for the prosthesis design. An external source would allow for a higher power, larger battery capacity, and easy modifications to the stimulating source. However, by transmitting the optical energy transcutaneously, a significant portion of the optical power would be lost. Percutaneous links, although possible, are much less desirable because of the risk of infection. A fully implantable optical prosthesis is desirable because it eliminates the transcutaneous link except for battery charging. However, implanted optical sources need to be more efficient than externally mounted sources to reduce the heat generated by powering the device. It remains to be seen if a solid-state device can be constructed with the size and power requirements to be fully implanted and to stimulate neurons.

A novel laser technology is evolving that will help in miniaturizing the stimulation source. Vertical-cavity surface-emitting lasers (VCSELs) are available for discrete wavelengths between 473 and 1064 mm, and are currently being developed for 1855 nm (Vixar, Plymouth, MN). VCSELs can be a few micrometers in size and can be placed close to the target structure. The challenge to place the optical source close to the neural structure is the heat development of the source. Only a fraction of the energy used by the light source is converted into photons; the rest is converted to heat. Local heating constitutes a problem. First prototypes for such optrodes have been presented recently (Xia et al. 2015). The same control unit for the three-channel system can be used to power multichannel optrodes with infrared VCSELs.

μLEDs possess a narrow spectral line width and a high temporal fidelity. They are an attractive light source for benchtop optogenetic applications (Hernandez et al. 2014). Recently, an individually controllable, high-power blue μLED array was fabricated and implanted in cats (Fig. 9.3) and will be tested for optogenetic application. Again, μLEDs generate substantial heat and their in vivo use requires caution to avoid heat damage of the tissue.

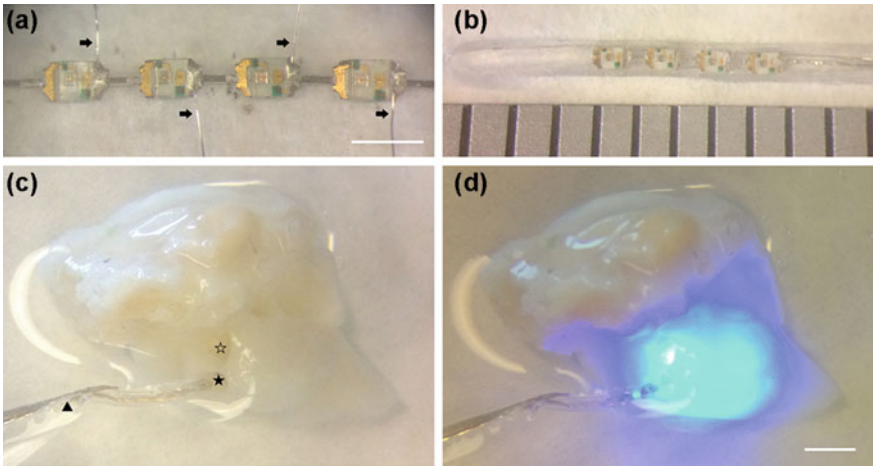

Fig. 9.3 Optrode fabrication. Step 1: μLEDs were placed on top of a 125-μm-diameter silver wire with all cathodes connected on the wire (also serving as a heat sink) using conductive silver epoxy. Step 2: The anodes of μLEDs were connected to the Teflon-coated silver wires (75 μm, *black arrows*) with conductive silver epoxy. The *white bar* on the lower right equals 1 mm (**a**). The tip of an implantable four-channel μLED optrode array with silicon embedded. The *scale bars* at the bottom are spaced 1 mm apart (**b**). The insertion of the optrode array into a cadaveric cat cochlea. The *hollow star* shows the round window, the *solid star* shows the cochleostomy accessing the scala tympani, and the *solid triangle* shows the optrode array (**c**). One μLED of the inserted optrode array is emitting in cadaveric cat cochlea. The *white bar* on the lower right equals 3 mm (**d**)

9.3 Mechanisms for Stimulation with Light

Photon–tissue interactions are complex and determined by the laser parameters and the tissue properties. Spot size, radiation wavelength, pulse duration, pulse repetition rate, and radiant energy, for example, characterize the laser properties, while absorption and scattering are important tissue properties. For both optogenetics and INS, a chromophore exists that absorbs the photons.

In optogenetics, the molecular chromophores are exogenous molecules, which are introduced into the tissue. The conversion of the photon energy results in a molecular conformational change, which opens an ion channel, allowing the control of neural activity (Zhang et al. 2006; Yizhar et al. 2011; Bernstein et al. 2012). The selection of the optogenetic tool determines whether excitation or inhibition can be achieved. As both inhibition and excitation are possible, the technique can be used to study and change the dynamics of neural networks.

In INS, the photon energy is converted into heat. Heating of the target structure results in both optoacoustic and other photothermal effects. It is unlikely that pulsed, mid-infrared lasers, such as the FEL, Ho:YAG, or Aculight diode lasers, evoke neural responses via a photochemical reaction. The photon energies are below the energies required to move an electron to an excited state, as is needed for a photochemical reaction. For example, the energy in individual photons from the Ho:YAG is approximately 0.58 eV. The value corresponds to approximately 52 kJ/mol bond energy. Typical ion bond energies are larger and are in the range of 100–1000 kJ/mol. Furthermore, data from Wells et al. did not identify a particular wavelength between 2 and 10 μm at which the laser stimulation was significantly enhanced, which would have suggested a photochemical reaction (Wells et al. 2007).

9.3.1 Photothermal Effects: Temperature-Sensitive Ion Channels

Photothermal effects include the activation of heat-sensitive ion channels (Rhee et al. 2008; Albert et al. 2012), changing the dynamics of ion channels (Wells et al. 2007; Feng et al. 2010), the increase of intracellular calcium (Rhee et al. 2008; Rajguru et al. 2010b; Dittami et al. 2011), and the change in membrane capacitance (Shapiro et al. 2012; Liu et al. 2014).

It has been proposed that the mechanism for INS is the direct activation of heat-sensitive ion channels such as transient receptor potential (vanilloid) or TRPV channels (Caterina et al. 1997; Güler et al. 2002; Albert et al. 2012). TRPV1 is perhaps best known for being activated by the chemical capsaicin, the main ingredient in hot chili peppers that produces a burning sensation. TRPV1 channels are also stimulated by other vanilloid compounds, acid (pH $\leq$ 5.9), and heat ($\geq$43 °C), making it a key channel in peripheral nociception. TRPV channels are found in

small neurons, including the sciatic nerve, the dorsal root, and trigeminal ganglia of rats (Caterina et al. 1997), as well as cochlear structures of both the rat and guinea pig (Balaban et al. 2003; Takumida et al. 2005; Zheng et al. 2003) and have been identified in vestibular neurons (Albert et al. 2012).

Rhee et al. (2008) stimulated cultured primary sensory neurons from the inferior ganglia of rat, which express the vanilloid transient receptor ion channel (TRPV1). Laser pulses (λ = 1,850 nm) from a diode laser were delivered with a 200-μm silica to stimulate the neuron cultures. During laser stimulation, the authors monitored the intracellular calcium concentration using the fluorescent calcium indicator fura-2. Short trains of 2-ms infrared pulses ($\sim$5 W instantaneous power) activated the TRPV1 ion channels rapidly and reversibly. Identical INS did not increase intracellular calcium in the absence of extracellular calcium or after the application of a TRPV1-channel blocker. In a different set of experiments, Albert et al. (2012) suggested that TRPV4 channels mediate the infrared laser–evoked response in sensory neurons. They showed in whole cell patch-clamp recordings that voltage-gated calcium and sodium channels contribute to a laser-evoked neuronal voltage variation. The application of micromolar concentration of ruthenium red and RN 1734 blocked the responses. The results suggested that the TRPV channels are the primary effectors of the chain reaction triggered by mid-infrared laser irradiation. Findings that argue against an activation of TRPV channels were obtained in studies conducted in dorsal root and the inferior ganglion of the vagus nerve (nodose ganglion) neurons. The results showed that depolarizations evoked by INS have multiphasic kinetics comprising fast and slow components (Katz et al. 2010). For their experiments, Katz et al. irradiated the neuron cultures with 5- to 10-ms pulses of λ = 1889 nm. They found a near-uniform distribution of responsive neurons with increased membrane conductance, and the negative reversal potential value (-41 ± 2.9 mV) suggests that INS is unrelated to the activation of heat-sensitive TRPV1 channels. The long duration of the responses to INS favors an involvement of second messengers.

9.3.2 Photomechanical Effects

For photomechanical effects, both laser-induced stress waves and volumetric thermal expansion must be considered as a mechanism for stimulation. Wells et al. (2007) measured cell surface displacements using differential phase optical coherence tomography (DP-OCT), which could result from heat-induced volumetric expansions. Pressure measurements with a needle hydrophone revealed values below 1 bar. From their experiments, they argued against a photomechanical mechanism from stress wave generation.

Laser-induced pressure waves in water are well documented for experiments with high local absorption. Pulsed 1850-nm laser light generates a measurable pressure (Teudt et al. 2011; Schultz et al. 2012a, b). Teudt et al. (2011) reported that for the laser's maximum energy levels and with a 200-μm-diameter optical fiber,

the peak-to-peak sound pressure can reach 62 dB SPL in air. Because the cochlea is filled by endo- and perilymph, it is of interest to what extent laser-induced sound waves exist when the absorbing volume is significantly decreased by immersion in water. Measurements in a swimming pool showed that radiant exposures of 0.35 J/cm^2 generated a pressure of 31 mPa in water. Note, radiant exposure at stimulation threshold for INS is about 0.016 J/cm^2.

It has been stated that the energy required for a primary photomechanical mechanism is much higher than those used by Wells et al. (2007) and Izzo et al. (2006). Valid arguments include that the parameter space of INS is outside stress confinement. Stress confinement occurs when the optical energy accumulates in the tissue before a laser-induced stress wave can propagate out of the irradiated area, leading to large stress waves. For stress confinement to occur when irradiating with these wavelengths, the pulse duration should be shorter than 500 ns, which is orders of magnitudes shorter than the pulse durations used for optical stimulation. On the other hand, results have been indicating that INS in the cochlea is dominated by a mechanical event and the stimulation of remaining hair cells (Baumhoff et al. 2013; Thompson et al. 2015). The discrepancies have not been completely resolved at this point, and direct stimulation of SGNs with INS is shown in other studies (Young et al. 2015).

9.3.3 Heat-Induced Capacitive Change of the Cell Membrane

Using oocytes, Human Embryonic Kidney 293 cells (HEK293 cells), and artificial lipid membranes, it has been demonstrated that infrared light excites cells through a general electrostatic mechanism. Infrared pulses are absorbed by water, producing a rapid local increase in temperature. This heating reversibly alters the electrical capacitance of the plasma membrane, depolarizing the target cell. This mechanism is fully reversible and requires only the most basic properties of cell membranes (Shapiro et al. 2012). The findings by Shapiro et al. are supported by a recent study in which initial results show that pulsed infrared radiation rapidly alters the capacitance of the membrane through charge redistribution and evokes mitochondrial Ca^{2+} currents (Liu et al. 2013). Although causality has not been shown, the present results are consistent with the hypothesis that these biophysical events underlie infrared entrainment of miniature postsynaptic currents. Several authors discussed the crucial role of mitochondria and calcium ions in the mechanism for INS (Rajguru et al. 2010b; Dittami et al. 2011). In a recent series of experiments, it has been shown that pulsed infrared radiation consistently evoked calcium-related responses in neurons (Lumbreras et al. 2013).

9.4 Conclusions and Future Directions

Recent research efforts have demonstrated that optical radiation can be used to stimulate neurons. With the development of compact light sources to evoke neural responses, it has been validated that stimulation with optical radiation is spatially selective. Stimulation with optical radiation has advantages and limitations when compared with stimulation with electric current. The differences between stimulation modalities could be selectively exploited for the next generation of neural interfaces and as a neurophysiology research tool.

With the objective to design and build INS prostheses, it is extremely important to understand the mechanism. Improved understanding will allow optimization of the laser parameter space and will aid the long-term safety of INS. Further work to understand the effect of beam quality (e.g., focused vs. collimated beam) on stimulation will aid in the design of efficient research and clinical stimulators.

The advancement of optogenetics and thermogenics also requires the development of enabling technology. Visible light is largely scattered in tissue and requires small light sources to be placed close to the target structures. These needs for the field will nurture engineering attempts for building small and powerful light sources and the development of advanced and more efficient waveguides.

The biggest challenge for optogenetics will be the translation into the clinic. It has to be demonstrated that expression of the optogenetics tools is safe. Furthermore, it will be important to show that effective stimulation of selected structures is possible in large volumes, different from those present in small rodents such as mice. This work is still in its early phase. However, it holds promise for the future given the potential opportunity for more precise stimulation of specific target neural populations and that with more channels may come improved performance in noisy listening environments or for the appreciation of music.

An additional challenge for optical stimulation is the relatively slow repetition rate of pulses that can be achieved. For INS, the heat that is generated from the infrared light during stimulation must be removed accordingly. Heat removal is limited in its speed. Therefore, fast pulse repetition rates would result in the heating and damage of the neural structures of the cochlea. For optogenetics, the speed is limited by the dynamics of the optogenetic tools, the ion channels. The development of novel sensitive channels is required to meet this need. Likewise, novel coding strategies must be developed that accommodate the limited repetition rates at each electrode but take advantage of the increased number of channels at which stimulation can occur simultaneously.

Compliance with Ethics Requirements

Xiaodong Tan declares that he has no conflict of interest.

Nan Xia declares that she has no conflict of interest. Nan Xia was supported bu the China scholarship council.Claus-Peter Richter is the founding Chief technology Officer (CTO) of Resonance Medical, LLC, and is inventor on several patents pertaining to optical stimulation and the design of optical implant electrodes.

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Chapter 10
Clinical and Translational Research: Challenges to the Field

Colleen G. Le Prell and Edward Lobarinas

Abstract Clinical and translational research are essential to patient care. Throughout the volume, numerous examples and cases were provided; these served to illustrate the unique challenges that must be overcome and the work that lies ahead for advancing hearing healthcare. This final chapter provides a summary of common themes across chapters. Across various "disorders" such as auditory processing disorders, tinnitus, and sudden onset hearing loss, there were challenges related to differential diagnosis. Other challenges cut across noise-induced hearing loss, drug-induced hearing loss, and the other disorders listed above; there is a need for standardized metrics that allow for results to be compared among studies and for assessing novel treatment by researchers and clinicians. The overall healthcare goal is to develop an evidenced-based practice approach so that emerging treatments reflect the highest standard of demonstrated efficacy. The chapters contained in this volume provide an essential introduction to the processes, successes, and challenges associated with translational research and the goal of better health outcomes.

Keywords Advances in hearing research · Auditory disorders · Best practices · Clinical research · Evidence-based practice · Translational research

10.1 Introduction

The chapters in this volume illustrate the extent to which translational research is a process whereby basic research makes its way into healthcare or other consumer applications. The goal of this process is to provide benefit to patients as part of evidence-based medicine (by physicians) or evidence-based practice (by other

C.G. Le Prell (✉) · E. Lobarinas
Callier Center for Communication Disorders, University of Texas at Dallas,
1966 Inwood Road, Dallas, TX 75235, USA
e-mail: colleen.leprell@utdallas.edu

E. Lobarinas
e-mail: edward.lobarinas@utdallas.edu

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clinicians such as audiologists or speech language pathologists). Throughout this volume, the authors have noted hurdles associated with moving results from basic and preclinical scientific investigation into clinical trials and additional hurdles to overcome in moving therapies out of clinical trials into widespread application. In this final summary chapter, a synthesis of the recurring themes from the case studies in previous chapters is presented, with an effort to point to commonalities across investigator experiences. Despite significant differences across the topics covered by each chapter and the specific goals and efforts of each investigator, there were many shared challenges among translational activities. Translational research is fundamentally important to the common goal shared by scientists, clinicians, and industry, with the ultimate goal of improved patient care options and better health care outcomes. The lessons from the case studies are synthesized in this final chapter with the intent of highlighting solutions and strategies for success. Common themes include Etiology and Diagnosis (Sect. 10.2), Objective Metrics (Sect. 10.3), Common Equipment Platforms (Sect. 10.4), Regulatory Requirements (Sect. 10.5), and Placebo Controls (Sect. 10.6).

10.2 Etiology and Diagnosis

One of the challenges discussed in several of the case studies was that of identifying appropriate treatment when the etiology of a disorder is unknown. The relevance of this issue should be immediately clear; it is difficult to assess the efficacy of any therapeutic intervention when the patient population does not have a single identifiable cause and there is no agreed upon diagnostic test or protocol. In Chap. 3, Kraus and Anderson discussed the typically unknown etiology of auditory processing disorder (APD), noting fundamental disagreement about whether APD and deficits in attention and memory are separate entities or multiple symptoms with a shared cause. They further pointed to APD as frequently being comorbid with other learning problems such as dyslexia and attention deficit disorder, further increasing the difficulty of identifying an appropriate study population.

Similarly, in Chap. 4, Montgomery, Bauer, and Lobarinas made it clear that sudden sensorineural hearing loss (SSHL) has many possible etiologies, which led them to classify SSHL as a syndrome rather than a diagnosis. As they discuss, the etiology of SSHL might be related to cochlear trauma, viral infection, vascular occlusion, an autoimmune response, or other unknown etiology. Consequently, clinicians must often select therapies based on their own professional clinical experiences or expert opinion guidance documents rather than a robust body of evidence of efficacy. As it relates to translational research, SSHL presents a number of challenges, primarily because of the spontaneous nature of the syndrome. Whereas objective measures can be used to quantify and describe the degree and configuration of the hearing loss associated with SSHL, this has been of limited use toward research efforts aimed at providing novel therapeutic strategies. As described in Chap. 4, objective testing for viral, autoimmune, and metabolic

abnormalities has not provided significantly better understanding of the disease process, a necessity for robust clinical trial design. Owing to the paucity of animal models and given the high rate of spontaneous recovery among humans, it has been challenging to assess proposed interventions adequately. Furthermore, the ethics of withholding treatment that "might" provide benefit must be considered carefully regardless of the degree of evidence supporting efficacy. Multicenter approaches have been used (Rauch et al. 2011), and it would be worthwhile for new multicenter studies across medical centers to collect a number of additional biometrics from each participant to determine if specific biomarkers among those who develop SSHL can be identified. Those data in turn could be used to develop animal models if those risk factors can be reliably induced in such models, or the data could provide strategies for identifying those at higher risk for SSHL for whom existing or promising interventions may be evaluated. Given the identified and associated risk factors, this would seem a plausible approach toward finding efficacious interventions for this syndrome.

Chapter 7, by Allman, Schormans, Typlt, and Lobarinas, described the multiple potential causes of tinnitus, the substantial disagreement regarding outcome measures for efficacy of treatment, the relevance of animal models, and the lack of clarity regarding the underlying pathophysiology. For example, current "theories" of tinnitus and therapeutic approaches are based on tinnitus as a centrally driven phenomenon that can occur independent of hearing loss, work that is supported by imaging studies (Gu et al. 2010). However, the majority of patients with tinnitus also have hearing loss (Chung et al. 1984), and one of the most cited references (House and Brackmann 1981) purported to support a central hypothesis showed that nearly half of the patients who had surgical excision of the auditory nerve reported an improvement in tinnitus. Thus it is clear that the symptoms of tinnitus could arise from either or both peripheral and central mechanisms, complicating the design and subject selection for clinical trials. The concept of subtyping tinnitus for evaluating pharmacotherapy has been recognized (Langguth et al. 2009), and like the aforementioned examples throughout this volume, subtyping is likely to play a major role in future clinical trial designs.

As discussed in the preceding paragraphs, continued advances in our understanding of APD, SSHL, and tinnitus, as well as continual data-driven refinement in therapies, will likely lead to tailored therapies for different subgroups of patients with each of these broad disorders.

When the etiology of a disorder is unknown, it is frequently difficult to identify effective treatments, as there may be only a subset of "responders" based on an unknown but shared etiology for which that treatment works. The concept of subgroup analysis was briefly introduced in Chap. 2 by Le Prell and has been discussed in detail by others for tinnitus as it relates to randomized controlled trials (RCTs). For example, Searchfield (2011, p. 422) explicitly cautions, "But the results of many RCTs may be misleading due to the treatment of persons with tinnitus as a homogeneous population, washing out real effects in groups of individuals due to comparisons based on mean data, lax inclusion/exclusion criteria, and nonspecific placebo effects (Dobie 1999). Subtypes of tinnitus appear to exist and likely respond

differently to treatments (Tyler et al. 2008); the use of antidepressants, for example, might be useful in treating tinnitus patients with comorbid depression but have no effect on the tinnitus population as a whole (Dobie et al. 1993)." In this same series of papers, Langguth et al. (2011, p. 432) also highlight shortcomings in applying group outcomes to individual patients, as not every patient achieves the average benefit. They eloquently state, "Evidence based on clinical studies and clinical relevance for the treatment of the individual patient are not identical. If a specific intervention has been demonstrated to have a small benefit in several controlled studies involving large samples, it is considered the highest level of evidence. However, this small benefit may be completely irrelevant, clinically, for a specific patient. In contrast, if an intervention has been shown to stop tinnitus in case series of a specific rare subform of tinnitus (e.g., carbamazepine treatment in "type-writer-tinnitus"), it is only considered as a recommendation of relative low evidence, but it has a huge clinical relevance for the affected patient." The lack of evidence that is available to guide treatment decisions for tinnitus patients makes evidence-based care difficult indeed (for additional discussion, see Hoare and Hall 2011).

In Chap. 8, Staecker, Klickstein, and Brough discussed the issue of unknown etiology of hearing loss from a different perspective. They are in the process of investigating a genetic therapy that specifically drives the regeneration of outer hair cells in the inner ear. The patients who will presumably derive the most benefit are those who retain afferent function but have significant outer hair cell loss, conditions that would allow for sound stimulation to be carried to the brain after outer hair cell replacement. If patients in whom the therapy is assessed do not have an intact ascending pathway, the regrowth of outer hair cells would be ineffective in driving functional improvement, even if hair cell growth is successfully accomplished. Thus, the enrollment criteria are critically important to the potential for success in the novel first-in-man (FIM) assessment of gene therapy for the inner ear in clinical trials. Similar challenges will be readily apparent for any future FIM assessment of the novel efforts to control neural activity using light, an emerging approach described in Chap. 9 by Tan, Xia, and Richter.

Clearly, there are challenges in precisely diagnosing the causes of auditory dysfunction given the wide variety of clinical symptoms presented by patients. In some cases, better animal models are urgently needed so that therapies can be assessed relative to a known deficit or etiology. In other words, researchers must do a better job producing models for each of the individual and specifically known "subtypes" of patients who are observed within a larger clinical population. This is not a challenge solely to basic scientists, however, as clinician-scientists (including MD-PhDs and AuD-PhDs) must also seek to identify what distinguishes patients within clinical subtypes in order to provide guidance on the necessary models for which therapeutics should be assessed. This is the fundamental process through which translational research best proceeds; observation of a clinical disorder in the course of patient care drives basic research to understand the mechanism of the disorder, thus providing a rationale for therapeutic intervention that can be assessed in preclinical research, hopefully leading to assessments in humans under clinical trial testing, and, if successful, adoption into evidence-based care.

10.2.1 The Case of Auditory Neuropathy/Auditory Dyssynchrony

Relevant to the current discussion of etiology and diagnosis is the issue of auditory neuropathy/auditory dyssynchrony (AN/AD). In AN/AD, the specific challenge for treatment is that there are multiple etiologies of auditory neuropathy. The classic profile of AN/AD is intact cochlear bioamplification as measured by otoacoustic emissions (OAEs), suggesting present and normal functioning outer hair cells in combination with an abnormal or absent auditory brainstem response (ABR), an indication of aberrant neural responses to acoustic stimuli. The precise locus of the underlying pathology, however, is not well understood and the specific pathology likely varies from patient to patient. There are likely multiple varieties of AN/AD. Patients may have either pre- or postsynaptic damage, and postsynaptic damage may be at the nerve terminal or involve the proximal auditory nerve (Starr et al. 2000; Santarelli et al. 2008). Because AN/AD could be the result of damage to inner hair cells, synapses, the auditory nerve, or the central nervous system, there is a wide range of functional deficits. Functional deficits vary from deafness in the most extreme cases to lesser deficits such as fluctuating hearing sensitivity, intact hearing but poor speech comprehension, or intact hearing with difficulties in noise (for discussion, see Sininger 2008). As a result of the varied etiology and variable severity of symptoms, the diagnosis or misdiagnosis is a significant issue in patient management (Berlin et al. 2003).

The data from patients with AN/AD reported by Starr et al. (1996, 2000) describe individuals with normal hearing sensitivity to audiometric stimuli but severe difficulties processing speech. Impaired temporal processing (Zeng et al. 1999; Michalewski et al. 2005) and impaired loudness adaptation (Wynne et al. 2013) have also been reported in patients with AN/AD. The poorer temporal processing is often accompanied by deficits in pitch discrimination at low frequencies, temporal integration, gap detection, temporal modulation detection, backward and forward masking, signal detection in noise, binaural beats, and sound localization using interaural time differences (Zeng et al. 2005). This pattern of perceptual deficits has been specifically described as the opposite of what is routinely observed in hearing-impaired individuals who have increased thresholds and impaired intensity perception but relatively normal temporal processing after adjusting for hearing sensitivity (Zeng et al. 2005).

In contrast to the descriptions by Starr and others, clinical diagnosis of AN/AD often extends to include individuals with elevated audiometric thresholds, resulting in an even greater diversity of clinical symptoms. The more recent AN/AD spectrum disorder terminology suggests that the disorder may arise from either a classic neuropathy, whereby neurons are missing or nonfunctional, or dyssynchrony, whereby synapses and neurons may be present but exhibit abnormal synchrony. With a broad inclusion criterion and multiple potential sites of dysfunction, translational research efforts at evaluating effective treatment approaches face

significant challenges. This is particularly problematic when therapeutic recommendations now include the surgical implantation of cochlear implants.

Cochlear prostheses have been implanted in some patients in an effort to restore discharge synchrony, with variable success across patients (Kontorinis et al. 2014; Ji et al. 2015). Predictors for successful rehabilitation with a cochlear implant have been offered (Jeong and Kim 2013) and there is some support for this invasive surgical intervention based on the possibility of benefit (Fernandes et al. 2015). The 2008 consensus statement (National Health Service [NHS] 2008; Simmons 2009) supports the use of cochlear implants for AN/AD if amplification has not been otherwise successful in rehabilitation of auditory function. However, there is also clear guidance that nonsurgical rehabilitation such as hearing aids, FM systems, clear speech training, and education to learn sign language should be considered before advocating surgery to implant such devices (Berlin et al. 2003; NHS 2008; Hood 2011).

In the Guidelines document, Sininger (2008) notes that there are many physicians who advocate expedited implantation if aided speech performance is poor. Aided speech performance in children with AN/AD is variable, but clearly there is a population that achieves benefit (Roush 2008). Given these findings, cochlear implant decisions should be made cautiously (Shallop 2008). Despite some success with cochlear implantation, there would be cause for concern in broadly adopting invasive therapeutic interventions for a disorder that is broadly defined, that is based on a wide range of symptoms, and where there is limited knowledge of the underlying pathology. Although cochlear implantation is an effective intervention for some patients, a review of the literature used to support the development of the guidelines suggests that the recommendations were not based on well-controlled clinical trials, a clearly defined disorder, or a robust body of scientific evidence but rather from reports with small sample sizes and varied levels of success (Buss et al. 2002; De Leenheer et al. 2008; Walton et al. 2008). The current recommendations are perhaps the best possible compromise in the absence of RCT data, with hearing aids advocated before implantation, and careful counseling on the potential that the implant may not yield benefit.

10.3 Objective Metrics

Throughout this book, most, if not all, of the chapters have discussed the importance of objective metrics that can be consistently applied across studies. This is important for determining the proper diagnosis for which a potential treatment plan can be developed as well as for allowing efficacy to be assessed and therapies to be compared. Objective, agreed-on measures are critically important. If the goal of clinical or translational research is to move promising therapies into healthcare application, there obviously must be clinical outcomes that can be used to assess the therapeutic value.

10.3.1 Objective Metrics: APD

Chapter 3, by Kraus and Anderson, described a major challenge for APD studies, as there are no agreed-on diagnostic criteria. Therefore, this team began by developing an objective test for APD. The most common manifestation of APD is difficulty understanding speech in noise, although paying attention to relevant sounds and ignoring sounds that are not relevant can also be problematic. Because the attention and memory requirements for tasks that directly assess these difficulties may reduce the validity of those tests, Kraus and her colleagues sought an objective measure. They proposed that the auditory brainstem response to complex sounds (cABR) might be an appropriate tool based on its high fidelity to the evoking stimulus (typically a speech sound [da]), its high reliability, and its repeatability from session to session. Finally, they describe the validation of the cABR showing that distinct pathological response patterns accompany different diagnoses. For example, reading disabilities were accompanied by delayed timing and reduced representation of the first harmonic, dyslexia was accompanied by increased variability from trial to trial, autism was accompanied by less accurate pitch tracking, and poor speech-in-noise performance was accompanied by poorer subcortical representation of the fundamental frequency and more neural signal degradation when noise was added.

These data are both encouraging and promising, but important additional work is needed to better define the cABR metric itself, to identify whether a given individual's response is normal or disordered, and to better quantify improvement and treatment efficacy. For instance, what are the parameters that would trigger a diagnosis of APD, and what would constitute a clinically significant improvement in the cABR? Also important, where does an "atypical" cABR begin? In other words, how different must an individual response be from the group normative data to be defined as atypical? If the cABR is indeed diagnosed as atypical, how is improvement quantified? That is, should it be quantified based on a percent improvement in amplitude, a numerical change in voltage, or perhaps the shifting of the cABR amplitude and latency such that it falls within population normative data? Perhaps most importantly, is there a strong, reliable correlation between change in cABR and the alleviation of the subjective symptoms that brought the patient to the clinician for care in the first place? Answers to these kinds of questions will be necessary to move toward clinical implementation, as well as third-party reimbursement for testing. Additional data on both the cABR and changes in the specific deficits or problems that motivated patients to seek care will be helpful in establishing the importance and validity of the cABR metric for therapeutic assessment. The data available from the studies reviewed in Chap. 3 are encouraging and provide promising proof of concept data, and it will be interesting indeed to monitor advances in this area.

10.3.2 Objective Metrics: Noise-Induced Hearing Loss

Chapter 5, by Lynch, Kil, and Le Prell, pointed to similar challenges in the selection of objective metrics for studies assessing the prevention of noise-induced hearing loss (NIHL). Pure-tone air-conduction audiometry is the gold standard for human hearing assessment and identification of hearing loss. In testing a drug developed for the prevention of NIHL, one could simply assess group differences in the amount of hearing threshold shift in participants randomized to a placebo condition and those randomized to an experimental condition (e.g., Quaranta et al. 2004, 2012). It is not clear that this is the most valid approach, however, as small differences in threshold shift might be statistically significant but have little clinical significance (e.g., the 2.5-dB shift in treated workers versus a 2.8-dB shift in placebo control condition, with $p = 0.03$, in Lin et al. 2010). Alternative approaches could include assessment of the percent of subjects with a given level of change, as was done recently by Kopke et al. (2015). Using pure-tone audiometry, they assessed whether the rate of subjects demonstrating significant threshold shift (STS), defined as an increase of more than 20 dB at any test frequency or an average increase of more than 10 dB at any two consecutive test frequencies, was different in the placebo group and the group treated with an experimental agent; the criteria used for ototoxic change according to the American Speech-Language-Hearing Association (ASHA). There are other explicit change criteria specifically developed for identification of a significant occupational noise-induced threshold shift (Occupational Safety and Health Administration [OSHA] 1983; National Institute for Occupational Safety and Health [NIOSH] 1998) that could be considered if a proportional analysis will be completed, as reviewed by Lynch, Kil, and Le Prell in Chap. 5. A concern about any proportional analysis, however, is that an important drug benefit could be "missed" if the majority of the control group falls just short of the criterion deficit, providing a very low baseline against which decreased prevalence can be assessed.

10.3.3 Objective Metrics: Drug-Induced Hearing Loss

Campbell and Fox describe a similar challenge, the selection of criteria for change, in Chap. 6. They note that the consensus guidelines provided by ASHA (1994) and specified in the position statement of the American Academy of Audiology (AAA) (2009) provide widely accepted guidance on the definition of ototoxic change. However, they note that this guidance was designed for detection of ototoxicity during clinical monitoring. These statements were not intended to be used for the determination or grading of hearing loss as an adverse event in a clinical trial nor were these designed to determine if a novel pharmaceutical agent reduced ototoxicity. There are no formal, universally accepted guidelines in place for reporting ototoxic adverse events in clinical trials or for determining the significance of obtained otoprotective benefits. Although the US Food and Drug

Administration (FDA) does not currently provide practice guidelines specifically for clinical trials in this area, Campbell and Fox review a number of scales and approaches that have been proposed or used in other studies. Indeed, there are multiple clinical trials on the prevention of cisplatin-induced hearing loss that have been completed, are now in progress, or will begin in the near future, and these trials may serve as models for future investigations (for review, see Anderson and Campbell 2015). As discussed in Chap. 1, Campbell and Fox note that the selection of the specific scale or measure of loss to be used as a primary end point is something that needs to be negotiated with the FDA as part of the approval process. Because the "best" measure may differ from study to study and FDA approval of the protocol is essential, they note that "cookbook" procedures cannot be offered within a chapter such as this one at this time.

10.3.4 Objective Metrics: Tinnitus

With respect to measuring changes in hearing induced by noise or ototoxic drug insult, there is at least consistency in that the measures are typically based on threshold measures that can be readily obtained using subjective or objective measures. Tinnitus, in contrast, presents a different scenario. In Chap. 7, Allman, Schormans, Typlt, and Lobarinas described the challenges of translational research on the alleviation of tinnitus. Human tinnitus assessment is typically based on surveys such as the tinnitus reaction questionnaire (Wilson et al. 1991), tinnitus handicap questionnaire (Henry and Wilson 1998), tinnitus handicap inventory (Baguley and Norman 2001; Zeman et al. 2011; Bauer et al. 2016), or the tinnitus functional index (Henry et al. 2016)—measures that reveal the degree of psychological distress associated with tinnitus. Clearly, the use of different surveys across studies has made it difficult to compare outcomes across agents that have been assessed for potential alleviation of tinnitus symptoms. As discussed in Sect. 10.3.1 with respect to changes in the cABR, however, it is not clear what constitutes a clinically significant improvement for an individual patient, or a treated group, within any given tinnitus survey. In other words, how much must the score on any given survey tool change for the change to be deemed clinically significant? In addition, given that tinnitus is a perceptual phenomenon, what if the sound of tinnitus is significantly reduced but there is no corresponding reduction in tinnitus distress? These and other questions regarding outcome measures and the need for objective measures will continue to be a challenge for tinnitus research and the translational process for the foreseeable future.

10.3.5 Objective Metrics: "Hidden" Hearing Loss

The current hot topic of "hidden hearing loss" is highly relevant to the issue of objective assessment. Sound-evoked ABR thresholds are the gold standard metric for assessing auditory function in animals, and the harmful functional consequences of noise are typically measured using ABR thresholds. Recent data, however, have shown that ABR thresholds provide an incomplete picture of recovery after a noise exposure because there can be evidence of lasting ABR amplitude decreases at suprathreshold presentation levels despite complete recovery of hearing sensitivity as indicated by a return to prenoise ABR thresholds in both mice (Kujawa and Liberman 2006, 2009; Wang and Ren 2012) and guinea pigs (Lin et al. 2011; Furman et al. 2013). Specifically, the ABR wave I amplitude, a correlate of cochlear output, is reduced even though the threshold of wave I and the amplitude of wave V, a correlate of central auditory system output, remain unchanged. These results suggest that noise exposures can result in damage to the inner ear that escapes detection by conventional threshold assessment.

The results from the animal studies have been widely interpreted by members of the scientific community as reflecting that any temporary threshold shift (TTS) is almost certainly hazardous across mammalian species, including humans. This assumption is questionable, however, as newer studies have now provided experimental evidence that smaller TTS deficits were not accompanied by lasting change in ABR amplitudes (Hickox and Liberman 2014; Fernandez et al. 2015; Jensen et al. 2015). The work by Maison et al. (2013) raises further questions with respect to whether there is a causal relationship or a direct correlation between the size of the TTS and observed synaptopathic change. In general, TTS deficits of 40 dB or greater, measured 24 h postnoise, have resulted in synaptopathy, whereas TTS deficits of 30 dB or less have not appeared to result in synaptopathic change (for discussion, see Spankovich et al. 2014; Le Prell and Brungart, in press).

Determining the critical boundary at which damage begins is essential because the decreased ABR wave I amplitude data from the animal studies have been used to suggest that federal guidelines on workplace noise exposure are flawed (Kujawa and Liberman 2009; Kujawa 2014; Kujawa and Liberman 2015). Specifically, in the absence of significant threshold shift and hearing loss (STS, as explicitly defined in 29 CFR 1910.95), there is no reportable injury to the worker. To be reportable, workers must not only experience an average change of 10 dB at frequencies of 2, 3, and 4 kHz, but the pure-tone average (PTA) threshold at those three frequencies must also be poorer than 25-dB hearing level (HL), with 0-dB HL being a normative reference level that is accepted nationally (ANSI S3.6-1989) and internationally (ISO/R226-1985). In contrast, the rodents in the animal studies do not have PTS. Instead, they show only decreased ABR amplitudes, which are attributed to decreased numbers of synaptic connections, a form of neuropathic damage (for recent review, see Kujawa and Liberman 2015).

There has been significant speculation that noise-induced neuropathic damage may explain the disproportionate difficulties processing speech in noisy

environments among some individuals without "hearing loss" (Kujawa and Liberman 2009; Lin et al. 2011; Makary et al. 2011). Given that a hallmark of the aforementioned clinical AN/AD disorder includes intact otoacoustic emissions in combination with absent or grossly abnormal ABR, Kujawa and Liberman (2015) have pointed to patients with AN/AD as examples of a human condition consistent with their results in animals. Moreover, they suggest that the frequent issues with speech processing in this clinical population as well as potentially many others are consistent with the speech-in-noise deficits they predict would accompany synaptopathy in mice with reduced ABR wave I amplitudes. Similarly, Moser et al. (2013) explicitly predicted that clinical features of AN/AD (as defined in mice) should be similar to those measured in patients with AN/AD. These are interesting and provocative predictions, but empirical data are necessary before concluding that there is a direct relationship between hearing-in-noise performance and synaptopathy. Hope et al. (2013) do report poorer speech-in-noise performance in Royal Air Force aircrew pilots than administrators in the absence of significant PTA threshold differences (PTA at 0.5, 1, 2, and 4 kHz; $n = 10$ per group), but use of the PTA metric may have masked higher frequency hearing differences (given that noise typically affects 3, 4, and/or 6 kHz thresholds) and ABR data were not collected. In contrast, Bramhall et al. (2015) were able to correlate poorer speech-in-noise performance (using the QuickSIN test) with smaller wave I ABR amplitude in English-speaking adults ages 19-90 with PTA thresholds of 45 dB HL or better (PTA at 0.5, 1, 2, and 4 kHz), but the relationship between QuickSIN scores and ABR amplitude was greatest within the subset of the population with overt threshold shift, which suggests pathology was not selective synaptopathy as defined in the animal models.

Noise exposure can be reliably manipulated in animal models and Lobarinas et al. (2015) recently exposed a group of rats to noise that produced 20–30 dB of TTS 24 h postexposure in some animals and 40–50 dB in other animals. The animals that developed 20–30 dB of TTS showed no decrease in ABR amplitudes and did not show any measurable deficits on a signal-in-noise detection task. Importantly, rats with the larger TTS (40–50 dB or greater) did show decreased ABR wave I amplitudes *alongside small decreases in postnoise performance on a signal-in-noise detection task* (Lobarinas et al. 2015). However, these deficits were limited to the most difficult listening condition (the condition with the poorest signal-to-noise ratio) and were limited to a very narrow subset of frequencies at which there had been both a robust TTS and a lasting decrease in ABR wave I amplitude. These data suggest that although a noise exposure that produces no long-term overt threshold shift *can* result in difficulties processing signals in noise, the functional sequelae are seen only for very difficult listening conditions and only for a very narrow range of stimuli corresponding to frequencies at which the most robust TTS deficits were observed (i.e., 40–50 dB TTS measured 24 h postnoise).

Given the call for potential changes in the occupational noise regulations, there is a clear and compelling rationale for psychophysical studies assessing suprathreshold auditory function in humans exposed to occupational or recreational noise. There is a rich history of such studies in aging patients and patients with

hearing loss of mixed (and frequently unknown) etiology, but there has been much less systematic effort to study suprathreshold processing deficits in noise-exposed populations (for review, see Shrivastav 2012). Recent studies in humans suggest that difficulties communicating in noise correlate with deficits in selective attention (Best et al. 2010; Ruggles et al. 2011). Interestingly, selective attention deficits are associated with differences in the fidelity of the auditory subcortical steady-state response (SSRS) (Bharadwaj et al. 2014, 2015). The exploratory data from Bharadwaj et al. (2015), suggesting a marginally significant relationship between noise exposure (dichotomized as "more exposed" and "less exposed") and subcortical temporal coding, highlight the need for focused attention assessing the issue of potential noise-induced suprathreshold functional deficits in humans. Unfortunately, any new studies are largely required to be cross-sectional, which provide lower levels of evidence than prospective designs. Although one can, of course, begin to prospectively track subjects longitudinally as part of a hearing conservation program, ethical considerations compel counseling of participants on the effects of noise on their hearing and provision of hearing protection devices (HPDs), potentially reducing the opportunity to assess the measure of interest, which is the effect of noise on suprathreshold hearing. Variable use of HPDs in the workplace will also be problematic, as the actual exposures as modified by HPD use will be unknown.

Acute changes in both ABR wave I amplitude and speech-in-noise performance might be tracked after a single loud event, but if there is an assumption that individuals are at risk of permanent harm based on expectations of a large event-related TTS, it will not be ethical to require these individuals to stay in the hazardous environment for any specific period of time, leaving investigators with only the opportunistic ability to measure changes after whatever exposure a given person chose recreationally, thus yielding little group data for any specific given exposure. This model was used previously in early studies on the effects of music-player use on hearing; those data typically included no more than a few participants with data at any given listening level and TTS measured in only a subset of the participants (Lee et al. 1985; Pugsley et al. 1993; Hellstrom et al. 1998). Even if a group of participants with recreational TTS can be identified, there is no clear agreement on which speech-in-noise test, among those already used clinically and for research, will prove the most sensitive to noise-induced changes in function (for discussion, see Le Prell and Lobarinas 2015; Le Prell and Brungart, in press).

Relevant to the discussion earlier in this section regarding the potential for synaptopathy in the human cochlea and assumptions that any TTS will be hazardous to the human inner ear, there have been a small number of efforts to identify potential effects of noise on evoked potential amplitudes in humans. In an early study, Klein and Mills (1981) assessed acute noise-induced changes in ABR amplitude in five normal-hearing human listeners exposed to narrowband noise (centered at 2.6 kHz) at 86 dBC for 8 h, resulting in approximately 30-dB TTS. A decrease in wave I amplitude was noted for only one of the four participants completing the exposure (see Subject TS in their Fig. 3). TTS measurements

conducted at the 4-hour midexposure test time revealed the fifth subject had experienced the targeted 30-dB TTS at that time and the exposure was therefore terminated after only 4 h. There was no noise-induced decrease in wave I amplitude even for this individual, who was seemingly more vulnerable to TTS (see Subject RZ in their Fig. 3) (Klein and Mills 1981). There are other more recent studies assessing the potential for chronic deficits in ABR amplitude in participants with known noise exposure. No such deficits were detected in a population of veterans assessed by Konrad-Martin et al. (2012); however, their study was designed to assess age-related, not noise-induced, changes and may have therefore been underpowered. In a smaller study on the effects of noise exposure, there were no reported differences in ABR amplitudes between 16 pop/rock musicians and 16 nonmusician controls, although again, with the small sample size, the study may have been underpowered (Samelli et al. 2012). Taken together, these studies have not provided any evidence for effects of noise on ABR amplitude in humans, although sample size and study design questions preclude any conclusion that there are *not* effects of noise on ABR amplitude in humans.

Stamper and Johnson (2015a), who more recently assessed the potential relationship between ABR wave I amplitude and noise history, had a similarly small sample that included 30 normal-hearing participants recruited on a college campus. In contrast to the other reports described earlier in this section, they showed a statistically significant relationship in which decreased ABR wave I amplitude was associated with noise exposure within the past 12 months. This relationship was reported as statistically significant only when the signal was a 90-dB nHL click and mastoid-placed electrodes were used. Similar trends with $p < 0.05$ were also observed for click signals at 70 dB nHL or greater, and for 4-kHz tone burst signals at 70 dB nHL or above (Stamper and Johnson 2015a), but the relationships were not reported as statistically significant because there was no effort to control for multiple statistical comparisons. The relationship disappeared at lower levels and was not statistically significant if tympanic membrane electrodes were used instead of mastoid-placed electrodes as there was more variability in the data collected from tympanic membrane electrodes (Stamper and Johnson 2015a). Should future investigations focus on mastoid-placed electrodes because that was the test condition in which a relationship was detected, or should tympanic membrane electrodes be used because these represent a more direct measurement of wave I amplitude as the response is measured more proximal to the auditory nerve discharge? Alternatively, might foil-wrapped TIPTrode electrodes provide a compromise in which a larger, cleaner signal is measured but without the increased variability? Sensitivity of ABR recordings is improved using electrodes that utilize the ear canal as a recording site, perhaps providing additional opportunities to study the effects of noise exposure history (Gaddam and Ferraro 2008). It is worth noting that the amplitude of ABR wave I was significantly larger and easier to identify when the ear canal was used as one of the recording sites relative to more conventional scalp (mastoid) recordings. Given that the work to date in animal models has revealed ABR wave I amplitude deficits, the ear canal-based recording protocol seems likely to optimize technical aspects of data collection.

At recent professional meetings, the Stamper and Johnson (2015a) report was cited in numerous presentations as confirmatory evidence that noise exposure produces neuropathic damage in the human ear; however, caution is clearly still warranted. First, correlational studies of this nature cannot confirm causal relationships. More importantly, however, Stamper and Johnson (2015a) unfortunately did not assess whether there was an interaction with sex. Males typically have smaller ABR amplitudes and longer ABR latencies than females (Hall 1992). Males typically also have more significant noise exposure histories than their female peers. Thus, there is a clear potential for confounded outcomes if the effect of sex is not controlled for in the analysis. Worth noting, Stamper and Johnson (2015b) recently reported that on sex-specific analysis, this purported relationship was statistically reliable within their female cohort, but for males, the trend was for wave I amplitude to *increase* (grow larger) with increasing noise exposure, although this relationship was not statistically significant. It may be the case that routine exposures encountered by this college student cohort did not induce the phenomena of interest. Noise exposures that resulted in smaller TTS (i.e., on the order of 20 dB measured 24 h postnoise) did not result in any decrease in ABR amplitudes in mice (Hickox and Liberman 2014; Jensen et al. 2015) or in rats (Lobarinas et al. 2015). In humans, when the effects of noise were previously studied in five male participants, there was no reliable noise-induced decrease in wave I amplitude despite 30-dB threshold shifts immediately postnoise (Klein and Mills 1981). New data continue to emerge, with Plack and colleagues recently presenting data indicating no reliable relationship between recreational noise exposure, evoked potential amplitude, and speech-in-noise performance (Prendergast et al. 2016). Our emerging data similarly show no relationship between recreational noise exposure and speech-in-noise performance (Le Prell and Lobarinas 2016).

Additional studies that control for multiple potentially important variables will be needed before meaningful discussions regarding changes in federal regulations can take place. Scientifically important issues should be considered separately from regulatory issues wherever possible. A relationship between noise exposure and suprathreshold deficits, such as speech-in-noise deficits, is important and indeed represents a novel target through which worker health protections might be lobbied to be strengthened. From a regulatory perspective, however, it is perhaps relatively unimportant whether the speech-in-noise deficit is related to a selective synaptopathy or some other pathology. Attributing psychophysical deficits in noise-exposed participants to synaptic damage as opposed to the possibility of subtle hair cell damage, which can modify the effects of selective synaptic or neural damage (for review and discussion, see Young 2012), is a scientific issue with perhaps translational importance for treatment strategies. In other words, if functional deficits in the form of significantly poorer speech-in-noise performance were reliably related to noise insult, this would be an important finding regardless of whether the functional deficit was linked to synaptopathic or stereocilia damage. However, distinguishing subtle outer hair cell from neuropathic damage would be essential for the purpose of designing pharmaceutical interventions and drug studies that target specific cell types. The level of evidence should be carefully considered

as part of any additional call for regulatory change. In an evidence-based practice model, being critical about the quality of the evidence is a goal, not a character flaw (Dollaghan 2004). Only with agreement on metrics such as where electrodes should be placed, what speech-in-noise tests are the most sensitive to change (given speculation that this will be the most disrupted functional metric), how to account for potential influence of earplugs that may or may not have been used consistently or correctly, and what additional independent variables to include (such as sex) can new studies begin to raise questions about the point at which hazard begins.

10.4 Common "Equipment" Platforms

With the potential metric of the cABR in hand, a key challenge facing Krause and Anderson was the development of a platform that could be readily available to clinicians. As they discuss in Chap. 3, the cABR test platform developed at Northwestern University was incorporated into the existing Bio-logic System ("BioMARK") in 2005 and in 2011 was incorporated into the Intelligent Hearing Systems SmartEP evoked potential device as a research module.

Similar "platform" challenges are evident with tinnitus as varying tinnitus surveys have been used across different studies. The lack of common platforms and the possibility that the method by which data are collected (by handing the subject a survey to independently complete on paper or asking the questions in an interview format) could conceivably influence the participant's response are significant concerns for translational research efforts. The Hawthorne effect is a phenomenon whereby participant behaviors (or beliefs, perceptions, etc.) are modified as a function of that behavior being under observation, and the effects are strongest when the participant interacts with a particularly "likable" observer and the participant wants to meet the observer's expectations (Berthelot et al. 2011). The total amount of time spent in follow-up (abbreviated testing at some visits versus comprehensive follow-up at all visits) can also influence study results and is consistent with the Hawthorne effect (McCarney et al. 2007). Consequently, researchers studying tinnitus and other perceptual disorders for which there are no clear objective metrics are at a distinct disadvantage that is further exacerbated by the subjective and varied nature of outcome measures.

The issue of common equipment platforms is clearly relevant to the efforts of Staecker, Klickstein, and Brough as well. As they discuss in Chap. 8, they are performing the first ever gene therapy intervention in the human cochlea and implementing a novel surgical approach, an approach that would be potentially useful to other surgeons in future clinical trials. Finally, readers will quickly see there has been significant variation with respect to different techniques in optogenetics, optoacoustics, and infrared neural stimulation, all of which are being assessed for use in novel cochlear prostheses platforms, as reviewed in Chap. 9 by Tan, Xia, and Richter. The technology for optical stimulation is still under development, and although it is too early to choose precise test parameters, animal

studies will hopefully include evoked potential assessments across a wide range of frequencies representative of the animals' full range of hearing sensitivity.

10.5 Regulatory Requirements

Interactions with the FDA process are discussed by Lynch, Kil, and Le Prell, Chap. 5; Campbell and Fox, Chap. 6; and Staecker, Klickstein, and Brough, Chap. 8. These interactions are also clearly relevant to Chap. 9 by Tan, Xia, and Richter. If devices that use light to stimulate auditory neurons are to be implanted in humans, there will obviously be a substantive safety review before the first devices can be surgically implanted.

10.5.1 Regulation of New Devices

Although the development of these potential next-generation implants is in its infancy, demonstrating efficacy and safety of these devices for long-term use will be an important next step. Richter and colleagues describe advances in infrared neural stimulation in detail and highlight the prospects for translation. Lessons regarding the necessary next steps can be readily drawn from the animal literature on implant technology. Early studies in animals will need to provide parametric data equivalent to those collected in studies on current flow, impedance, site of stimulation, and frequency-response relationships (Clopton and Spelman 1982; Spelman et al. 1982). Patterns of damage observed after electrode insertion and stimulation were of particular importance in these early studies (Miller et al. 1983; Duckert and Miller 1984, 1986). There is a fascinating history of human testing and development of cochlear implantation first performed by Djurno and Eyriés in Paris in 1957 (Eshraghi et al. 2012). Although these early efforts failed, they demonstrated that electrical stimulation of the inner ear was possible and led to continued efforts by House in the United States beginning in the 1960s. Some 50 years later, the development of the implant is still active and ongoing with respect to new electrode coatings (Tykocinski and Cowan 2005; Richardson et al. 2009), new implant materials (Gwon et al. 2015), and an exciting new prosthesis that is being actively modified to allow local drug delivery (Hendricks et al. 2008; Nguyen et al. 2009; Farhadi et al. 2013). These advances will allow for agents of interest, including not only dexamethasone but also particles developed using advances in nanotechnology, to be infused to improve outcomes (Meyer et al. 2012). The potential benefits of combined electroacoustic function are also being assessed in animals (Tanaka et al. 2014; Reiss et al. 2015) as well as being adopted in humans (Santa Maria et al. 2014; Causon et al. 2015). In addition to modifications to allow drug delivery and the three novel strategies for neural stimulation, as described by Tan et al. in Chap. 9, other strategies continue to emerge. For example, penetrating electrode

arrays have been developed (Middlebrooks and Snyder 2007, 2008) to move away from delivering electrical charge within the fluid space to direct electrical stimulation, results that produce a narrower and more focused spread of excitation than traditional electrode stimulation. Taken together, the kinds of studies that set the stage for new surgical interventions are well established. As noted in several chapters (see, e.g., Chap. 5), the device side of the FDA is well versed, particularly for audiometric testing within clinical trials, and there is a relatively clear path forward for the implant of devices to restore hearing to the profoundly deaf.

10.5.2 Regulation of Drug Research

Lynch, Kil, and Le Prell (Chap. 5) and Campbell and Fox (Chap. 6) discussed clinical testing and other developmental steps in the pathway to the development of a new ethical (prescription) drug. With the move to develop regenerative therapies, the complexity of the task increases. This was discussed in detail by Staecker, Klicktein, and Brough in Chap. 8. Gene therapy is also being combined with cochlear implants. Conversely, cochlear implant interventions have also driven gene therapy, whereby genes that drive neurotrophin production can be used to achieve better implant performance (Pinyon et al. 2014). The promise of stem cell research (Hu and Ulfendahl 2013) has been highlighted in recent descriptions of FDA-approved studies for treating hearing loss, one of which is being conducted at Children's Memorial Hermann Hospital in Houston, Texas. Although in-depth discussion on the role of stem cell therapy is beyond the scope of this chapter, it is likely to play a significant complementary role in cochlear implants and inner ear repair/regeneration research in the not so distant future.

10.6 Placebo Controls

Placebo control conditions are used to assess the extent of improvement or percent of participants who improve in the absence of an active treatment agent, with all other study conditions held equal. A fascinating development in the understanding of placebo effects comes from the recent work of Kathryn Hall (Hall et al. 2012, 2015; Hall and Kaptchuk 2013). They first reported a link between the gene that encodes the enzyme catechol-*O*-methyltransferase (COMT), which breaks down catecholamines, and the size of the placebo response in patients with irritable bowel syndrome (Hall et al. 2012); those with a particular genetic configuration (i.e., the met-met genotype for the COMT enzyme) had more robust improvements after a sham acupuncture treatment. Excluding strong placebo responders from a clinical trial would theoretically reduce the size of the placebo effect and would potentially allow drug benefits to be measured in smaller, and less expensive, studies. A patent based on this concept has been filed (Winkler et al. 2015). According to one of the

inventors, "Drug discovery is not about whether a drug works. It's about whether it works better than a placebo control" (Ted Kaptchuk, quoted in Servick 2014, p. 1446). To put this into perspective, Winkler points to placebo response rates ranging from 5 to 30 % and states, "Where do you start? Assume 5 %, run a small trial, and fail? Or start with the assumption of 30 %, and have a very big trial which costs a lot of money and may preclude the drug developer from running other studies?" (Gunther Winkler, quoted in Servick 2014, p. 1446). As discussed by Servick (2014), this screening strategy might ultimately be more appropriate for speeding early-phase small-scale tests, as there are concerns that come with systematically excluding a participant population that may also be good drug responders. Regardless of whether there is a relationship between the mechanisms of placebo response and those of the response to the investigative agent, excluding people with a particular genetic background modifies the population such that it is systematically different from the targeted patient population, a strategy that is not typically preferred for clinical trials.

In Sect. 10.2, the ethics of withholding treatment that "might" provide benefit was questioned. This is a difficult issue for cases in which it is not clear that there is an effective standard of care that a new drug should be compared against. When there is no accepted treatment, a placebo control is generally deemed appropriate and ethical. However, when there is an accepted therapeutic intervention, a new drug would be more likely to be assessed in an equivalency analysis to ensure it is at least "as good" as the current standard of care. In Chap. 1, Le Prell and Lobarinas noted that multiple systematic reviews suggest there to be little or no systematic evidence of benefit when steroid-treated patients are compared to patients who received a placebo (Wei et al. 2013; Crane et al. 2015). In the case of SSHL, however, steroid treatment is the standard of care regardless of whether there is robust evidence suggesting it provides benefit. Because there is a conventional care option, it is extremely difficult to recruit subjects to new clinical studies if they may be randomized to a placebo condition rather than to the best available treatment currently identified (Rauch 2015).

10.7 Summary

There is an increasing emphasis on evidence-based practice (EBP) among health and health-related professions. This is driven in part by managed care considerations due to third-party payers increasingly demanding evidence that the procedures and treatments being reimbursed are efficacious. There is a much larger landscape, however, with a moral and ethical imperative to deliver the best possible care to patients. There is increasing consensus that the "best" care is evidence-based care, embedded in EBP. Healthcare within the EBP model requires that healthcare decisions be based on evidence that the recommended treatments or interventions

are likely to provide benefit, and this model has been advocated with respect to hearing healthcare (Dollaghan 2004; Valente 2005; Moodie et al. 2011). The precursors to EBP are discussed in Chap. 2 by Le Prell, and one of the central themes of this text is that translational research is urgently needed across the field of hearing and related sciences as these data provide the foundation upon which clinical care is advanced.

Millions of dollars are devoted to hearing-related research every year. According to the FY 2016 Congressional Justification, the budget for extramural hearing & balance research was US $203M in FY 2014 and US $204M in FY 2015 and is US $210M in the president's FY 2016 budget (http://www.nidcd.nih.gov/about/plans/congressional/Pages/CJ16.aspx). In their discussion of key advances in the past year, the NIDCD summary highlights investments in translating discovery into health through studies linking hearing loss and depression and studies identifying strategies for improving communication in children with autism. The two highlighted priorities for FY 2016 are both translational in nature: "Harnessing Data and Technology to Improved Health—Hearing Health Care" and "Translating Discovery into Health—Global Health and Reducing Health Disparities among Minority and Underserved Children." There is a keen interest in application of knowledge generated in basic research investigations to applied investigations in order to determine health-related benefit and impact. The number of Americans with hearing loss is expected to increase given the aging of the American population. The major advances in knowledge have the potential to significantly improve hearing and communication outcomes in this aging population as a result of successful clinical translation.

The chapters in this volume stress the need for basic mechanistic understanding of disorders and diseases, objective diagnostic tools and criteria, and agreed-on metrics for measuring improvements in human populations. Teams are needed to successfully marry basic and applied investigations and to seamlessly move back and forth between the benchtop in the laboratory and the bedside in the clinical trial and patient care areas. Funding can be challenging and regulatory procedures that protect human participants can be onerous, but the end goal of improved patient outcomes is something that all parties seek and prioritize.

Compliance with Ethics Requirements

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