

Chapter 2

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

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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

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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/wMKItN>) 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 (TRI-H).” 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).

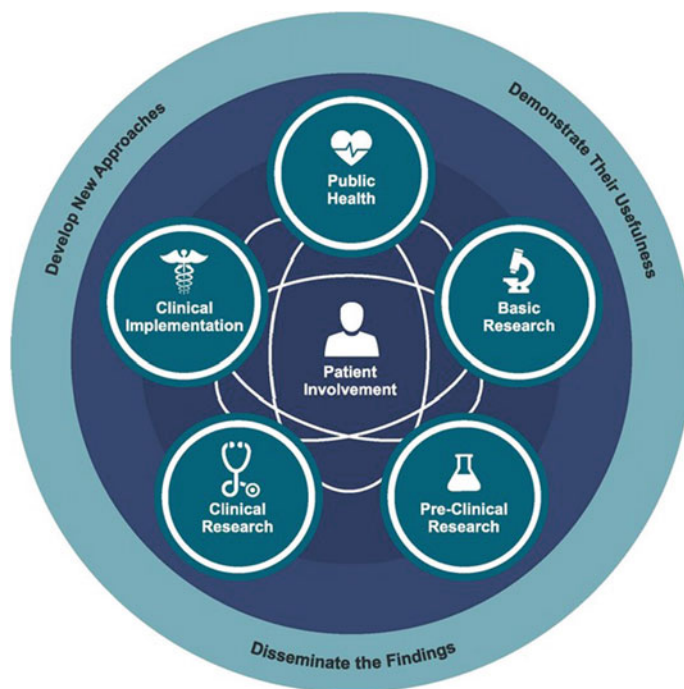


Fig. 2.1 Translational science spectrum. “The translational science spectrum represents each stage of research along the path from the biological basis of health and disease to interventions that improve the health of individuals and the public. The spectrum is not linear or unidirectional; each stage 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/LguyS4>).

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](https://clinicaltrials.gov/ct2/show/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 event 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 EXPOSM 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/qGWxOI>). 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 (McKibbin 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 McKibbin 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 CTSA 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 Collier 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 (Guillon 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

¹¹Colleen Le Prell was the principal investigator on the contract between Sound Pharmaceuticals, Inc. and the University of Florida.

²Colleen 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, Collier 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.

Acknowledgments Translational research must be approached as team science, with scientists, clinicians, physicians, statisticians, experts in the regulatory rules and IND preparation, and, of course, a clinical trial manager all contributing important pieces. I am grateful to the many friends and colleagues who have partnered with me on the studies described in this chapter, including Patrick Antonelli, Edward Lobarinas, Christopher Spankovich, Scott Griffiths, and Leigh Anne Marshall at the University of Florida; Josef Miller, Glenn Green, Bill Reisdorph, and Kenneth Guire at the University of Michigan; Kathleen Campbell at Southern Illinois University; Eric Lynch and Jonathon Kil at Sound Pharmaceuticals, Inc., and Matt Klein and Erin Johnson at Edison Pharmaceuticals, Inc. I appreciate helpful comments on an earlier version of this manuscript from Edward Lobarinas, Art Popper, and Jianxin Bao.

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Translational Research in Audiology, Neurotology, and
the Hearing Sciences

Le Prell, C.; Lobarinas, E.; Popper, A.N.; Fay, R.R. (Eds.)
2016, XVIII, 265 p. 25 illus., 19 illus. in color., Hardcover
ISBN: 978-3-319-40846-0