Published in final edited form as:

J Commun Disord. 2010 ; 43(4): 311–318. doi:10.1016/j.jcomdis.2010.04.002.

Curing hearing loss: Patient expectations, health care practitioners, and basic science

Kazuo Oshima^{a,*}, Steffen Suchert^b, Nikolas H. Blevins^a, and Stefan Heller^a

^a Departments of Otolaryngology – Head & Neck Surgery and Molecular & Cellular Physiology, Stanford University School of Medicine, Stanford, CA 94305, USA

^b FAUN Foundation, PO Box 119402, 90104 Nürnberg, Germany

Abstract

Millions of patients are debilitated by hearing loss, mainly caused by degeneration of sensory hair cells in the cochlea. The underlying reasons for hair cell loss are highly diverse, ranging from genetic disposition, drug side effects, traumatic noise exposure, to the effects of aging. Whereas modern hearing aids offer some relief of the symptoms of mild hearing loss, the only viable option for patients suffering from profound hearing loss is the cochlear implant. Despite their successes, hearing aids and cochlear implants are not perfect. Particularly frequency discrimination and performance in noisy environments and general efficacy of the devices vary among individual patients. The advent of regenerative medicine, the publicity of stem cells and gene therapy, and recent scientific achievements in inner ear cell regeneration have generated an emerging spirit of optimism among scientists, healthcare practitioners, and patients. In this review, we place the different points of view of these three groups in perspective with the goal of providing an assessment of patient expectations, healthcare reality, and potential future treatment options for hearing disorders.

Learning outcomes—(1) Readers will be encouraged to put themselves in the position of a hearing impaired patient or family member of a hearing impaired person. (2) Readers will be able to explain why diagnosis of the underlying pathology of hearing loss is difficult. (3) Readers will be able to list the main directions of current research aimed to cure hearing loss. (4) Readers will be able to understand the different viewpoints of patients and their relatives, health care providers, and scientists with respect to finding novel treatments for hearing loss.

Keywords

Hearing loss; Patient expectations; Gene therapy; Stem cells; Cochlear implants

1. Introduction

Hearing impairment is the most frequent sensory deficit in the human population and can occur at any age, although many cases of hearing impairment are of genetic origin, by recessive or dominant inheritance. Hearing loss ranges from mild to severe, profound and congenital – sometimes including vestibular dysfunction. Low frequencies are often differently affected

© 2010 Elsevier Inc. All rights reserved.

* Tel.: 650 725 8502; fax: 650 725 8502. oshimak@stanford.edu..

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

from high frequencies; impairment also differs from patient to patient, even when of equal genetic origin.

Here, we provide an overview from three different backgrounds: patients, health care providers, and scientists. We focus on discussing expectations and views from these different groups about hearing loss and potential future treatments. Finally, we attempt to identify why finding a cure for hearing loss is so difficult and whether there are ways to expedite the search.

Individuals affected by hearing loss struggle in their daily activities and their quality of life suffers. Immanuel Kant distinctly clarified this point of view, “Not being able to hear isolates from people.”¹ The challenge to overcome the dimension of hearing impairment is directly linked to the expectations of impaired people who have learned in their lives: Disability comes from the outside through disabling factors; the hope for an effective treatment or therapy lies in the belief of success in translational research; social integration depends on caretakers who do not primarily see a disability of a person but a person with a disability. One has to realize that cognitive, emotional and social communication skills of others, parents and caretakers deal with four main areas:

1. **Family relationship:** as the inner circle of “friends” who contribute most to a person's well being, emotions, sensibility, mental health and self-confidence.
2. **Social integration and interaction,** which takes place in everyday situations like telephoning, talking, eating out in a restaurant, visiting a doctor, shopping, social networking in the online world, walking around, travelling etc. All this is based on social competence and communication skills: listening, questioning and keeping a dialogue at a natural level which is the essence of understanding each other.
3. **Relationship with society as a whole** due to the fact that hearing impairment, which is already a major public health problem, will become even more acute in the future, especially for unrestricted access to schools, education, employment and business related skills. There is by nature no difference between a hearing-impaired person and others in our society, everyone should be entitled to reach any position and not be treated as a minor. Hospitals and all institutions, authorities, and organizations should offer sign-language and lip-reading options. On the other hand, among the elderly one can see a psychosocial problem which not only affects them directly but others just as much. Lacking flexibility leads to diminishing social contacts and into isolation.
4. **The economic consequences** of inadequate “unfair” education are enormous. This can result in intellectual, professional and social isolation; in diminished expectations of the hearing impaired disregarding their individual potential to finding the best job or occupation. The circle of a negative self-fulfilling prophecy starts here. Untreated hearing loss is estimated to cost billions annually. Adequate special education will be more and more required to accommodate the hearing impaired in our society because of the fact that loss of productivity leads to a substantial burden on our economy. Early identification and intervention have proved to be the most cost-effective element. The enjoyment of the highest standards of health is one of the fundamental rights of every human being. The 2006 UN Convention on the Rights of Persons with Disabilities states that they “have equal rights to education, employment and culture life; they should not be discriminated against on account of (sensory or other) impairment; they are entitled to take part in all human activities (sport, travel, games

¹Kant, Immanuel. “Nicht sehen können, trennt von den Dingen, nicht hören können von den Menschen” has been widely attributed to the German philosopher Immanuel Kant (1724-1804; http://en.wikipedia.org/wiki/Immanuel_Kant). The English version, “Not being able to see isolates you from objects. Not being able to hear isolates you from people,” has also been attributed to the American author Helen A. Keller (1880-1968; http://en.wikipedia.org/wiki/Helen_Keller).

etc.).”² If these expectations are not fulfilled, the hearing impaired will be left out of this new “social contract”: Society owes the disabled all the necessary “facilitators”, prosthesis, personal support, and that includes research. The WHO revision of the 1980 ICIDH states, “...people with a disability are entitled to the same opportunities and choices as the rest of the community. And generally desire participation in all areas of human and social life ...”³

2. Patient expectations

The expectations of hearing impaired to the scientific community center around treatments, which will provide a true perspective and are of direct benefit to the hearing impaired individual. To improve their insufficient knowledge base, patients seek empowerment and for developing meaningful relationships, information is a key issue. Common questions for which patients are seeking answers are:

Gene based therapy strategies: patients are well aware of scientific key words and they ask whether we can expect therapy options by introduction of genes via DNA, PEG, nanoparticles, or viruses such as rAAVs? Are there pharmacogenetic therapies available in the near future? Does one need mutation-specific treatments or are there general therapies on the horizon?

Stem cell based treatments with embryonic stem cells (hESC) or induced pluripotent stem cells (iPS) may show a high potential in “turning back the clock,” e.g. auditory disease modeling, drug discovery, hair cell rescue, cell replacement and customized treatments?

Cochlear implants: The current implant technology is considered to be sophisticated and effective, but new technologies could offer developments in thin-film microelectrode arrays with high-tech processors including optimized algorithms, driving more than 100 channels for more than 100 micro contacts, including hearing related data reduction, individual patient-focused speech coding strategies, etc?

Will neuroprotective chemicals and drugs with the ability to stop or slow down degenerative processes be of a dominant role in the future, and will they be available for each individual patient?

From the perspective of the patient community, the most effective tool to have science and research move forward to clinical trials and therapies is to build partnerships, networks or alliances, as a platform from all groups of stakeholders in the field of auditory research, together with patient organizations and patient advocacy groups. These partnerships should include scientists and researchers; units from governmental health care systems, funding agencies, national and international patient groups; other non-profit organizations; and finally, private equity and industry. Patients are highly motivated to strengthen scientific collaborations and to cooperate and support scientific efforts actively. They are, of course, highly interested in establishing effective therapies as soon as possible. On this level, it will be important to advocate intensively the importance of this area of research to decision makers such as the Senate (in the US) or Brussels/EU to foster a roadmap to structure programs and strategies for treatments or cures. For patients, it is very important to stress the urgent need for major financial support and priority funding for research, improved patient care, logistics, services etc. Furthermore, a global alliance and platform offers the potential of increased international cooperation, acquisition and diffusion of scientific knowledge, and the exchange of results, expertise and finally experts themselves. The patient community shows quite clearly that disability is not an excuse in itself. From a perspective of people living with a sensory disability,

²<http://www.un.org/disabilities/>

³<http://www.who.int/classifications/icf/en/>

hope needs an active involvement and direct actions in trying to fulfill their aspirations to become active research partners.

3. Health care provider

From a health care provider's perspective, the prospect of “curing hearing loss” seems to be paradoxically just within reach while remaining simultaneously unattainable. The core of this dichotomy rests within the nature of the auditory pathway. Anatomically, the inner ear provides a nearly ideal tonotopic organization, where relatively simple geometry can map almost directly to highly abstract perception. Our understanding of this microanatomy has been the basis for tremendous advances in hearing restoration. At the same time, the inner ear's complex anatomy has also made it one of the most inaccessible areas in the human body. We continue to lack nondestructive means of diagnosing or manipulating specific pathology for even the most common disorders. Similarly, the plasticity of the central auditory pathways has allowed patients to make the most of the highly simplified stimulation we can provide with auditory prostheses. The same central processing complexity, however, leaves an overwhelming list of unanswered questions about what is actually needed to completely restore normal function. So, although we can now routinely make significant improvements to the most devastating effects of hearing loss, we continue to fall short in addressing the deficits that impact the everyday lives of so many individuals.

Before we have the means of regenerating a dysfunctional inner ear, additional incremental clinical advances will be needed. First, we need improved means of diagnosing inner ear pathology. Currently, we are often forced to treat a highly heterogeneous group of disorders based on common presenting clinical features. Until we better understand patient-specific pathology, we will lack optimally directed intervention. Similarly, an improved means of non-destructive inner ear access is needed for cellular, pharmacologic, and physical manipulation. The technical challenges of working in such a complex and fragile environment continue to be quite daunting but need to be addressed so that appropriately targeted therapy can be applied. Advances in micro-optical technology and micro-robotics offer some hope in this regard.

It is likely that continued advances in prosthesis design will precede purely regenerative therapy. Less-invasive electrode placement and more highly selective spatial and temporal neural stimulation (whether electrical, optical, or chemical) offer considerable promise through combined electrical and acoustic stimulation. We will likely benefit from additional inner ear manipulation to make the neural elements more receptive to stimulation. This may be through minimizing cellular damage or encouraging beneficial neural growth. No matter how advanced our prostheses become, they are still not likely to be the final “cure” for hearing loss. Problems inherent to all implantable devices will persist to some degree, including surgical risks, device failure, infection, and unfavorable tissue reactions. Also, despite the benefits of neural plasticity and advances in sound delivery strategies, we will still not restore the entirely “normal” perception that is so important to our patients with hearing loss.

Finding methods to prevent the hearing loss in the first place will likely play an increasingly important role. This may be through identifying genetic risks early and intervening to enable normal development of the auditory pathways. Similarly, we will need to identify and eliminate exposure to other exogenous factors causing hearing loss. It will likely always remain easier to prevent an inner ear from deteriorating than it will be to rebuild one.

We are starting to see the promise of inner ear regeneration in early animal studies. The successes, however exciting and encouraging they are, still show us just how far we need to go before it's clinically useful. The complexity of safely regenerating anatomically and physiologically functional inner ear elements is enormous, even in cases of highly specific pathology. The issue only becomes geometrically more difficult when applied to ears with the

expected broad spectrum of injuries, with variable duration and severity, in highly variable genetic and immunologic environments. Still, we can remain confident that each step brings us closer to that ultimate goal of a “cure for hearing loss”, and, until then, even incremental advances can still result in substantive improvements for so many of our patients.

4. Scientific discoveries

Electronic devices such as hearing aids and cochlear implants are the state-of-the-art options for patients suffering from mild to profound hearing loss and even for completely deaf patients. The impact of a cochlear implant on the future life of a deaf child is, without any doubt, immense. With appropriate listening and speech training, the auditory pathways of these young patients learn to fully utilize the implant by establishing implant-adapted connections in the brain. This central nervous system plasticity allows the children, when grown up, to communicate without any impediments when compared with their normal hearing teenage peers.

Despite their success, cochlear implants and hearing aids are not perfect. In patients that do not receive a cochlear implant during the first years of their life, the efficacy of the devices vary substantially with regard to frequency discrimination, performance in noisy environments, as well as simple day-by-day tasks such as speaking on the telephone. Increased computing power and engineering of smaller and smaller hearing aids will very likely lead to better hearing aids in the future, but even in a world of bluetooth ear devices, some patients still refuse to wear stigmatizing hearing aids.

Biological treatment strategies for hearing loss emerged in the late 80s when two research groups independently reported that cochlear hair cells regenerate after acoustic trauma in birds (Corwin & Cotanche, 1988; Ryals & Rubel, 1988). Because sensory hair cell loss is the major culprit for hearing loss in patients, this discovery raised expectations that hair cell regeneration might be possible if we would be able to find the molecular pathways that control regeneration in birds.

The basis of most research on potential treatment strategies has been the cell signaling pathways that are involved in generating the cochlear sensory epithelium in the first place, during embryonic development. The cochlear sensory epithelium develops from a group of cells that, after ceasing cell division, begin to differentiate into young hair cells and surrounding cells, which are summarized under the term supporting cells. All these cell types become morphologically very specialized in the adult organ. An obvious difference between a regenerating bird cochlea and the complex mammalian cochlea is the level of cell type specialization. In birds, only two morphologically distinct main cell populations exist: hair cells and supporting cells. In mammals, one can clearly distinguish inner and outer hair cells, as well as at least six types of supporting cells.

When a hair cell dies in the bird cochlea (for example after acoustic trauma), a surrounding supporting cell either directly differentiates into a replacement hair cell, or a supporting cell first divides into two cells, one of which becomes a replacement hair cell and the other one remains a supporting cell. The latter scenario is a so-called stem cell-based mechanism: The stem cell (in this case the supporting cell) generates replacement cells and self-renews, and the result is a complete repair of the damage that is indistinguishable from the situation before the damage occurred. Neither of the two hair cell replacement mechanisms naturally occur in the mammalian organ of Corti, where research has mainly focused on strategies to induce cell replacement and regeneration after damage. We will briefly introduce the major approaches consisting of gene therapy, stem cell research, and pharmacotherapeutics.

4.1. *Gene therapy* has been focused on generating replacement hair cells by re-expression of the atonal homolog 1 (Atoh1, also known as Math1) gene. This gene is essential for hair cell development as its targeted disruption in mice results in the absence of auditory and vestibular hair cells (Bermingham et al., 1999). Virus-mediated gene transfer of Atoh1 into the deafened cochlea of adult Guinea pigs resulted in improved auditory brainstem responses (Izumikawa et al., 2005). Although the extent of hearing improvement that is possible with Atoh1 gene transfer in adult laboratory animals requires further investigation, it is obvious from a number of studies that the Atoh1 gene is able to convert some types of cochlear cells into hair cells (Woods, Montcouquiol, & Kelley, 2004; Zheng & Gao, 2000). These Atoh1-induced hair cells are functional, at least when the Atoh1 gene is overexpressed in a developing cochlea (Gubbels, Woessner, Mitchell, Ricci, & Brigande, 2008). The major limitation of virus-mediated gene therapy is, beside safety concerns, the problem of delivering the virus into all regions of the cochlear spiral. An injection at the base of the cochlea will very likely only affect the high frequencies and treatment of middle and lower frequencies will require multiple injections at different sites. Opening of the cochlea always bears a high risk of doing additional damage, and it is inconceivable that utilization of multiple sites along the cochlear spiral will be a surgically feasible approach in the future, particularly in humans. Beside virus delivery obstacles, there is another limitation of the approach, which is that the therapeutic agent is able to induce so-called ectopic or supernumerary hair cells. These additional hair cells that are not located at the correct location within the organ of Corti do not contribute to proper hearing; instead, in all experimental cases investigated thus far, their presence is accompanied with profound hearing loss (Chen & Segil, 1999; Chen et al., 2003; Lowenheim et al., 1999).

4.2. *Pharmacotherapeutics*, or drug development, becomes more and more focused on small molecules that are able to activate or interfere with cell signaling pathways or specific genes. A plausible example for this approach would be molecules that specifically activate the Atoh1 gene, which would make viral gene delivery obsolete. Research aimed at identifying such potent compounds is just emerging. In general, it is conceivable that novel drugs will act on cellular pathways that are utilized during embryonic development or avian hair cell regeneration. Coaxing an organ of Corti supporting cell to divide again, for example, would be an important step toward replacing lost hair cells. A number of genes that are potent inhibitors of cell cycle re-entry are highly active in supporting cells of the mammalian organ of Corti and interference with these genes in the mouse cochlea indeed leads to generation of new cells, even new hair cells (Chen & Segil, 1999; Chen et al., 2003; Lowenheim et al., 1999; Sage et al., 2005). Compounds that reversibly inhibit cell cycle inhibitors in an organ of Corti-specific manner are probably at the top of the list of current drug discovery searches. Likewise, modulators of Notch signaling are another group of potentially therapeutic molecules bearing promise for utilization in inner ear therapy. Notch is a cellular receptor that is utilized by neighboring cells during embryonic development and during avian hair cell regeneration. Pharmacological inhibition of Notch signaling has been effective in initiating hair cell formation in the embryonic, neonatal, and the damaged adult cochlea (Hori et al., 2007; Takebayashi et al., 2007; Yamamoto et al., 2006). Despite the promise of novel drugs, it remains to be seen whether such drugs are effective in different animal models of hearing loss. The encapsulation of the cochlea offers an advantage for localized drug treatment, which would potentially allow the use of otherwise systemically inapplicable drugs. However, the same limitations that apply for gene therapy also apply for drug treatment and access to the complete cochlear spiral remains one of the major future challenges that need to be overcome.

4.3. Finally, *stem cell research* has recently emerged as additional avenue for sensory hair cell regeneration. In principle, there are two different approaches in this direction. First, because avian hair cell regeneration is a stem cell-based mechanism, it has been hypothesized that mammals have lost their stem cells or that certain inner ear cell types have lost "stemness", defined by ability to regenerate lost hair cells (Brigande & Heller, 2009). Indeed, remnants of

regenerative ability in the form of cells with stem cell features can be detected in the neonatal, but not in the adult, mouse cochlea (Diensthuber, Oshima, & Heller, 2009; Oshima et al., 2007; Senn, Oshima, Teo, Grimm, & Heller, 2007; White, Doetzlhofer, Lee, Groves, & Segil, 2006). Particularly some supporting cell types of the organ of Corti have the transient potential to divide and to generate new cells with hair cell features under certain culture conditions (Oshima et al., 2007; White et al., 2006). In mice, this ability, however, is lost during the third postnatal week. The search for cellular signaling pathways that enable cochlear supporting cells to re-activate stem cell features is virtually addressing the same topics as discussed above for pharmacological modulation of specific genes and signaling pathways. It appears that the holy grail indeed is a small molecule or combinations of small molecules that coax supporting cells in the damaged organ of Corti to behave similarly as supporting/stem cells in the damaged bird cochlea, which is cell division followed by generation of a new hair cell and maintenance of the original supporting/stem cell.

A second approach is the implantation of stem cell-derived precursor cells into the damaged cochlea. Despite some evidence for cell survival, no robust occurrence of new hair cells has been observed (for a review see Beisel, Hansen, Soukup, & Fritzsche, 2008). However, these experiments were done with neural stem cells whose capacity to generate inner ear cell types is unknown. Embryonic stem cell-derived inner ear progenitors appear to be much better suited for transplantation studies because these cell types have the ability to differentiate into hair cell-like cells, at least in cell culture or when transplanted into embryonic ears (Li, Roblin, Liu, & Heller, 2003). Another potentially useful cell type in this regard is induced pluripotent stem cells, which can be generated from a patient's skin (Beisel et al., 2008). Nevertheless, the prospect of curing hearing loss with a stem cell-based implantation remains rather weak unless several technical roadblocks can be overcome. These obstacles include finding suitable surgical access to the cochlea (as already discussed for gene therapy and drugs); establishing that the stem cell-derived cells survive, integrate, and mature at the correct locations (and not at ectopic places); and finally, it needs to be ensured that the stem cell-derived grafts do not develop into tumors.

In summary, all approaches that we introduced aim to (re-)generate the correct number and the correct hair cell type at the right place within the organ of Corti. Realistically, in the upcoming decades, research will be focusing on overcoming the numerous obstacles that we discussed, and clinical trials will likely be rare exceptions.

5. Perspectives

Although the general diagnosis of hearing loss is rather simple, the underlying causes are much more difficult to diagnose because of the large heterogeneity ranging from genetic disposition, drug-side effects, acoustic trauma, and idiopathic varieties. As a result, it is often impossible to predict with certainty whether a cochlear implant will be successful in a patient with idiopathic hearing loss. Foremost for the patient but also for the health care professional, these shortcomings can be very frustrating. Even more frustrating, despite availability of hearing aids and cochlear implants, is the lack of options. Gene therapy, novel drugs, and stem cells are being widely discussed in the public, and patients naturally ask if and when novel treatments will become available. Researchers are constantly reporting “breakthroughs,” but where are the treatments? From the researcher's perspective, a breakthrough could mean an important discovery, the development of a novel technique, or a proof-of-principle experiment in a culture dish. These advances indeed bring us closer to potential therapeutic applications, but it is highly unlikely that such “breakthroughs” will immediately result in a clinical trial.

Overall, health care providers are probably the best source of information for patients. It is therefore important, particularly for otologists and audiologists, to stay informed about novel

treatment options. Patients are far more involved and often very well informed about scientific developments. Nevertheless, it is often difficult for them to realistically assess whether a novel discovery is going to directly impact their life and when such an impact is going to happen. Likewise, it is important for researchers to discriminate between advancing science and publicly announcing potential “breakthroughs” for treatment. The latter has become an unfortunate byproduct of press releases from public relation offices at universities and also through public comments made by individual researchers. As a result, patients become utterly confused and are often unable to discriminate between valid and absurd treatment options. For patients, it is important to have realistic expectations that can only be formed by staying informed and by speaking to health care professionals. Particularly for the patients, it is important to work on the formation of a global alliance and partnership that includes patient advocacy groups, units from health care systems, physicians, communication science professionals, basic researchers, funding agencies and foundations, as well as others who are able to expedite the process of bringing new scientific discovery from the bench to the patient.

It is very obvious that without a global partnership, increased funding, and without attracting the best scientific minds to our field, state-of-art treatment for hearing loss in the next decade, and probably beyond, will not change fast enough to become beneficial for the current generation of patients. There are only a few laboratories working on novel treatment strategies and even fewer laboratories are prepared to translate basic science findings, via animal models, into the clinical setting. As researchers, we are convinced and optimistic that biological or cellular treatment options for hearing loss will become available in the future, but being realistic, we doubt that the current generation will be able to fully benefit from the current research. It would be disastrous if a parent of a deaf child decides against a cochlear implant because of unrealistic expectations of gene therapy, stem cells, or novel drugs. As a reader of this article, either as a patient, health care professional, or scientist, we ask you to think about what you can do to curb the hype, and to stay calm and realistic about treatment options for hearing loss. Most patients have options, but it is important to understand that there is no miracle cure, and that we all have to be very patient when it comes to novel treatments for hearing loss.

Appendix A. Continuing education

1. Isolation of a hearing impairment person affects:
 - a. family relationships, social integration and interaction, ability to join health clubs.
 - b. ability to flourish professionally, family relationships, social integration and interaction.
 - c. social integration and interaction, mechanical skills, family relationships.
 - d. ability to navigate in dusk or dawn, ability to flourish professionally, family relationships.
 - e. all of the above.
2. A cure for hearing loss is expected:
 - a. in 5 years.
 - b. in 10 years.
 - c. in 25 years.
 - d. It is difficult to predict, but perhaps within the next decade.

- e. It is not possible to predict when treatment options will become available, but realistically, only future generations are expected to fully benefit from the current research.
3. Hearing loss and inner ear pathology often presents itself as:
 - a. easy to diagnose with clear prognosis.
 - b. highly heterogeneous and difficult to prognosticate.
 - c. impossible to predict.
 - d. mostly dependent on the patient's genotype.
 - e. dependent on the medical history of the patient.
 4. Stem cells are:
 - a. the emerging cure for all diseases including hearing loss.
 - b. dangerous cells that cause cancer.
 - c. providing a platform for research on possible ways to regenerate the damaged cochlea.
 - d. already available as valid option to cure hearing loss.
 - e. all of the above.
 5. Current research to ameliorate hearing loss is focusing on:
 - a. improving cochlear implant technology.
 - b. gene therapy and nanotechnology.
 - c. stem cells.
 - d. drug design and animal models.
 - e. all of the above.

Answers: 1: b; 2:e; 3:b; 4:c; 5:e

References

- Beisel K, Hansen L, Soukup G, Fritzsche B. Regenerating cochlear hair cells: Quo vadis stem cell. *Cell and Tissue Research* 2008;333:373–379. [PubMed: 18575894]
- Bermingham NA, Hassan BA, Price SD, Vollrath MA, Ben-Arie N, Eatock RA, et al. Math1: An essential gene for the generation of inner ear hair cells. *Science* 1999;284:1837–1841. [PubMed: 10364557]
- Brigande JV, Heller S. Quo vadis hair cell regeneration? *Nature Neuroscience* 2009;12:679–685.
- Chen P, Segil N. p27(Kip1) links cell proliferation to morphogenesis in the developing organ of Corti. *Development* 1999;126:1581–1590. [PubMed: 10079221]
- Chen P, Zindy F, Abdala C, Liu F, Li X, Roussel MF, et al. Progressive hearing loss in mice lacking the cyclin-dependent kinase inhibitor Ink4d. *Nature Cell Biology* 2003;5:422–426.
- Corwin JT, Cotanche DA. Regeneration of sensory hair cells after acoustic trauma. *Science* 1988;240:1772–1774. [PubMed: 3381100]
- Diensthuber M, Oshima K, Heller S. Stem/progenitor cells derived from the cochlear sensory epithelium give rise to spheres with distinct morphologies and features. *Journal of the Association for Research in Otolaryngology* 2009;10(2):173–190. [PubMed: 19247714]
- Gubbels SP, Woessner DW, Mitchell JC, Ricci AJ, Brigande JV. Functional auditory hair cells produced in the mammalian cochlea by in utero gene transfer. *Nature* 2008;455:537–541. [PubMed: 18754012]

- Hori R, Nakagawa T, Sakamoto T, Matsuoka Y, Takebayashi S, Ito J. Pharmacological inhibition of Notch signaling in the mature guinea pig cochlea. *Neuroreport* 2007;18:1911–1914. [PubMed: 18007185]
- Izumikawa M, Minoda R, Kawamoto K, Abrashkin KA, Swiderski DL, Dolan DF, et al. Auditory hair cell replacement and hearing improvement by Atoh1 gene therapy in deaf mammals. *Nature Medicine* 2005;11:271–276.
- Li H, Roblin G, Liu H, Heller S. Generation of hair cells by stepwise differentiation of embryonic stem cells. *Proceedings of the National Academy of Sciences, U.S.A* 2003;100:13495–13500.
- Lowenheim H, Furness DN, Kil J, Zinn C, Gultig K, Fero ML, et al. Gene disruption of p27(Kip1) allows cell proliferation in the postnatal and adult organ of Corti. *Proceedings of the National Academy of Sciences, U.S.A* 1999;96:4084–4088.
- Oshima K, Grimm CM, Corrales CE, Senn P, Martinez Monedero R, Geleoc GS, et al. Differential distribution of stem cells in the auditory and vestibular organs of the inner ear. *Journal of the Association for Research in Otolaryngology* 2007;8:18–31. [PubMed: 17171473]
- Ryals BM, Rubel EW. Hair cell regeneration after acoustic trauma in adult Coturnix quail. *Science* 1988;240:1774–1776. [PubMed: 3381101]
- Sage C, Huang M, Karimi K, Gutierrez G, Vollrath MA, Zhang DS, et al. Proliferation of functional hair cells in vivo in the absence of the retinoblastoma protein. *Science* 2005;307:1114–1118. [PubMed: 15653467]
- Senn P, Oshima K, Teo D, Grimm C, Heller S. Robust postmortem survival of murine vestibular and cochlear stem cells. *Journal of the Association for Research in Otolaryngology* 2007;8:194–204. [PubMed: 17334849]
- Takebayashi S, Yamamoto N, Yabe D, Fukuda H, Kojima K, Ito J, et al. Multiple roles of Notch signaling in cochlear development. *Developmental Biology* 2007;307:165–178. [PubMed: 17531970]
- White PM, Doetzlhofer A, Lee YS, Groves AK, Segil N. Mammalian cochlear supporting cells can divide and trans-differentiate into hair cells. *Nature* 2006;441:984–987. [PubMed: 16791196]
- Woods C, Montcouquiol M, Kelley MW. Math1 regulates development of the sensory epithelium in the mammalian cochlea. *Nature Neuroscience* 2004;7:1310–1318.
- Yamamoto N, Tanigaki K, Tsuji M, Yabe D, Ito J, Honjo T. Inhibition of Notch/RBP-J signaling induces hair cell formation in neonate mouse cochleas. *Journal of Molecular Medicine* 2006;84:37–45. [PubMed: 16283144]
- Zheng JL, Gao WQ. Overexpression of Math1 induces robust production of extra hair cells in postnatal rat inner ears. *Nature Neuroscience* 2000;3:580–586.