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Emerging Therapies for Sensorineural Hearing Loss

Matthew G. Crowson, MD[1], **Ronna Hertzano, M.D., Ph.D.**[2], and **Debara Tucci, MD, MS, MBA, FACS**[1]

[1]Division of Head & Neck Surgery & Communication Sciences, Department of Surgery, Duke University Medical Center, Durham, NC USA

[2]Department of Otorhinolaryngology Head & Neck Surgery, Anatomy and Neurobiology and Institute for Genome Sciences, University of Maryland School of Medicine, Baltimore, MD USA

Abstract

Objective—To critically review and evaluate the proposed mechanisms and documented results of the therapeutics currently in active clinical drug trials for the treatment of sensorineural hearing loss.

Data Sources—U.S. National Institutes of Health (NIH) Clinical Trials registry, MEDLINE/PubMed.

Study Selection & Data Extraction—A review of the NIH Clinical Trials registry identified candidate hearing loss therapies, and supporting publications were acquired from MEDLINE/PubMed. Proof-of-concept, therapeutic mechanisms, and clinical outcomes were critically appraised.

Data Synthesis—22 active clinical drug trials registered in the United States were identified, and six potentially therapeutic molecules were reviewed. Of the six molecules reviewed, four comprised mechanisms pertaining to mitigating oxidative stress pathways that presumably lead to inner ear cell death. One remaining therapy sought to manipulate the cell death cascade, and the last remaining therapy was a novel cell replacement therapy approach to introduce a transcription factor that promotes hair cell regeneration.

Conclusion—A common theme in recent clinical trials registered in the United States appears to be the targeting of cell death pathways and influence of oxidant stressors on cochlear sensory neuroepithelium. In addition, a virus-delivered cell replacement therapy would be the first of its kind should it prove safe and efficacious. Significant challenges for bringing these bench-to-

Corresponding Author: Matthew G. Crowson, Duke University Medical Center, 2301 Erwin Road, Division of Otolaryngology-Head & Neck Surgery, Durham, NC USA 27710, Tel.: +1 603 306 1182, matthew.crowson@dm.duke.edu.

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bedside therapies to market remain. It is never assured that results in non-human animal models translate to effective therapies in the setting of human biology. Moreover, as additional processes are described in association with hearing loss, such as an immune response and loss of synaptic contacts, additional pathways for targeting become available.

Keywords

Hearing loss; molecular therapy; gene therapy

INTRODUCTION

According to the most recent estimates of the World Health Organization, 360 million people, or approximately 5.3% of the world's population, live with disabling hearing loss.[1] In children, hearing loss has repeatedly been demonstrated to affect their academic, behavioral and cognitive development as well decreased overall quality of life.[2–7] Deleterious effects of hearing loss in adults also generate morbidity as hearing loss has been linked to poor overall physical functioning and social interaction, as well decreased overall quality of life.[8–11] Medical therapies for hearing loss have remained elusive despite the number of persons living with disabling hearing loss world-wide and the multi-dimensional burden of hearing loss.

The most common form of hearing loss world-wide is sensorineural hearing loss (SNHL). [12,13] The development of drugs to treat or prevent SNHL has proven challenging. Many investigators have sought to characterize the biochemical, molecular, and intra-cellular mechanisms in both normal-state hearing function and in pathological processes that impair hearing function. Over the past decade, academic institutions and pharmaceutical firms around the world have begun to commit significant resources to development of therapies for treatment of SNHL. These combined efforts have resulted in a relatively recent burst of clinical trial activity and increased hope that these emerging therapies can be brought to market. The objective of this review is to critically review and evaluate the proposed mechanisms and data of the therapeutics currently in active randomized clinical drug trials for the treatment of sensorineural hearing loss. In addition, we briefly discuss new drugs proposed to be on the short track for clinical trials.

METHODS

This review comprised periodicals and previously published data and therefore IRB approval was not required.

Clinical Trial Registry Review and Therapy Identification

Interventional clinical trials that investigated sensorineural hearing loss in phase 1 or later were included. Clinical trials that evaluated steroids, natural supplements (e.g. Gingko Biloba), treatments for conditions other than specifically for sensorineural hearing loss (e.g. Meniere's Disease, autoimmune inner ear disease, cerumen impaction, congenital cytomegalovirus infection), or trials that were withdrawn/terminated were excluded.

RESULTS

We identified 22 active clinical drug trials registered in the United States (Table 1) as of the writing of this manuscript. Of the 22 active clinical trials, we reviewed six potentially therapeutic molecules (Table 2; Figure 1). Sufficient basic science and available clinical data were obtained for each molecule to inform a balanced discussion on the foundation and rationale of the therapy. Of the six molecules reviewed, four addressed mechanisms pertaining to mitigating oxidative stress pathways that presumably lead to auditory cell death. One remaining therapy sought to manipulate the cell death cascade, and the last remaining therapy was a novel cell replacement therapy approach to introduce a transcription factor that induces hair cell regeneration.

Several studies were not included as specific details for therapies registered in the ClinicalTrials.gov registry were not available on either sponsor-controlled web sites or media, or through directed searches in MEDLINE. The omitted therapies included anakinra (interleukin-1 (IL-1) receptor antagonist), ancrod (Malayan Pit Viper venom), AUT00063 (voltage gated potassium ion channel modulator), EPI-743 (AKA. Vatiquinone), HPN-07 (anti-oxidant 2,4-disulfonyl α-phenyl tertiary butyl nitrone), PF-04958242 (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid potentiator), vestipitant (NK_1 receptor selective antagonist), and zonisamide (anti-convulsant).

DISCUSSION

Efforts to develop drugs to treat SNHL have resulted in over twenty active randomized clinical drug trials for the prevention or treatment of hearing loss registered in the United States in the past decade (Table 1). The number of late phase trials is promising and the prospect of the near-availability of a drug to address hearing loss carries the hope that sensorineural hearing loss will no longer be a permanent disability. An understanding of the therapies and mechanisms is needed to accurately counsel patients on the potential role of these hearing loss therapies should they make it to market. Considering the need for this understanding, we sought to critically evaluate the proposed mechanisms and data related to the therapeutics currently in active randomized clinical drug trials. We identified 22 active randomized clinical drug trials, and reviewed 6 therapeutic molecules.

Cochlear Hair Cell Regeneration Therapy – The '*Atoh1*' Gene

Sensorineural hearing loss is most commonly caused by the degeneration of hair cells from either internal or external pathologic factors including infectious or inflammatory processes, ototoxic drugs, noise over-stimulation as well as the normal process of aging. Hair cells are essential to hearing and balance function, and are the mechanotransducers that convert mechanical energy produced by sound or head movement into electrical potentials that are subsequently relayed to the brain. While many genes contribute to the normal differentiation and development of the cochlear sensory epithelium, the '*Atoh1*' gene, also known as '*Math1*,' was first discovered as a vital regulator of cochlear and vestibular hair cell generation in mice.[14] It has been shown that the natural expression of *Atoh1* occurs in a population of the primordial sensory cells of the cochlea, and plays an essential role in the differentiation of these cells into hair cells.[15] If in mouse models expression of *Atoh1* is

blocked, the sensory epithelium of the cochlea is completely disrupted and hair cell development is stymied.[16] Conversely, if *Atoh1* expression is induced in sensory epithelia of embryonic or neonatal mouse or rat cochleae hair cell formation occurs.[16–18]

Other animal models used for testing *Atoh-1* have produced interesting results. Using a guinea pig model, 4–5 week old normal hearing animals were inoculated with the *Atoh1*-containing virus vector through direct delivery to the cochlea.[19] The investigators reported the formation of occasional, immature hair cell-like cells in non-sensory regions of the cochlea four days after inoculation. Because these were normal hearing animals, it was difficult to determine if new hair cell formation occurred within the boundaries of the organ of Corti. Therefore, with this encouraging result, subsequent studies tested the ability of *Atoh1* to create hair cells in deafened mammalian models. One such study evaluated the effects of *Atoh1* overexpression on hair cell regeneration in the deafened cochlea of young guinea pigs.[20] In this study, guinea pigs were deafened with systemic injection of ototoxic drugs and confirmed deaf by auditory brainstem response (ABR). The Atoh1 gene was placed in an adenovirus vector, and infused into the scala media of the deafened guinea pig cochleae 4 days after the ototoxic injury. Scanning electron microscopy 8 weeks after infusion demonstrated a variable degree of inner and outer hair cell regeneration in the organ of Corti along with a dramatic improvement in hearing. The new hair cells, were noted to be positioned on the basement membrane, suggestive of trans-differentiation of supporting cells into hair cells. The authors suggested, based on these findings, that expression of the *Atoh1* gene alone is sufficient to restore hearing through hair cell regeneration.[20] However, when the study was repeated with a delay of 7 days to the viral treatment after deafening, no hair cell regeneration occurred.[21] The authors examined the cochleae and noted that within six days of treatment differentiated supporting cells were absent. Of note, the deafening treatment was also different from the treatment used in the first study: in lieu of using kanamycin and ethacrynic acid, neomycin, which can also induce changes in supporting cells, was used. The authors concluded that differentiated supporting cells are necessary for the successful regeneration of hair cells using the *Atoh1* gene delivery approach. However, with such a narrow therapeutic window, a question remains to the appropriate indication for the use of this treatment in humans. It has been shown that people with a sudden sensorineural hearing loss have a variable loss of supporting cells and their cochleae consist of areas with flat epithelium.[22,23] In addition, to date, no other studies have been published replicating these findings of cochlear hair cell regeneration and hearing restoration following *Atoh1* gene delivery to adult inner ears, thereby raising concerns regarding the feasibility of this approach.

Novartis Pharmaceuticals is currently evaluating ‘CGF166’ – an adenovirus vector encoding the human Atonal transcription factor ‘*Hath1’* in safety and efficacy Phase 1 and Phase 2 clinical trials[24] (Table 1). Little background information has been made available through the clinical trial registry or commercial websites. Inclusion criteria include adults with a long standing, stable (greater than a year with minimal change), non-fluctuating hearing loss that is at least 50 dB HL at 125 and 250 Hz and greater than 70 dB HL in higher frequencies. The adenovirus vector with *Hath1* is to be administered as an infusion via a stapedotomy into the vestibule. While peer-reviewed published data to directly support feasibility of hearing restoration of long standing hearing loss using *Atoh1* gene is not available, the study

was approved by the United States Food and Drug Administration (FDA), and represents the first gene transfer clinical trial for hearing restoration.

In parallel to the development of targeted therapies for hearing loss, methods of drug delivery to the inner ear have been investigated. Various methods for delivery have been explored including osmotic mini-pump infusion, direct microinjection, and dissolvable drug-infused packing.[25] The most effective approach will depend upon the properties of the molecule or agent to be delivered. Directed surgical feasibility studies of inner ear adenovirus delivery have also demonstrated that both a round window and cochleostomy approach are feasible, but a round window approach may result in less hearing loss than a cochleostomy approach in mice.[26] The efficacy and safety of the adenovirus delivery vector to the inner ear in humans remains unknown. No current human study data are available to characterize the risks of direct intra-labyrinthine application of an adenovirus vector and/or spread to the CSF or other routes. Direct intra-labyrinthine inoculation many not be the most practical means for drug delivery in humans given the need for an invasive approach. It is possible that direct inoculation of the labyrinth may confer efficacy and tolerability benefit versus systemic administration as used with traditional oral and parenteral methods, but this remains to be explored.

Manipulating the Cell Death Cascade – JNK Stress Kinase Inhibition

When a cell experiences significant stress or injury, intrinsic cell death cascades may be activated that result in death of the injured cell. Upon activation of cell death pathways, biochemical changes can occur including the generation of free-radical and reactive oxygen species, acidic cytoplasmic pH changes, and protein denaturation.[27,28] With respect to hearing, it has been demonstrated that significant stressors can cause cell death, as well as structural damage, resulting in sensorineural hearing loss.[29] If the sensory neuroepithelium were made more resilient to cell death by changing the balance between the signaling pathways for death (e.g., caspase 9, MAPK, cJNK) and survival (e.g., Bcl-2), it is plausible that sensorineural hearing loss could be prevented.

The mitogen-activated protein kinase/c-Jun N-terminal kinase (MAP-JNK) signaling pathway has been shown to be activated following damaging levels of aminoglycoside and noise trauma stressors.[30–34] Specifically, it is hypothesized that cellular stress such as aminoglycoside exposure in the cochlea results in the formation of reactive oxygen species and free radicals that cause the JNK kinase to activate c-Jun.[35] The activated c-Jun transcription factor binds other transcriptional complexes which ultimately results in the complete loss of cochlear hair cells.[36] Regardless of the molecular pathway under consideration, it is believed that a therapy designed to intervene prior or immediately following the cochlear neuroepthielial injury may prevent sensorineural hearing loss.[29]

Animal studies using synthetically created JNK inhibitory molecules have demonstrated protective effects in the face of established cochlear neuroepthielial stressors. Mouse *in vitro* and adult guinea pig *in vivo* models exposed to noise trauma, ototoxic agents, and trauma-induced hearing loss (such as with electrode implantation stressors), when treated with direct co-application of synthetic JNK inhibitor peptides, demonstrated near-complete prevention of hair cell death.[37,38] However, most studies did not perform dose-response curves which

are critical to development of a full understanding of the therapeutic potential of a drug. One such study, for example, found that CEP-11004, an indirect inhibitor of JNK signaling, can inhibit hair cell death in utricles exposed to moderate but not high doses of neomycin.[39] Prevention of cell death in cochlear neuroepithelia is the basis of treatment with AM-111 – the Auris Medical AG JNK inhibitor peptide currently in clinical trials.[40] AM-111 purportedly prevents cellular death from different stressors leading to sensorineural hearing loss by preventing JNK-mediated apoptosis.[41] Specifically, AM-111 binds to JNK and prevents activation by the c-jun and c-fos transcription factors. In animal studies, AM-111 has prevented cochlear hair cell death in response to noise trauma, ischemic cochlear damage, acute labyrinthitis and aminoglycoside ototoxcity.[37,42–44] AM-111 has also been shown to protect against hearing loss in cases of semicircular canal transection in a guinea pig otitis media model.[45] AM-111 is administered topically in a biodegradable gel scaffold that is applied at the round-window membrane. Reported benefits of this delivery method include potential for intraoperative application and ease of trans-tympanic injection.[42]

AM-111 Phase 2 trial efficacy data from a prospective double-blind randomized placebo-controlled study was made available by Auris in 2015.[46,47] In patients with severe-to-profound sudden sensorineural hearing loss, patients treated with a single trans-tympanic dose of AM-111 realized significant improvements in absolute and relative pure tone average and speech discrimination scores compared to the placebo group. The patients were treated within a mean 29 hours of acute onset sensorineural hearing loss. No treatment benefits were observed for patients with mild-moderate sensorineural hearing loss. The investigators reported only mild procedure-related adverse effects including otalgia, incision site complications, and otitis media in less than 5% of their patient population.

Oxidative Stress Mitigation – D-Methionine, N-Acetylcysteine, Glutathione Peroxidase Mimicry, & Sodium Thiosulfate

As discussed previously, reactive oxygen species and free radicals are generated in cochlear hair cells from exposure to stressors of different etiologies. The release of these molecules can result in cellular damage, and in some cases cell death. Molecules with antioxidant properties prevent the formation of or disarm potentially destructive free radicals and reactive oxygen species that facilitate cellular death.[48] After a measurable noise exposure, reactive oxygen species and free radicals increase in hair cells.[49,50] In current clinical trials for sensorineural hearing loss, several studies are investigating possible benefit of various antioxidant molecules including D-methionine, N-acetylcysteine, glutathione peroxidase mimicry, and sodium thiosulfate.

D-methionine

The exact antioxidant mechanism of D-methionine is not known, however it is purported to be a scavenger of free radicals and supporter of other antioxidant enzymatic processes that serve to decrease oxidant stressors within a cell.[51,52] Multiple *in vitro* and *in vivo* animal studies with D-methionine have demonstrated otoprotective properties when rat, mice, and guinea pig models were subjected to ototoxic agents such as cisplatin chemotherapies, aminoglycoside antibiotics, and noise-induced trauma.[53–58] In a recent investigation of the optimal timing of administration of D-methionine after noise exposure, chinchillas who

were administered the agent between three and seven hours post-exposure had decreased ABR threshold shifts three weeks after exposure.[59] The fact that D-methionine is available in a stable oral formulation, coupled with evidence of otoprotective effects with post-exposure administration, has spurred interest in human studies for noise induced hearing loss,[59] especially in military settings.[60] However, again, investigation did not include a drug dose-response curve or utilization of a range of loudness of noise exposures. Can results from otoprotection of chinchillae exposed for six hours to 105 dB SPL octave band noise (centered at 4 kHz) be generalized to a variety of noise exposures in human?

Military environments are fraught with potential expected and unexpected noise trauma. New onset hearing loss has been positively associated with combat deployment, exposure to improvised explosive devices (IED), and head trauma.[61,62] Economic models are currently in development to assess the burden of hearing loss in the U.S. military, but the burden is thought to be significant.[63] The objective of a recent Department of National Defense trial was to augment hearing protection devices, such as ear plugs, for noise exposure that may exceed the protective capability of these devices.[60] The trial will determine the efficacy of D-methionine in preventing either noise-induced hearing loss or tinnitus after eleven days of weapons training for drill sergeant instructor trainees.[60]

N-acetylcysteine

The mechanism of action of N-acetylcysteine (NAC) is thought to be one of free radical scavenger, as well as augmentation of glutathione enzymatic activity, similar to D-methionine described above.[64–66] NAC has been extensively studied in medicine and is FDA-approved for use as a mucolytic for pulmonary disorders and in the treatment of acute hepatotoxicity after acetaminophen overdose. Given the established link between oxidant-induced cellular injury in the cochlea and sensorineural hearing loss, considerable interest in NAC as a possible therapy for the prevention or treatment of sensorineural hearing loss has emerged in numerous settings and applications.

Significant evidence of the protective effects of NAC across multiple animal model and simulated pathological circumstances has amassed. NAC has been demonstrated to protect against hair cell loss and/or temporal threshold shifts in numerous noise-induced hearing loss models in chinchillas and rats, as well as blast-noise exposed rats, and rabbits.[67–77] In other pathologic conditions, such as meningitis-induced hearing loss, NAC appeared to reduce long-term hearing loss measured at 14 days in a rat model, in age-related hearing loss in γ-glutamyl transferase 1 deficient mice, and in a murine industrial-solvent induced cochlear injury model.[78–80] In cochlear implant explant rat and guinea pig cochlea, the administration of NAC partially preserved inner hair cells compared to controls in response to simulated surgical trauma.[81,82]

Previously completed clinical evaluations of NAC have shown promise. An Iranian study of textile workers exposed to continuous noise greater than 85 decibels for at least 8 hours daily were randomly allocated to either receiving placebo, ginseng, or two doses of NAC.[83] Both NAC and ginseng reduced temporary threshold shifts at 14 days, with the larger response seen in the NAC treated cohort. A similar prospective, randomized, double-blinded, placebo-controlled clinical trial of military-based individuals receiving NAC to prevent hearing loss

after weapons training showed a small reduction in threshold shifts in the participants' trigger-hand ear, but there was no significant reduction in the overall rate of threshold shifts.[84] No significant adverse effects were reported. Another retrospective study evaluated the use of oral NAC in conjunction with intratympanic dexamethasone injections for sudden sensorineural hearing loss, and found that the addition of NAC conferred increased benefit in hearing recovery.[85] Multiple active clinical trials are investigating NAC in the treatment of sensorineural hearing loss. Three active trials are seeking to characterize the protective effects of N-acetylcysteine on either cisplatin-, aminoglycoside-, or noise-induced ototoxicity. A pediatric trial is investigating cisplatin-induced ototoxicity in children being treated for different malignancies and is open for recruitment as of the writing of this manuscript.[86] In Turkey, NAC is being investigated as an otoprotective adjunct in patients who have developed peritonitis while receiving continuous ambulatory peritoneal dialysis.[87] Peritonitis is a common complication of this form of dialysis and the microbiology of these infections has called for aminoglycosides and vancomycin as the antibiotic of choice, despite their known ototoxicity.[87] The last is a closed trial in Taiwan that studied 53 steel industry workers exposed to noise. In a double cross-over placebo design, the steel workers were provided with 1200 mg/day of NAC with complete pre- and post-treatment audiometry performed.[88] The authors reported that NAC administration significantly reduced temporary threshold shifts by 2.45 dB compared to 2.75 after placebo when exposed to daily ambient noise exposure of 88.4 to 89.4 dB. However, the clinical significance of this difference is questioned.

Glutathione Peroxidase Mimicry

Chemotherapeutic drugs, particularly the platinum-based agents, have been shown to be directly ototoxic to the cochlea through the generation of a free radicals.[89–91] Specifically, cisplatin causes depletion of glutathione and other antioxidant enzymes in the cochlea resulting in outer hair cell loss and damage to the organ of Corti.[92] Early studies sought to counter the deleterious effects of cisplatin by introducing various molecules with anti-oxidant properties, and it was shown that these properties can prevent hair cell loss in the cochlea.[92] Around the time of this work, ischemia and stroke researchers introduced ebselen [2-phenyl-1, 2-benzisoselenazol-3 (2H)-one], a neuroprotective molecule that mimics the activity of endogenous glutathione peroxidase and phospholipids hydroperoxide glutathione peroxidase.[93] Providing glutathione to glutathione-deficient guinea pigs has also been shown to limit noise-induced hearing loss.[94] With the characterization of the hearing protective effects of glutathione, and the anti-oxidant effects of ebselen, investigators interested in stress-induced oxidizing damage of the cochlea demonstrated ebselen as protective of auditory cells when subjected to cisplatin *in vitro*.[95] Moreover, endogenous glutathione peroxidase was demonstrated as active and present in the organ of Corti, spiral ganglia, stria vascularis, and spiral ligament, suggesting that ebselen may have direct activity at multiple cochlear sites where oxidant-stress related injury may occur.[96]

Soon after ebselen was shown to be protective against cisplatin-mediated ototoxicity *in vitro*, data from animal studies followed that were increasingly encouraging, demonstrating ebselen as a potential therapy for preventing oxidative sensorineural hearing loss for stress mechanisms including and beyond that caused by cisplatin. In noise-exposed rats, ebselen

has been demonstrated to protect against the loss of outer hair cells and reduce acute stria vascularis edema purportedly through direct free radical scavenging activity, and by promoting endogenous glutathione peroxidase expression.[96] Studies utilizing auditory brainstem responses in rats after noise-exposures demonstrated that ebselen protected against both temporary and permanent threshold shifts.[97]

Clinical data in the past five years has kindled the prospect for ebselen-mediated sensorineural hearing loss protection in human subjects. Preliminary data of a randomized double-blind, placebo-controlled Phase 2 clinical trial in adults with normal or slight hearing loss who were subjected to four hours of noise exposure through a MP3 player has been made available in an abstract.[98] Oral ebselen administration resulted in a significant reduction in temporary threshold shift incidence, severity and duration when compared to the placebo group. The full details of this study were not available to review at the writing of this manuscript. Currently, ebselen is under evaluation for safety and efficacy in 4 clinical trials sponsored by Sound Pharmaceuticals as the trial drug ‘SPI-1005’ in settings of noise exposure and cisplatin-mediated ototoxicity.[99–102]

Sodium Thiosulfate

As discussed above, platinum-based chemotherapeutics have well-established ototoxicity. Sodium thiosulfate is a sulfur containing molecule that has the ability to bind and inactivate platinum-based chemotherapeutics such as cisplatin.[103]

Specifically, sodium thiosulfate has been shown to bind and inactivate carboplatin, allowing renal excretion and ultimately less systemic toxicity, without a decrease the anti-tumor activity of carboplatin, if infused in a delayed fashion.[104,105] Sodium thiosulfate has also been shown to have direct otoprotective effects against carboplatin in the guinea pig cochlea. There may be a dose-dependent relationship as continuous, direct infusion to the middle ear space resulted in improved hearing preservation, as compared with single daily doses, as measurable by auditory brainstem responses.[106,107] However, the time course of protective effect of sodium thiosulfate is limited to co-administration with cisplatin, and protection is lost if administered even a few hours after cisplatin.[108] Beyond direct binding and inactivation of platinum-based chemotherapeutics, sodium thiosulfate may also have intrinsic anti-oxidant properties that may serve to protect hearing, but this has yet to be extensively explored.[109]

Clinical data for the use of sodium thiosulfate to prevent chemotherapy-induced ototoxicity has produced promising results. A cohort study of adult patients receiving parenteral cisplatin for advance carcinoma of the head and neck analyzed the effect of co-administered systemic sodium thiosulfate, and reported a decrease in measured hearing loss except for higher frequencies.[110] A retrospective study with a similar patient population also demonstrated that co-infusion of parenteral sodium thiosulfate results in less severe cisplatin ototoxicity than when intravenous cisplatin is provided exclusively.[111] Specifically, patients who did not receive sodium thiosulfate had detectable hearing loss at both high and ultra-high frequencies, whereas patients who received sodium thiosulfate had hearing loss only at ultra-high frequencies. Last, a randomized control trial of patients receiving cisplatin-based chemoradiation analyzed the effect of providing co-administered sodium thiosulfate and

found that it conferred a significant protective effect at frequencies in the range of speech perception, and fewer ears qualified for hearing aids.[112] As of the writing of this paper, one active phase III clinical trial is evaluating the otoprotective effect of intravenous sodium thiosulfate in children receiving cisplatin for a variety of malignancy types.[113]

Presbycusis & Mitochondrial Dysfunction – The Holy Grail of Hearing Loss?

Presbycusis, or 'age-related hearing loss,' has received much attention as the prevalence of presbycusis exceeds 40% in adults over 65 years-old in the United States.[114] Despite this substantial unmet need, an effective therapy has yet to be developed. Akin to the causes of other forms of sensorineural hearing loss, the discovery of causal mechanisms of presbycusis has remained elusive. Theories to explain the pathophysiology of presbycusis have evolved over time, but contemporary impressions report that a diffuse pattern of cochlear degeneration, including a combination of strial hearing loss with both primary and secondary loss of hair cells, may be more credible than aberrancies in cochlear conductive processes.[115] The extent to which presbycusis shares similar pathologic molecular mechanisms with other forms of sensorineural hearing loss reviewed in this paper is notable. In a novel presbycusis mouse model, an inbred mouse strain which suffers from early multi-system aging (senescence-accelerated mouse prone 8; SAMP8), oxidative stress and markers of chronic inflammation were all demonstrated using lipid peroxidation product measurements as well as oxidative mitochondrial and nuclear DNA damage biomarker assays.[116] Interestingly, ultrastructural analysis of mitochondria from the organ of Corti in these animals demonstrated unrecognizable mitochondria cristae and evidence of mitochondrial wall damage. Moreover, mitochondrial complex I and II, as well as cytochrome c oxidase enzymatic activity showed perturbations that signaled significant mitochondrial dysfunction. As a caveat, one should consider that this model of age related hearing loss may be secondary to a process that is unique to the SAMP8 strain, or a result of a combination of mutations that is different from those which underlie age related hearing loss in humans. Other animal models of hearing loss have been used extensively to study presbycusis, specifically the Fischer 344 rat as outlined in a recent review.[117] However, the review synthesizes evidence that the mechanism of degenerative hearing loss in the Fischer 344 rat may not be related to cochlear hair cell loss. Despite the disappearance of otoacoustic emissions and elevated ABR thresholds, cochlear hair cells can still be found on histologic analysis.[118] This suggests a significant limitation for the use of the Fischer 344 rat for the study of presbycusis in humans. The generation of an animal model that closely mimics the pathophysiology of human presbycusis will be needed for the development and testing of targeted therapies.

Evidence in the last 20 years suggests that mitochondrial DNA defects and resulting dysfunction play a key role in inherited hearing loss, and possibly presbycusis.[119–123] Mitochondrial-mediated cell death has been postulated to be a causal factor for presbycusis.[120] This cell death pathway is governed in part by the *Bcl-2* family of genes and gene products.[124] Silencing of one of the Bcl-2 genes implicated in mitochondrial-mediated cell death, the pro-apoptotic gene *Bak*, has been shown to prevent presbycusis in a mouse model.[121] However, a recent review reports that there may be other mechanisms behind mitochondrial-mediated presbycusis including calcium-regulation aberrancies, and specific

mitochondrial DNA deletions.[125] What remains to be confirmed is if mitochondrial dysfunction in presbycusis occurs through mechanisms either shared or distinct to that of the well-described oxidant-antioxidant pathways. If there are separate mitochondrial mechanisms driving presbycusis, the investigation of pathways leading to mitochondrial dysfunction in presbycusis may yield novel therapy targets.

Conclusion & Future Directions

We are entering an exciting era in the development of directed therapies for sensorineural hearing loss. A common theme in recent clinical trials registered in the United States appears to be the targeting of cell death pathways and influence of oxidant stressors on cochlear sensory neuroepithelium. In addition, a virus-delivered cell replacement therapy using the ATOH1 gene, or other genes which would likely follow, would be revolutionary, if proven safe and efficacious. Finally, there is an increase in our knowledge and understanding of the pathophysiology of hearing loss, leading to the identification of additional pathways for targeting.[126–128] For example, of particular interest will be molecular pathways identified through cell type-specific transcriptomic analyses of the signaling cascades induced after noise exposure. Significant challenges for bringing these bench-to-bedside therapies to market still remain. It is never assured that *in vitro* and *in vivo* results in non-human animal models may translate to effective therapies in the setting of human biology. Characterization of dose-response curves in animals not only for the proposed treatments, but also for the known offending stressors will be important to validate and calibrate therapy. Moreover, as additional processes that impact etiology of hearing loss - such as an immune response and neuronal retraction - are discovered, additional pathways for targeting become available.

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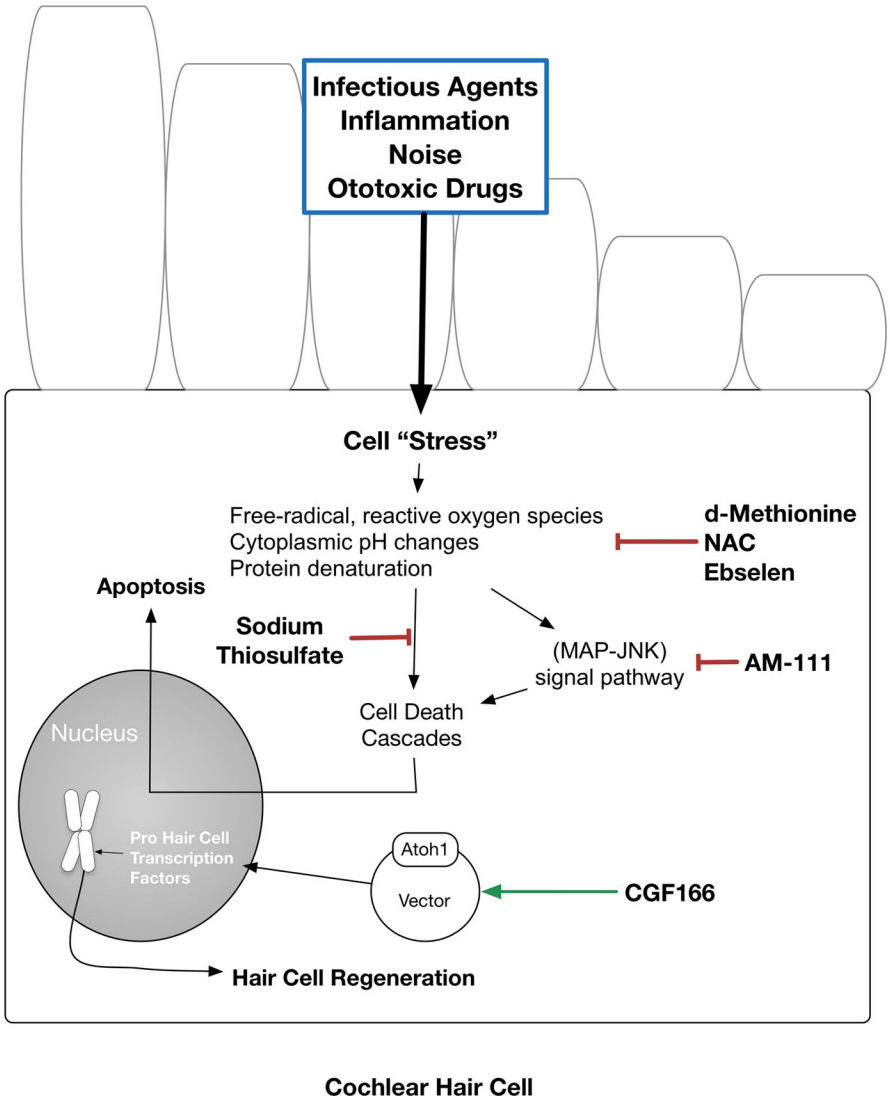

Figure 1.

Schematic of reviewed candidate molecules for the treatment of sensorineural hearing loss.

Table 1

Curated list of active clinical drug trials for the prevention or treatment of sensorineural hearing loss. Source: Clinicaltrials.gov, as of July 9, 2016. DB – Double Blind, OL – Open Label. NIDCD - National Institute on Deafness and Other Communication Disorders.

Trial Drug	First Listed Sponsor	Recruitment	Trial Phase	Funding	Masking	Start Date	End Date
PF-04958242	Pfizer	Completed	Phase 1	Industry	DB	Dec. 2011	Feb. 2013
SPI-1005	Sound Pharmaceuticals Inc.	Completed	Phase 1	Industry	DB	May 2006	Aug. 2006
HPN-07	Otologic Pharmaceutics, Inc.	Completed	Phase 1	Industry	DB	Oct. 2014	Jan. 2015
N-Acetylcysteine	Children's Hospital Los Angeles	Recruiting	Phase 1	Other	OL	Mar. 2016	Feb. 2018
Anakinra	Northwell Health	Completed	Phase 1 & 2	Other	OL	Oct. 2013	Jul. 2015
Ancrod	Nordmark Arzneimittel GmbH & Co. KG	Recruiting	Phase 1 & 2	Industry & Other	DB	May 2013	Aug. 2016
Zonisamide	Washington University School of Medicine	Not yet	Phase 1 & 2	Other	OL	Jun. 2017	Dec.2019
Anakinra	NIDCD	Completed	Phase 1 & 2	Other& NIH	OL	Jun. 2011	Sept. 2014
CGF166	Novartis Pharmaceuticals	Recruiting	Phase 1 & 2	Industry	OL	Oct. 2014	Aug. 2017
AUT00063	Autifony Therapeutics Limited	Active, not recruiting	Phase 2	Industry	DB	Jan. 2015	Apr. 2016
AM-111	Auris Medical, Inc.	Completed	Phase 2	Industry	DB	Dec.2008	Jul. 2012
N-acetylcysteine	National Taiwan University Hospital	Completed	Phase 2	Other	DB	Nov. 2007	Jan. 2008
SPI-1005	Sound Pharmaceuticals, Inc.	Not yet	Phase 2	Industry & U.S. Federal	DB	Aug. 2016	Jan. 2018
SPI-1005	Sound Pharmaceuticals, Inc.	Not yet	Phase 2	Industry	DB	Sept. 2016	Aug. 2017
EPI-743	Edison Pharmaceuticals Inc.	Completed	Phase 2	Industry	DB	Oct. 2014	Nov. 2015
SPI-1005	Sound Pharmaceuticals Inc	Completed	Phase 2	Industry & Other	DB	Sept. 2011	Dec. 2013
Vestipitant	GlaxoSmithKline	Completed	Phase 2	Industry	DB	Dec. 2006	Aug. 2009
N-acetylcysteine	TC Erciyes University	Completed	Phase 2 & 3	Other	OL	Jun. 2010	Nov. 2011
Alpha-lipoic acid	VA Office of Research and Development	Completed	Phase 2 & 3	U.S. Federal & Other	DB	Oct. 2007	Mar. 2011
Sodium thiosulfate	Children's Oncology Group	Active, not recruiting	Phase 3	Other & NIH	OL	Jun. 2008	Sept. 2012
AM-111	Auris Medical, Inc.	Recruiting	Phase 3	Industry	DB	Jun. 2016	Jun. 2018
D-methionine	Southern Illinois University	Recruiting	Phase 3	U.S. Federal	DB	Sept. 2013	Dec. 2016

Table 2

Currently investigated therapies and mechanisms for sensorineural hearing loss in humans.

Trial Agent	Application	Mechanism	Therapeutic Molecule	Administration Method	Clinical Data Available
AM-111	Sensorineural Hearing Loss, Multiple Applications	Cell Death Cascade Manipulation	JNK Stress Kinase Inhibitor	Trans-Tympanic Gel	No
CGF166	Sensorineural Hearing Loss, Multiple Applications	Hair Cell Regeneration	*Atoh1* Transcription Factor	Intra-Labyrinthine Infusion	No
D-methionine	Noise-Induced Hearing Loss, Oxidant Induced	Oxidant Stress Mitigation	D-methionine	Oral	No
N-acetylcysteine	Sensorineural Hearing Loss, Oxidant Induced	Oxidant Stress Mitigation	N-acetylcysteine	Oral, Trans-Tympanic	Yes
Sodium thiosulfate	Sensorineural Hearing Loss, Chemotherapy-Induced	Oxidant Stress Mitigation	Sodium thiosulfate	Systemic	Yes
SPI-1005	Sensorineural Hearing Loss, Oxidant Induced	Oxidant Stress Mitigation	Ebselen	Oral	Yes