PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS (PIHL)
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Animal Model Series

EDITORIAL

Tinnitus and hearing loss remain #1 and #2 at the top of the list for most prevalent "service-connected disabilities" for both new Veterans and for all Veterans. This has been the case for years now. However, "Help is on the way." While it is becoming increasingly clear that genetics play a significant role in the pathophysiology of hearing loss, even when it is the result of traumatic events such as blast wave injuries or as a side effect of ototoxic drugs, the mechanisms that lead from traumatic event, lengthy noise exposure or ototoxic therapy to hearing disorders are only now being elucidated step by step.

You will find that in the list of clinical trials listed in the last part of this newsletter, cisplatin, the drug of choice for many cancers and a sensitizer for radiotherapy, is mentioned in no less than 14 different clinical trials. Cisplatin treatment leads to severe hearing loss in at least 30% of patients, and leads to some hearing loss in all patients. The fact that this hearing loss, long thought an unavoidable

side-effect of cancer treatment, is now being addressed at the level of clinical trials shows how far we have come in the last few years.   Yet, caution is still the order of the day: it was found recently that the inner ear contains endogenous stem cells, which may differentiate into support cells or hair cells throughout life. Cited in this newsletter, one paper ("*Cisplatin exposure damages resident stem cells of the mammalian inner ear*") shows that cisplatin damages these stem cells, so that a treatment against the immediate ototoxicity of cisplatin might only delay the cisplatin-related hearing loss. Furthermore, it has been shown that cisplatin treatment compromises supporting cell cytoskeletons, so that even remaining stem cells might not find the environment and support needed to regenerate a working organ of hearing.

The list of papers recently published and listed here is too long to receive a detailed treatment. We will only highlight a few in this brief space.

In a paper titled "*How to bury the dead: elimination of apoptotic hair cells from the hearing organ of the mouse,*" the authors examine the glial-like behavior of Deiters' cells in response to ototoxic trauma: the rapid sealing of the epithelial surface (called the reticular lamina) by Deiter's cells prevents expansion of damage by limiting the entry of the potassium-rich endolymph into the transduction organ, which will thus remain bathed through the permeable basilar membrane in the potassium-poor perilymph. Their paper elucidates the "healing process" that occurs after hair cell loss, and also offers a possible explanation for the absence, as far as we know, of hair cell regeneration in mammals. But their data also reveal the resealing of the epithelial surface by Deiters' cells extensions, reinforced by polymerized F-actin belts. These findings lead to serious concerns about therapeutic regenerative interventions, as any hair cell regeneration will need to both penetrate this actin belt while maintaining barrier integrity in the long run. These results might indicate that a more fruitful short term strategy to recover from hearing loss might be to target the organ of hearing during or soon after an ototoxic event, be it chemical of mechanical, but either way before the loss of hair cells has occurred, or when the effect is still confined to the synaptopathy presented in "*Aging after noise exposure: acceleration of cochlear synaptopathy in recovered ears.*"

Two papers in this issue demonstrate the importance and effectiveness of delivering BDNF and NT3 as a possible therapy to mitigate degeneration of the auditory nerve. In the paper "*Neurotrophin-3 regulates ribbon synapse density in the cochlea and induces synapse regeneration after acoustic trauma,*" the authors demonstrate that Neurotrophin-3 (Ntf3) and BDNF are necessary to

establish neural connection between the inner ear and the rest of the auditory pathway. They also establish that the supporting cells already mentioned act as sources for the growth factors, Furthermore, they show that Ntf3 helps in synapse regeneration and preservation of cochlear function after trauma. This indicates that localized delivery of NTf3 to the cochlea of (human) patients is a very promising therapeutic pathway to prevent noise-, trauma- or generally ototoxicity-induced hearing loss.

Along these lines, in "*Local delivery of brain-derived neurotrophic factor on the perforated round window membrane in Guinea pigs: a possible clinical application,*" the authors show the effectiveness of placing BDNF-loaded gelfoam on the round window membrane of animals whose hearing was damaged by kanamycin and a diuretic. The BDNF treatment reduced neural loss, particularly when the window membrane was perforated. This leads us to think that an even better outcome and a lower probability of complication would be expected if one delivered the drug with the use of nanoparticles (possibly similar to those used in the paper "*Solid lipid nanoparticles loaded with edaravone for inner ear protection after noise exposure*"), particularly if those nanoparticles could be actively transported across the window membrane via an externally applied force generation system.

As this newsletter shows, these are exciting times for the field of hearing and hearing disorders. The recent upsurge in understanding the mechanisms that lead to hearing loss and other hearing disorders, the better understanding of the role of the different cells in the inner ear, from the inner and outer hair cells to the support cells to the cells in the auditory nerve, the discovery of the many molecules involved in protecting and repairing the cochlear mechano-electrical transduction system, and finally (though under-represented in this edition) the new methods of drug delivery, all point to a near future in which hearing loss and tinnitus will be mitigated, trauma-induced damage will be reversed , and ototoxicity of life-saving drugs such as antibiotics and antineoplastics will be reduced or even ended. Help is on the way!

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RESEARCH GUIDANCES

Critical Issues of Cochlear Synaptopathy and Hidden Hearing Loss

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Recent findings

It has been long recognized that traditional audiogram do not adequately predict performance on complex auditory tasks. Difficulties understanding speech in noise have been observed in both older adults with normal audiometric thresholds (e.g. Working Group on Speech Understanding, Committee on Hearing, Bioacoustics, and Biomechanics, 1988; Dubno et al., 1997; Frisina, 1996) and younger listeners with significant noise exposure histories (Hope, Luxon & Bamiou, 2013; Kumar et al., 2012). Recent evidence suggests that even relatively low noise exposure can selectively damage synaptic connections between inner hair cells (IHCs) and spiral ganglion neuron (SGN) fibers that encode suprathreshold information without evoking concurrent obvious changes in auditory thresholds (Kujawa & Liberman 2006; 2009). Loss of fidelity in encoding suprathreshold signals may provide one explanation for acquired deficits in central auditory coding.

During aging, slow, progressive damage to SGNs was believed to occur secondary to hair cell loss, and to reflect the time course of retrograde axonal degeneration coupled with as yet unidentified downstream triggers of neuronal death. However, our studies have showed that normal age-related loss of cochlear synapses, IHCs, outer hair cells (OHCs), and SGNs can incur independently (Fu et al., 2010; Jin et al., 2011). In contrast, after noise-induced hearing loss, a growing body of recent literature has suggested that synaptic damage can be the primary insult after noise exposure; cochlear synaptic

damages can occur with only temporary threshold shifts (TTS) and lead to accelerated age-related loss of SGNs, although SGN degeneration was previously only linked to noise-induced hearing loss with permanent threshold shifts (PTS) (Kujawa & Liberman 2006; 2009; Lin et al., 2011). Specific sound levels and duration of noise exposure induced significant reversible threshold changes but irreversible damage to synaptic connections between IHCs and SGNs, specifically to low spontaneous-rate (LSR) SGNs (Furman et al., 2013). This synaptic damage can be detected electrophysiologically based on ABR wave I amplitudes if there is a full recovery of otoacoustic emission amplitudes and pure tone audiometric thresholds. These two latter findings indicated that OHCs, IHCs and high spontaneous-rate (HSR) SGNs ultimately retained normal levels of function – at least by our current standards of measurement.

These recent findings challenge the long-held belief that noise exposures resulting in TTS are benign, and indicate that traditional audiometric clinical assessments of hearing thresholds are insensitive to synaptic damage. The currently under-diagnosed form of injury from noise exposure or aging has been termed "synaptopathy" or "hidden hearing loss" (Schaette & McAlpine, 2012). One of the next important questions is whether cochlear synaptopathy could be the underlying driver for downstream (centrally mediated) compensatory and/or pathologic alterations that alter the fidelity of auditory processing and may contribute to the generation of abnormal synaptic plasticity in the brain. However, before exploring this important clinical hypothesis, vital questions must be addressed in preclinical animal models, which will ultimately have a profound impact on the direction of major translational research on acquired hearing loss.

Critical issues to be addressed by animal studies
While the pre-clinical evidence for synaptic damage after noise exposure in the presence of normal auditory thresholds is compelling, crucial questions remain. First, there are other contributors to TTS (potential stereocilia damage, hair cell metabolic dysfunction, conduction block, etc). Therefore, the audiometric boundaries of noise exposure at which long-term synapse damage, specifically, is incurred should be established (Le Prell & Lobarinas, 2015). These are likely to vary according to age at testing, species, breed, sex. Second, the detailed metabolic and pathologic consequences cannot be resolved in humans, thus must be addressed pre-clinically - various noise exposure parameters coupled with functional and histological measurements of cochleae. Third, the broader functional consequences of this damage need to be established. This can be defined in terms of downstream changes in brainstem and cortical

electrophysiology, but more importantly, in terms of behavioral consequences. Finally, if the ultimate goal is to develop pre-clinical models that support translation of interventions, identifying critical molecular cascades underlying synaptic loss is likely to provide requisite insight. Candidate pathways and targets have been proposed and are under investigation, but these are still relatively new lines of exploration (for reviews, see Kopecky et al., 2014; Abi-Hachem, et al., 2010; Henderson et al., 2006; Le Prell et al., 2007, Le Press et al., 2001).

Critical issues to be addressed by clinical studies

Currently, we foresee two major themes required to move this preclinical finding of synaptic damage into clinical applications: (1) developing validated, reliable and minimally invasive tools to establish the degree of synaptic damage at any point in time and prospectively monitor changes and (2) defining clinically meaningful thresholds for "hidden hearing loss". At present, cochlear function is evaluated by combining methods of OHC assessment (i.e. OAEs) with ABR/electrocochleography (EcochG) to help distinguish pre-neural from neural pathology. Without the benefit of post-mortem immunohistochemical studies, the site of damage must be inferred, based on context and previous precedent. However, since we are beginning to try to understand cochlear deafferentation at the level of synaptopathy, new methods that are time efficient and sensitive to the defining properties of subsets of vulnerable fibers need to be developed. ABR wave I amplitude can and is measured both pre-clinically and in the clinical setting – although not routinely in the latter. While ABR wave I amplitude correlates well with cochlear deafferentation in animal models (Kujawa & Liberman, 2009; Lin et al. 2010), that same level of confidence in clinical applications is far from being established. Additionally, absolute ABR amplitude, and particularly of wave I, can show significant variation even in normal hearing subjects, thus potentially limiting the ability to identify small degrees of synaptic damage and monitor patients across time. Capitalizing on innate differences in low- and high-threshold neurons (e.g. dynamic range, resistance to masking, recovery from prior stimulation), first in animal models, could lead to the development of highly translatable algorithms for detecting synaptic loss across species, including man.

Despite the limitations of examining absolute amplitude of ABR waveforms, there is some evidence to suggest that this may be a promising avenue to investigate. Systematic decreases in wave I amplitude, with and without changes in later waves, have been seen in "normal" hearing listeners with higher

self-reported noise exposure backgrounds (Stamper & Johnson, 2014) and those with tinnitus (Gu et al., 2012; Schaette & McApline, 2011). However, the cross-sectional nature of these studies imposes limitations on the conclusions that can be made. Prospectively designed longitudinal studies fully assessing baseline hearing status and post- exposure changes are required to determine whether relatively isolated synaptic damage significantly contributes to hearing impairments in the real world. However, these measures are limited to instances when there is pre-existing baseline data and when IHC and OHC integrity remains relatively well preserved.

In the context of listeners exposed to pathologic noise, selective damage to LSR SGNs and impaired encoding of suprathreshold sounds may contribute to reduced auditory capabilities (Bharadwaj et al., 2014; Ruggles et al., 2011), since these neurons have a higher threshold and wider dynamic range of induced electrical activity than HSR neurons (Costalupes et al., 1984; Costalupes, 1985). Listeners with audiometric profiles within normal range, but significant noise exposure histories show deficits in temporal processing (Kumar, Ameenudin & Sangamantha, 2012; Stone, Moore & Greenish, 2008), detection of deviant stimuli in background noise (Kujala et al., 2004), amplitude modulation detection (Stone & Moore, 2014) and understanding of speech in noise, particularly in reverberant backgrounds (Hope, Luxon & Bamiou, 2013; Kumar et al., 2012) when tested in carefully controlled and time-intensive psychophysical experiments. The innate properties of the different subgroups of SGNs may theoretically and ultimately in practice explain the perceptual difficulties that listeners with "normal" pure tone thresholds experience with speech in noise and temporal processing. However, the identification of synaptic damage after noise exposure is relatively recent and the future challenges are to fully explore the current hypotheses and attempt to identify direct links between noise exposure, synaptic damage, and perceptual difficulties.

Summary
Based on the pre-clinical literature to date, both direct and indirect evidence for synaptic damage after noise exposure suggests a plausible testable hypothesis that is likely, at least in part, to explain clinical reports of difficulties in adverse listening situations despite pure tone thresholds within normal limits. Currently there are a number of informational gaps that limit our approach to interrogating the validity of the hypothesis, both at the pre-clinical and clinical levels. In pre-clinical models, identifying the boundary between TTS with and without synapse loss and the underlying molecular cascades are vital for developing future interventions. At the clinical level, translatable algorithms for

detecting synaptic loss and validated approaches for identifying clinically meaningful perceptual consequences must be developed.

This is an exciting new theme in hearing research that requires a concerted effort with both pre-clinical and clinical endeavors. The task ahead of us is long including the dissection of the biology underlying synaptic disconnection and repair, the development of a variety of new animal models, translatable audiometric and behavioral assays to identify underlying anatomic changes, and to assess reserve in critical inner ear circuits and predict capacity for repair to best match potential therapeutics to patients who will benefit from them.

Acknowledgments

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Military Working Dogs (MWDs)

Peter Scheifele, Ph.D.

The US Military employs military working dogs (MWDs) as force multipliers. The primary breeds of dogs used as MWDs are the Belgian Malanois and the German Shepherd Dog. Yet, unlike other organizations, the US government has never developed a baseline audiology program adequate to their needs as it applies to noise effects on canine hearing.

As a result of the number of cases of congenital deafness in dogs the veterinary and breeding communities have made an extensive effort to have puppies undergo auditory screening between the ages of five (5) to eight (8) weeks of age (1). The only acceptable audiological test for determining baseline hearing acuity is the Brainstem Auditory Evoked Response (BAER) test (2). BAER testing can also be used in diagnostic situations and as a baseline for establishing hearing acuity in dogs (3) and. Although this is the case two concerns still exist with the use of the BAER test as a diagnostic/baseline determinant tool:

1- No universally accepted normative data regarding the latency and intensity of BAER waveforms has been established by the veterinary community, and
2- The exact neural generator sites have not been accurately determined for the BAER waveforms especially for the later latency waves (wave-IV and V).

Moreover, although the BAER electrophysiological test is objective in its output (waveforms) the establishment of which peak on the resultant waveforms is subjective with the possible exception of Wave-V and the subsequent trough (VT) of Wave-V. This routine technique that has been used with humans since 1967 (Picton, 2011) and slowly introduced into the animal industry since the 1980's (4, 5, 6, 7) (Kay et al., 1984; Myers et al., 1984; Sims & Moore, 1984; Sims, M., 1988).

Outside of congenital deafness, noise-induced hearing loss (NIHL) is a big factor in kenneled working dogs and those transported in trucks and in helicopters. (15) Most occupied military kennels may have peak noise at 110 dB SPL and even require hearing protection of the handlers upon entering. The consequence of NIHL in MWDs is a failure of the dog to properly behave to voice commands and to miss critical acoustic cues while on target in theatre.

Canines may be a viable model for use in specific drug testing in accordance with the "Animal Rule" as specified by the FDA Guidance for Industry. Although the "Animal Rule" typically specifies the use of small animals, the canine auditory pathway and function as well as susceptibility to ototoxic drugs mimic that of humans. The issue may be the low possibility of controlling genetic variation in dogs as opposed to rodents.

Table 1: A summary of studies utilizing the BAER in dogs

BAER Category	Specific Aim(s)	Author/Researcher(s)
General use of BAER for hearing testing	Use of BAER for assessing hearing in dogs; Munro & Cox specified on Cavalier King Charles spaniels, Holliday & Marshall specified on Dalmatians.	Kay et al., 1984; Myers et al., 1984; Sims & Moore, 1984; Marshall, 1986; Knowles et al., 1988; Sims, M., 1988; Holliday et al., 1992; Munro & Cox, 1997; Wilson, W. & Mills, 2005, Webb, 2009
Latency/Intensity function	Presence of Latency-Intensity function	Marshall, 1985; Sims & Moore, 1984a; Poncelet et al., 2000a & 2000b
Auditory pathway development and maturation	Complete development and maturation of the auditory pathway as indicated by BAER testing in puppies	Strain et al., 1991; Poncelet et al., 2002
Etiology and prevalence of hearing loss in dogs	Etiology, prevalence and diagnosis of deafness in dogs and cats	Strain, 1996
Etiology and prevalence of hearing loss in dogs	Presbycusis in aging dogs indicated by histological evidence of cochlear lesions	Ter Haar et al., 2009
Etiology and prevalence of hearing loss in dogs	Central Nervous System (CNS) lesions result in abnormalities of BAER test	Steiss et al., 1994

Etiology and prevalence of hearing loss in dogs	Effects of otitis on hearing in dogs during and after treatment (BAER)	Eger & Lindsay, 1997
Etiology and prevalence of hearing loss in dogs	Successful use of Bone-Conduction in dogs with Conductive HL	Munro et al, 1997
Nomenclature and establishing normative data	Labeling of BAER peaks in dogs: electrode configuration and click polarity was also addressed. ***	Kawasaki & Inada, 1994
Nomenclature and establishing normative data	Researchers suggest there is a dual structure within the ABR of the dog using an over-complete discrete wavelet transform (OCDWT)	Wilson et al., 2006
Nomenclature and establishing normative data	Normative ABR latencies for hearing thresholds in two dog breeds.	Shiu et al., 1997
Acquisition effects of BAER response	Electrode placement effects on the BAER	Holliday & Te Selle, 1985
Acquisition effects of BAER response	Filter effects on the BAER ***	Kawasaki & Inada, 1992
Acquisition effects of BAER response	Use of high-pass filtered noise with clicks to identify high-frequency hearing loss in dogs (up to 13 kHz) ***	Poncelet et al., 2006
Acquisition effects of BAER response	Comparison of click verses tone burst stimuli for frequency specificity of the BAER	Uzuka et al., 1998; Ter Haar et al., 2002; Shelton et al., FIND YEAR
Acquisition effects of BAER response	Effect of stimulus rate on BAER waveform. ***	Wilson et al., 2009

Effects of sedation	Latency effects for unanesthetized and anesthetized dogs	Myers et al., 1985
Use of OAE's to assess canine hearing	Electrodiagnostic evaluation of auditory function in dogs using OAEs and the ASSR	Scheifele & Clark, 2012
Use of OAE's to assess canine hearing	Presence of spontaneous OAEs in dogs around 9100 Hz	Ruggero et al, 1984
Individual subject effects on testing	Head size does not have effect on BAER screening	Munro et al., 1997; Kemper et al., 2013; Shiu et al., 1997
Individual subject effects on testing	BAER abnormalities found in dogs with equilibrium deficit and seizures, BAER is most useful when used in conjunction with EEG	Myers et al., 1986

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RESEARCH HIGHLIGHTS

Articles determined to be of particular interest will be listed with full abstract in "Research Highlights" below, followed by the remainder of the "Relevant Literature," all published between September 1, 2014 (the end of the last Animal Model Newsletter search term) and August 31, 2015.

Editors evaluated 151 article abstracts and full text articles as needed for inclusion in this edition's listing of recently published PIHL-related literature. All duplicate references were removed. While the final retention of articles was a subjective decision by the editors, care was taken to ensure that articles met at least a basic criterion of relevance or interest to the PIHL community. Searching only PubMed, the following searches were conducted:

"Hearing Injury" AND "Animal"
"Hearing Loss" AND "Prevention" AND "Animal"
"Hearing Loss" AND "Treatment" AND "Animal"
"Hearing Loss" AND "Prophylaxis" AND "Animal"
"Hearing Loss" AND "Therapy" AND "Animal"
"Hearing Loss" AND "Ototoxic" AND "Animal
"Hearing Loss" AND "Ototoxicity" AND "Animal"

The Safety Pharmacology of Auditory Function.
Handb Exp Pharmacol, 229: 267-290. (2015)

Abernathy, M. M.

Safety pharmacology satisfies a key requirement in the process of drug development. Safety pharmacology studies are required to assess the impact of a new chemical entity (NCE) or biotechnology-derived product for human use on vital systems, such as those subserving auditory function. Safety pharmacology studies accordingly are defined as those studies that investigate the potential undesirable effects of a substance on auditory functions in relation to exposure in and above the therapeutic range. Auditory safety studies should be designed with the primary objective of determining how administration of a compound influences normal hearing. If an effect on hearing is identified, then it is necessary to determine through histopathology the underlying mechanism for the observed hearing loss. Since the auditory system contains a heterogeneous mixture of structural and cellular components that are organized in a very

complex and integrated manner, it is necessary to clearly identify the underlying primary mechanism or target of the new chemical entity that produced the hearing loss. This chapter will highlight major components of auditory function with regard to potential opportunities for drug interaction. Aspects of designing ototoxicity studies will be discussed with an emphasis on standards deemed necessary by the US Food and Drug Administration. Additionally, classes of ototoxic compounds and their proposed mechanisms of action are described in depth.

How to bury the dead: elimination of apoptotic hair cells from the hearing organ of the mouse.
J Assoc Res Otolaryngol, 15(6): 975-992. (2014)

Anttonen, T. Belevich, I., Kiriavainen, A., Laos, M., Brakebusch, C., Jokitalo, E., & Pirvola, U.

Hair cell death is a major cause of hearing impairment. Preservation of surface barrier upon hair cell loss is critical to prevent leakage of potassium-rich endolymph into the organ of Corti and to prevent expansion of cellular damage. Understanding of wound healing in this cytoarchitecturally complex organ requires ultrastructural 3D visualization. Powered by the serial block-face scanning electron microscopy, we penetrate into the cell biological mechanisms in the acute response of outer hair cells and glial-like Deiters' cells to ototoxic trauma in vivo. We show that Deiters' cells function as phagocytes. Upon trauma, their phalangeal processes swell and the resulting close cellular contacts allow engulfment of apoptotic cell debris. Apical domains of dying hair cells are eliminated from the inner ear sensory epithelia, an event thought to depend on supporting cells' actomyosin contractile activity. We show that in the case of apoptotic outer hair cells of the organ of Corti, elimination of their apices is preceded by strong cell body shrinkage, emphasizing the role of the dying cell itself in the cleavage. Our data reveal that the resealing of epithelial surface by junctional extensions of Deiters' cells is dynamically reinforced by newly polymerized F-actin belts. By analyzing Cdc42-inactivated Deiters' cells with defects in actin dynamics and surface closure, we show that compromised barrier integrity shifts hair cell death from apoptosis to necrosis and leads to expanded hair cell and nerve fiber damage. Our results have implications concerning therapeutic protective and regenerative interventions, because both interventions should maintain barrier integrity.

The effect of radiotherapy on gentamicin ototoxicity: an animal model.
Otolaryngol Head Neck Surg, 152(6):1025-1039. (2015)

Bezdjian, A., Mujica-Mota, M.A., Devic, S., & Daniel, S.J.

OBJECTIVE: Patients undergoing radiotherapy (RT) often present with serious bacterial infections requiring the use of antibiotic treatment. Gentamicin is a commonly used aminoglycoside antibiotic, whose ototoxicity remains a major problem in clinical use. The objective of this study was to determine whether radiation exposure can influence gentamicin-induced ototoxicity. STUDY DESIGN: Prospective animal study. SETTING: Animal care facilities of the Montreal Children's Hospital Research Institute. METHODS: Sixteen guinea pigs received low-dose RT unilaterally for 4 weeks (total: 48 Gy). Animals then received low or high doses of gentamicin (40 mg/kg/d and 80 mg/kg/d) for 10 days. The ears were divided into 4 groups: gentamicin 40 mg, gentamicin 80 mg, gentamicin 40 mg + RT, and gentamicin 80 + RT. Auditory brainstem responses and distortion products otoacoustic emissions were assessed at baseline and before and after gentamicin treatment. Cochlear morphology using light and scanning electron microscopy were evaluated. RESULTS: High-dose gentamicin caused significant auditory brainstem response threshold shifts (P = .020), with greater hearing loss in the irradiated ear (difference of 23.6 + 7.5 dB). All animals exposed to high-dose gentamicin had head tilts toward the radiated side. Cochlear morphology revealed the greatest hair cell damage in the gentamicin 80 + RT group followed by gentamicin 80. CONCLUSION: Results suggest that radiation can exacerbate the ototoxicity of gentamicin at high doses.

Investigation of protective role of curcumin against paclitaxel-induced inner ear damage in rats.
Laryngoscope, 125(5): 1175-1182. (2015)

Bucak, A., Ozdemir, C., Ulu, S., Gonul, Y., Aycicek, A., Uysal, M., & Cangal, A.

OBJECTIVES/HYPOTHESIS: The aim of this study was to investigate the potential protective effect of curcumin on paclitaxel-induced ototoxicity in rats by means of immunohistochemical and histopathological analysis and distortion product otoacoustic emissions (DPOAEs). STUDY DESIGN: Animal study. METHODS: Forty Sprague-Dawley rats were randomized into five groups. Group 1 was administered no paclitaxel and curcumin during the study. Groups 2, 3, 4 and 5 were administered 5 mg/kg paclitaxel; 200 mg/kg curcumin; 5 mg/kg paclitaxel,

followed by 200 mg/kg curcumin; 200 mg/kg curcumin and a day later 5 mg/kg paclitaxel followed intraperitoneally by 200 mg/kg curcumin once a week for 4 consecutive weeks, respectively. After the final DPOAEs test, the animals were sacrificed and their cochlea were prepared for hematoxylin and eosin and caspase-3 staining. RESULTS: The DPOAEs thresholds and histopathological and immunohistochemical findings were substantially correlated in all groups. The histopathologic findings in the cochlea of the paclitaxel-treated animals showed not only changes in the organ of Corti, but also damage to the stria vascularis and spiral limbus, including nuclear degeneration, cytoplasmic vacuolization, and atrophy of intermediate cells. Additionally, cochlear changes in group 2, such as intense apoptosis, were confirmed by caspase-3 immunohistochemical staining. In group 4, coreceiving curcumin could not sufficiently prevent paclitaxel-induced ototoxicity, and the results in group 5 were similar to the control group. CONCLUSIONS: In our study, we have concluded that pre- and coreceiving curcumin can significantly protect the cochlear morphology and functions on paclitaxel-induced ototoxicity in rats. Curcumin might be considered as a potential natural product that, used as a dietary supplement, could be easily given to patients undergoing paclitaxel chemotherapy. LEVEL OF EVIDENCE: NA

Prolonged noise exposure-induced auditory threshold shifts in rats.
Hear Res, 317: 1-8. (2014)

Chen, G.D., Decker, B., Krishnan Muthaiah, V.P., Sheppard, A., & Salvi, R.

Noise-induced hearing loss (NIHL) initially increases with exposure duration, but eventually reaches an asymptotic threshold shift (ATS) once the exposure duration exceeds 18-24 h. Equations for predicting the ATS have been developed for several species, but not for rats, even though this species is extensively used in noise exposure research. To fill this void, we exposed rats to narrowband noise (NBN, 16-20 kHz) for 5 weeks starting at 80 dB SPL in the first week and then increasing the level by 6 dB per week to a final level of 104 dB SPL. Auditory brainstem responses (ABR) were recorded before, during, and following the exposure to determine the amount of hearing loss. The noise induced threshold shift to continuous long-term exposure, defined as compound threshold shift (CTS), within and above 16-20 kHz increased with noise level at the rate of 1.82 dB threshold shift per dB of noise level (NL) above a critical level (C) of 77.2 dB SPL i.e. CTS = 1.82(NL-77.2). The normalized amplitude of the largest ABR peak measured at 100 dB SPL decreased at the rate of 3.1% per dB of NL

above the critical level of 76.9 dB SPL, i.e., %ABR Reduction = 3.1%(NL-76.9). ABR thresholds measured >30 days post-exposure only partially recovered resulting in a permanent threshold shift of 30-40 dB along with severe hair cell loss in the basal, high-frequency region of the cochlea. In the rat, CTS increases with noise level with a slope similar to humans and chinchillas. The critical level (C) in the rat is similar to that of humans, but higher than that of chinchillas.

Gene therapy for sensorineural hearing loss.
Ear Hear, 36(1): 1-7. (2015)

Chien, W. W., Monzack, E. L., McDougald, D.S., & Cunningham, L.L.

Gene therapy is a promising treatment modality that is being explored for several inherited disorders. Multiple human gene therapy clinical trials are currently ongoing, but few are directed at hearing loss. Hearing loss is one of the most prevalent sensory disabilities in the world, and genetics play an important role in the pathophysiology of hearing loss. Gene therapy offers the possibility of restoring hearing by overcoming the functional deficits created by the underlying genetic mutations. In addition, gene therapy could potentially be used to induce hair cell regeneration by delivering genes that are critical to hair cell differentiation into the cochlea. In this review, we examine the promises and challenges of applying gene therapy to the cochlea. We also summarize recent studies that have applied gene therapy to animal models of hearing loss.

Aging after noise exposure: acceleration of cochlear synaptopathy in "recovered" ears.
J Neurosci, 35(19): 7509-7520. (2015)

Fernandez, K. A., Jeffers, P. W., Lall, K., Liberman, M. C., & Kujawa, S. G.

Cochlear synaptic loss, rather than hair cell death, is the earliest sign of damage in both noise- and age-related hearing impairment (Kujawa and Liberman, 2009; Sergeyenko et al., 2013). Here, we compare cochlear aging after two types of noise exposure: one producing permanent synaptic damage without hair cell loss and another producing neither synaptopathy nor hair cell loss. Adult mice were exposed (8-16 kHz, 100 or 91 dB SPL for 2 h) and then evaluated from 1 h to approximately 20 months after exposure. Cochlear function was assessed via distortion product otoacoustic emissions and auditory brainstem responses

(ABRs). Cochlear whole mounts and plastic sections were studied to quantify hair cells, cochlear neurons, and the synapses connecting them. The synaptopathic noise (100 dB) caused 35-50 dB threshold shifts at 24 h. By 2 weeks, thresholds had recovered, but synaptic counts and ABR amplitudes at high frequencies were reduced by up to approximately 45%. As exposed animals aged, synaptopathy was exacerbated compared with controls and spread to lower frequencies. Proportional ganglion cell losses followed. Threshold shifts first appeared >1 year after exposure and, by approximately 20 months, were up to 18 dB greater in the synaptopathic noise group. Outer hair cell losses were exacerbated in the same time frame (approximately 10% at 32 kHz). In contrast, the 91 dB exposure, producing transient threshold shift without acute synaptopathy, showed no acceleration of synaptic loss or cochlear dysfunction as animals aged, at least to approximately 1 year after exposure. Therefore, interactions between noise and aging may require an acute synaptopathy, but a single synaptopathic exposure can accelerate cochlear aging.

Solid lipid nanoparticles loaded with edaravone for inner ear protection after noise exposure.
Chin Med J (Engl), 128(2): 203-209. (2015)

Gao, G., Liu, Y., Zhou, C. H., Jiang, P., & Sun, J. J.

BACKGROUND: Antioxidants and the duration of treatment after noise exposure on hearing recovery are important. We investigated the protective effects of an antioxidant substance, edaravone, and its slow-release dosage form, edaravone solid lipid nanoparticles (SLNs), in steady noise-exposed guinea pigs. METHODS: SLNs loaded with edaravone were produced by an ultrasound technique. Edaravone solution or edaravone SLNs were administered by intratympanic or intravenous injection after the 1 st day of noise exposure. Guinea pigs were exposed to 110 dB sound pressure level (SPL) noise, centered at 0.25-4.0 kHz, for 4 days at 2 h/d. After noise exposure, the guinea pigs underwent auditory brainstem response (ABR) threshold measurements, reactive oxygen species (ROS) were detected in their cochleas with electron spin resonance (ESR), and outer hair cells (OHCs) were counted with silvernitrate (AgNO 3) staining at 1, 4, and 6 days. RESULTS: The ultrasound technique was able to prepare adequate edaravone SLNs with a mean particle size of 93.6 nm and entrapment efficiency of 76.7%. Acoustic stress-induced ROS formation and edaravone exerted a protective effect on the cochlea. Comparisons of hearing

thresholds and ROS changes in different animal groups showed that the threshold shift and ROS generation were significantly lower in treated animals than in those without treatment, especially in the edaravone SLN intratympanic injection group. CONCLUSIONS: Edaravone SLNs show noticeable slow-release effects and have certain protective effects against noise-induced hearing loss (NIHL).

A low-dose regimen of cisplatin before high-dose cisplatin potentiates ototoxicity.
Laryngoscope, 125(2): E78-83. (2015)

Harrison, R. T., DeBacker, J. R., Bielefeld, E. C.

OBJECTIVES/HYPOTHESIS: Cochlear preconditioning with low doses of kanamycin or noise can reduce susceptibility to noise- and ototoxic drug-induced hearing loss. The current study was undertaken to investigate whether a preconditioning regimen of low-dose cisplatin would alter susceptibility to ototoxicity induced by a single large dose of cisplatin. STUDY DESIGN: In vivo study using an animal model. METHODS: Twenty-six Fischer 344/NHsd rats were used in the study. The low-dose regimen consisted of cisplatin (2 or 3 mg/kg) given every 2 weeks by intraperitoneal injection. Control animals received injections of saline on the same schedule as the cisplatin injections. Four injections were done in total. Following the preconditioning interval, seven of the animals were sacrificed for hair cell analyses. The remaining 19 animals were exposed to 12 mg/kg cisplatin by intraperitoneal infusion to induce cochlear injury. Auditory brainstem response (ABR) thresholds were measured 3 days after cisplatin, and the cochleae from the 19 animals were harvested and analyzed. RESULTS: Statistical analyses revealed no threshold shifts, but mild outer hair cell losses, after the low-dose regimen. ABR threshold shifts in the rats exposed to the 12 mg/kg cisplatin dose were significantly higher at day 3 in the animals that underwent preconditioning with low-dose cisplatin. Outer hair cell losses were also greater in the preconditioned animals. CONCLUSIONS: Preconditioning with low-dose cisplatin, using the protocol applied in the current experiment, created potentiation of cisplatin ototoxicity, rather than protection from it. There are numerous possible explanations for this effect that should be considered. LEVEL OF EVIDENCE: NA.

Local delivery of brain-derived neurotrophic factor on the perforated round window membrane in Guinea pigs: a possible clinical application.
Otol Neurotol, 36(4): 705-713. (2015)

Havenith, S., Versnel, H., Klis, S. F., & Grolman, W.

HYPOTHESIS/BACKGROUND: Local delivery of neurotrophic factors on the intact round window membrane (RWM) of hair cell-deprived cochleas reduces degeneration of the cochlear nerve. In an animal model of profound hearing loss, we investigated whether this otoprotective effect could be enhanced by perforation of the RWM. Such method could be highly relevant for future clinical applications. METHODS: Guinea pigs were deafened by coadministration of kanamycin and furosemide. Two weeks after deafening, Gelfoam cubes infiltrated with brain-derived neurotrophic factor (BDNF) were deposited onto the RWM of the right cochlea. In the experimental condition, the RWM was perforated. Electrically evoked auditory brainstem responses (eABRs) were recorded weekly. Two or four weeks after Gelfoam placement, both left (untreated) and right (BDNF-treated) cochleas were processed for histology. RESULTS: In BDNF-treated cochleas, both with and without perforation, neural survival in the basal turn of the cochlea was significantly larger than in untreated cochleas. Amplitudes of electrically evoked auditory brainstem responses were larger in BDNF-treated cochleas with an RWM perforation than in those without a perforation and comparable to those of normal-hearing controls. Perforation did not lead to collateral cochlear damage. CONCLUSION: When considering clinical applications of neuroprotective agents such as BDNF, delivery on a perforated RWM seems to be a safe and effective option.

Prevention of cisplatin-induced ototoxicity by the inhibition of gap junctional intercellular communication in auditory cells.
Cell Mol Life Sci, 71(19): 3859-3871. (2014)

Kim, Y. J., Kim, J., Tian, C., Lim, H. J., Kim, Y. S., Chung, J. H., & Choung, Y. H.

Cis-diamminedichloroplatinum (cisplatin) is an effective chemotherapeutic drug for cancer therapy. However, most patients treated with cisplatin are at a high risk of ototoxicity, which causes severe hearing loss. Inspired by the "Good Samaritan effect" or "bystander effect" from gap junction coupling, we investigated the role of gap junctions in cisplatin-induced ototoxicity as a potential therapeutic method. We showed that connexin 43 (Cx43) was highly

expressed in House Ear Institute-Organ of Corti 1 (HEI-OC1) cells, mediating cell-cell communication. The viability of HEI-OC1 cells was greatly decreased by cisplatin treatment, and cisplatin-treated HEI-OC1 cells showed lower Cx43 expression compared to that of untreated HEI-OC1 cells. In particular, high accumulation of Cx43 was observed around the nucleus of cisplatin-treated cells, whereas scattered punctuate expression of Cx43 was observed in the cytoplasm and membrane in normal cells, suggesting that cisplatin may interrupt the normal gap junction communication by inhibiting the trafficking of Cx43 to cell membranes in HEI-OC1 cells. Interestingly, we found that the inhibition of gap junction activity reduced cisplatin-induced apoptosis of auditory hair cells. Cx43 siRNA- or 18alpha-GA-treated HEI-OC1 cells showed higher cell viability compared to control HEI-OC1 cells during cisplatin treatment; this was also supported by fluorescence recovery after photobleaching studies. Inhibition of gap junction activity reduced recovery of calcein acetoxymethyl ester fluorescence compared to control cells. Additionally, analysis of the mechanisms involved demonstrated that highly activate extracellular signal-regulated kinase and protein kinase B, combined with inhibition of gap junctions may promote cell viability during cisplatin treatment.

Growth factors have a protective effect on neomycin-induced hair cell loss.
Cell Biol Int, 39(1): 65-73. (2015)

Lou, X., Yuan, H., Xie, J., Wang, X., Yang, L., & Zhang, Y.

We have demonstrated that selected growth factors are involved in regulating survival and proliferation of progenitor cells derived from the neonatal rat organ of Corti (OC). The protective and regenerative effects of these defined growth factors on the injured organ of Corti were therefore investigated. The organ of Corti dissected from the Wistar rat pups (P3-P5) was split into apical, middle, and basal parts, explanted and cultured with or without neomycin and growth factors. Insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), and epidermal growth factor (EGF) protected the inner hair cells (IHCs) and outer hair cells (OHCs) from neomycin ototoxicity. Using EGF, IGF-1, and FGF-2 alone induced no protective effect on the survival of auditory hair cells. Combining 2 growth factors (EGF + IGF-1, EGF + FGF-2, or IGF-1 + FGF-2) gave statistically protective effects. Similarly, combining all three growth factors effectively protected auditory hair cells from the ototoxic insult. None of the growth factors induced regeneration of hair cells in the explants injured with neomycin. Thus various combinations of the three defined factors (IGF-1, FGF-2, and EGF) can

protect the auditory hair cells from the neomycin-induced ototoxic damage, but no regeneration was seen. This offers a possible novel approach to the treatment of hearing loss.

Circadian variation of gentamicin toxicity in rats.
Laryngoscope, 125(7): E252-256. (2015)

McKinney, W., Yonovitz, A., & Smolensky, M. H.

OBJECTIVES/HYPOTHESIS: Two undesired effects of the aminoglycoside antibiotic gentamicin are ototoxicity and nephrotoxicity. This study investigated if these adverse effects vary according to the circadian time of its administration. STUDY DESIGN: This study entails laboratory animal research. METHODS: Four groups of Sprague-Dawley rats were synchronized to a 12:12 light/dark schedule. Each group receiving the antibiotic (100 mg/kg gentamicin sulfate) at a different circadian time. Auditory brainstem response was obtained at pretreatment and at 2, 4, and 6 weeks. RESULTS: At all measured frequencies, hearing losses were significantly ($P < .001$) greater when gentamicin was administered during the diurnal rest span than the nighttime activity span. At 4 weeks, the average total hearing loss, quantified by elevation of threshold values over the tested auditory frequencies, was 31.3 and 25.6 dB for the 2 hours after lights on (HALO) and 8 HALO groups, respectively. The loss progressed at 6 weeks to 42.5 (2 HALO) and 37.5 (8 HALO) dB. At 6 weeks, the 14 and 20 HALO groups had losses of 17.5 and 26.3 dB, respectively. Trough serum gentamicin concentration significantly ($P < .01$) increased during treatment, being the highest at 4 weeks. Urine urea nitrogen 24-hour levels of the 2 and 8 HALO groups differed significantly ($P < .01$) from the 14 and 20 HALO groups. CONCLUSIONS: Ototoxicity was greater when gentamicin was administered during their diurnal rest than during nocturnal activity. A dosing paradigm may be used to deliver a lower therapeutic antimicrobial concentration during the nighttime rest period when the studied adverse effects are of highest risk.

Oxidative Stress in Applied Basic Research and Clinical Practice: Free Radicals in ENT Pathology.
New York: Humana Press. (2015)

Miller, J. M., Le Prell, C. G., & L.P. Rybak (eds.)

Assembles comprehensive reviews on a broad variety of ENT pathology, including areas partially covered in current literature, such as the role of nutrition and heavy metals in hearing. Discusses the interrelationship of basic and translational studies. Uniquely outlines a path for future research and development of antioxidant interventions.

Low-cost blast wave generator for studies of hearing loss and brain injury: blast wave effects in closed spaces.
J Neurosci Methods, 242: 82-92. (2015)

Newman, A. J., Hayes, S. H., Rao, A. S., Allman, B. L., Manohar, S., Ding, D., Stolzberg, D., Lobarinas, E., Mollendorf, J. C., & Salvi, R.

BACKGROUND: Military personnel and civilians living in areas of armed conflict have increased risk of exposure to blast overpressures that can cause significant hearing loss and/or brain injury. The equipment used to simulate comparable blast overpressures in animal models within laboratory settings is typically very large and prohibitively expensive. NEW METHOD: To overcome the fiscal and space limitations introduced by previously reported blast wave generators, we developed a compact, low-cost blast wave generator to investigate the effects of blast exposures on the auditory system and brain. RESULTS: The blast wave generator was constructed largely from off the shelf components, and reliably produced blasts with peak sound pressures of up to 198dB SPL (159.3kPa) that were qualitatively similar to those produced from muzzle blasts or explosions. Exposure of adult rats to 3 blasts of 188dB peak SPL (50.4kPa) resulted in significant loss of cochlear hair cells, reduced outer hair cell function and a decrease in neurogenesis in the hippocampus. COMPARISON TO EXISTING METHODS: Existing blast wave generators are typically large, expensive, and are not commercially available. The blast wave generator reported here provides a low-cost method of generating blast waves in a typical laboratory setting. CONCLUSIONS: This compact blast wave generator provides scientists with a low cost device for investigating the biological mechanisms involved in blast wave injury to the rodent cochlea and brain that may model many of the damaging effects sustained by military personnel and civilians exposed to intense blasts.

Cisplatin exposure damages resident stem cells of the mammalian inner ear.
Dev Dyn, 243(10): 1328-1337. (2014)

Slattery, E. L., Oshima, K., Heller, S., & Warchol, M. E.

BACKGROUND: Cisplatin is a widely used chemotherapeutic agent that can also cause ototoxic injury. One potential treatment for cisplatin-induced hearing loss involves the activation of endogenous inner ear stem cells, which may then produce replacement hair cells. In this series of experiments, we examined the effects of cisplatin exposure on both hair cells and resident stem cells of the mouse inner ear. RESULTS: Treatment for 24 hr with 10 microM cisplatin caused significant loss of hair cells in the mouse utricle, but such damage was not evident until 4 days after the cisplatin exposure. In addition to killing hair cells, cisplatin treatment also disrupted the actin cytoskeleton in remaining supporting cells, and led to increased histone H2AX phosphorylation within the sensory epithelia. Finally, treatment with 10 microM cisplatin appeared to have direct toxic effects on resident stem cells in the mouse utricle. Exposure to cisplatin blocked the proliferation of isolated stem cells and prevented sphere formation when those cells were maintained in suspension culture. CONCLUSION: The results suggest that inner ear stem cells may be injured during cisplatin ototoxicity, thus limiting their ability to mediate sensory repair.

Identification of small molecule inhibitors of cisplatin-induced hair cell death: results of a 10,000 compound screen in the zebrafish lateral line.
Otol Neurotol, 36(3): 519-525. (2015)

Thomas, A. J., Wu, P., Raible, D. W., Rubel, E. W., Simon, J. A., & Ou, H. C.

HYPOTHESIS: The zebrafish lateral line can be used to identify small molecules that protect against cisplatin-induced hair cell death. BACKGROUND: Cisplatin is a commonly used chemotherapeutic agent, which causes hearing loss by damaging hair cells of the inner ear. There are currently no FDA-approved pharmacologic strategies for preventing this side effect. The zebrafish lateral line has been used successfully in the past to study hair cell death and protection. METHODS: In this study, we used the zebrafish lateral line to screen a library of 10,000 small molecules for protection against cisplatin-induced hair cell death. Dose-response relationships for identified protectants were determined by quantifying hair cell protection. The effect of each protectant on uptake of a fluorescent cisplatin analog was also quantified. RESULTS: From this screen, we identified 2 compounds exhibiting dose-dependent protection: cisplatin hair cell protectant 1 and 2 (CHCP1 and 2). CHCP1 reduced the uptake of a fluorescent cisplatin analog, suggesting its protective effects may be due to decreased

cisplatin uptake. CHCP2 did not affect uptake, which suggests an intracellular mechanism of action. Evaluation of analogs of CHCP2 revealed 3 additional compounds that significantly reduced cisplatin-induced hair cell death, although none exceed the effectiveness or potency of the parent compound. CONCLUSION: The zebrafish lateral line was used to identify 2 small molecules that protected against cisplatin-induced hair cell death.

Neurotrophin-3 regulates ribbon synapse density in the cochlea and induces synapse regeneration after acoustic trauma.
Elife, 3. (2014)

Wan, G., Gómez-Casati, M. E., Gigliello, A. R., Liberman, M. C., & Corfas, G.

Neurotrophin-3 (Ntf3) and brain derived neurotrophic factor (Bdnf) are critical for sensory neuron survival and establishment of neuronal projections to sensory epithelia in the embryonic inner ear, but their postnatal functions remain poorly understood. Using cell-specific inducible gene recombination in mice we found that, in the postnatal inner ear, Bbnf and Ntf3 are required for the formation and maintenance of hair cell ribbon synapses in the vestibular and cochlear epithelia, respectively. We also show that supporting cells in these epithelia are the key endogenous source of the neurotrophins. Using a new hair cell CreER(T) line with mosaic expression, we also found that Ntf3's effect on cochlear synaptogenesis is highly localized. Moreover, supporting cell-derived Ntf3, but not Bbnf, promoted recovery of cochlear function and ribbon synapse regeneration after acoustic trauma. These results indicate that glial-derived neurotrophins play critical roles in inner ear synapse density and synaptic regeneration after injury.

RECENTLY PUBLISHED LITERATURE

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FUNDING OPPORTUNITIES

Refer to the HCE website (http://hearing.health.mil/Research/FundingInformation.aspx) for up-to-date hearing-related research funding opportunities.

CLINICAL TRIALS

ClinicalTrials.gov was searched using the following search terms: ("noise induced hearing loss" OR "hearing loss" OR tinnitus) AND (pharmaceutical OR drug). "Include only open studies" was selected and the search results, retrieved December 2015, derived 123 results. Studies were further eliminated from inclusion based on subjective determination of relevance by the editors for a total of 33 studies included below.

Title: Safety, Tolerability and Efficacy for CGF166 in Patients With Bilateral Severe-to-profound Hearing Loss
NCT Number: NCT02132130
Responsible Party: Novartis Pharmaceuticals
Conditions: Severe-to-profound Bilateral Hearing Loss With Intact Vestibular Function in the Non-operative Ear.
Interventions: Drug: CGF166
Phases: Phase 1; Phase 2
Start Date: June 2014
Description Provided: The current study will evaluate the safety, tolerability, and potential efficacy of CGF166 and the associated delivery procedures in patients with severe-to-profound bilateral hearing loss. Eligible patients are required to have documented, non-fluctuating hearing loss. Part A will include a safety and tolerability cohort (N=3). Patient dosing will be staggered; dosing the next patient in a cohort will be based on a safety review of all available data through 4 weeks post-dose of the previously dosed patient(s). Part B includes a volumetric escalation design to evaluate infusion volumes of the same CGF166 concentration (5.0 x 10E11vp/mL) in 4 cohorts of patients (n=3/cohort; total of 12 patients). Part C is an expansion cohort of the highest safe and tolerable dose identified in Part B, for further assessment of efficacy.

Title: SPI-1005 for Prevention and Treatment of Chemotherapy Induced Hearing Loss

NCT Number: NCT01451853
Responsible Party: Sound Pharmaceuticals, Incorporated
Conditions: Lung Cancer; Head and Neck Cancer; Hearing Loss; Ototoxicity; Tinnitus; Neuropathy
Interventions: Drug: SPI-1005 Low Dose; Drug: SPI-1005 Middle Dose; Drug: SPI-1005 High Dose; Drug: Placebo
Phases: Phase 2
Start Date: July 2016
Description Provided: Chemotherapy treatment with the platinum containing chemotherapies (e.g. cisplatin, carboplatin) are well noted and studied for their ability to cause ototoxicity which includes hearing loss, tinnitus, vertigo, or dizziness. It is the objective of this study to determine the safety and efficacy of SPI-1005 at three dose levels when delivered orally twice daily for 3 days, surrounding each cycle of platinum chemotherapy for head and neck or non-small cell lung cancer patients to prevent and treat chemotherapy induced hearing loss and tinnitus. SPI-1005, a proprietary oral formulation of ebselen is a small molecule mimic and inducer of the enzyme Glutathione Peroxidase. GPx reduces reactive oxygen species (ROS) by reacting with glutathione. SPI-1005 has been shown to reduce cisplatin induced hearing threshold shift in animal studies.

Title: Study to Evaluate SPI-1005 in Adults With Meniere's Disease
NCT Number: NCT02603081
Responsible Party: Sound Pharmaceuticals, Incorporated
Conditions: Meniere's Disease
Interventions: Drug: SPI-1005
Phases: Phase 1; Phase 2
Start Date: December 2015
Description Provided: Randomized, double-blind, placebo-controlled safety, pharmacokinetic, pharmacodynamic study of oral SPI-1005 in adults with Meniere's disease. All subjects will undergo baseline audiometric testing and have their severity of sensorineural hearing loss, tinnitus and vertigo determined before the start of a 21-day course of treatment with SPI-1005 or placebo. During treatment with SPI-1005, and 7 days and 28 days following the cessation of SPI-1005, subjects will have their hearing loss, tinnitus and vertigo assessed. Additional testing including electrocochleography will be performed at baseline, at the end of SPI-1005 treatment, and 28 days after the SPI-1005 treatment has stopped. Six outpatient visits will be performed over a 7-week period.

Title: Prevention of Noise-induced Hearing Loss
NCT Number: NCT02049073
Resposible Party: Judith Lieu, Washington University School of Medicine
Conditions: Noise-induced Hearing Loss
Interventions: Drug: Zonisamide; Drug: Methylprednisolone
Phases: Phase 1; Phase 2
Start Date: June 2017
Description Provided: Noise-induced hearing loss (NIHL) affects an estimated 5% of the worldwide population, with 30-40 million Americans exposed to hazardous sound or noise levels regularly. Sources of noise may be occupational (e.g., manufacturing, construction), blast noise (e.g., firearms or explosions), or recreational (e.g., loud music, power tools). Trauma to the inner ear can occur through transient hearing loss (temporary threshold shifts, TTS) or permanent hearing loss (permanent threshold shift, PTS). Although hearing recovers after a TTS in about 24-48 hours, growing evidence suggests that repeated TTS may lead to PTS. Both TTS and PTS lead to a decrease in hearing thresholds at 3000 to 6000 Hz.

Currently, there are no treatments for human NIHL although this is an area of active investigation. Protection against NIHL consists of limiting noise exposure through Occupational Safety and Health Administration (OSHA) limits to occupational noise and the wearing of hearing-protection devices (e.g., ear muffs or earplugs). There are no known medications that can be used clinically to prevent NIHL in humans.

LePrell and colleagues have successfully established a protocol for inducing TTS using digitally-modified pop or rock music. This model of experimentally-induced TTS was intended to provide an ethical way of testing medications that might prevent NIHL.

In a mouse model, Bao and colleagues were able to use zonisamide, an anti-epileptic medication approved for the treatment of partial seizures, and methylprednisolone, a glucocorticoid medication, to protect against noise-induced PTS. The long-term goal of this research is to find medications that can prevent NIHL. The goal of the present pilot study is to evaluate zonisamide and methylprednisolone as medications to prevent TTS in humans.

Title: Treating Tinnitus Using Eutectic Mixture of Local Anesthetics (EMLA) 5% Cream
NCT Number: NCT02266160
Resposible Party: HaEmek Medical Center, Israel
Conditions: Tinnitus

Interventions: Drug: EMLA cream 5%; Other: cetomacrogol cream (lotion cream)
Phases: Phase 4
Start Date: November 2014
Description Provided: The purpose of the study is to investigate whether EMLA 5% cream decreases tinnitus by comparing pretrial questionnaires to post trial questionnaires.

First we are going to invite tinnitus patients for the first visit. In the first visit we will confirm that the patients is suitable for the trial (no exclusion criteria are present), perform ear investigation to exclude ear inflammation, perform audiometry to prove sensorineural hearing loss. Then the patient will fill 3 questionnaires that reflect the tinnitus severity and show how much the patient does suffer from these conditions. The questionnaires are- beck depression index, tinnitus handicap inventory, Pittsburgh sleep quality index.

Then we will perform randomization: the investigational group will get EMLA 5% cream, the control group will get cetomacrogol cream (a lotion cream).

In the next 4 days the patients (investigational and control groups) will spread the cream for 4 hours a day in the post auricular area of the ear/ ears that suffer/s from tinnitus.

The patient will be instructed to stop the spreading and call the chief investigator When any kind of side effect occurs (topical/ systemic)after 4 days of treatment the patient will come to the clinic once again and fill the same questionnaires. 3 weeks after the beginning of the trial the patient will fill the questionnaires for the third time.

Title: NAC to Prevent Cisplatin-induced Hearing Loss
NCT Number: NCT02094625
Responsible Party: Etan Orgel, Children's Hospital Los Angeles
Conditions: Neuroectodermal Tumors, Primitive; Liver Neoplasms; Neoplasms, Germ Cell and Embryonal; Osteosarcoma; Other Childhood Cancers Using Cisplatin-based Regimens
Interventions: Drug: N-Acetylcysteine
Phases: Phase 1
Start Date: October 2015
Description Provided: The study is a dose-finding study of N-acetylcysteine (NAC) to protect hearing in children receiving cisplatin for the treatment of their cancer. NAC also has potential to protect the kidneys from cisplatin toxicity. The study uses a 3+3 dose-escalation scheme to determine the dose of NAC necessary to achieve serum levels consistent with hearing protection in pre-

clinical animal models. Three dose levels are predefined. Once the maximum tolerated dose is determined, an expansion cohort will then be enrolled to further evaluate tolerability as well as intra-patient and inter-patient variability in achieved serum levels. An option to enroll in a separate arm for study assessments only is available for those who do not wish to receive NAC. Hearing loss in the cohort will be assessed in the entire cohort in comparison to historical and non-treated children to evaluate for trends toward efficacy.

Title: Efficacy and Safety of AUT00063 Versus Placebo in Age-Related Hearing Loss
NCT Number: NCT02345031
Responsible Party: Autifony Therapeutics Limited
Conditions: Age-Related Hearing Loss
Interventions: Drug: AUT00063; Drug: Placebo
Phases: Phase 2
Start Date: January 2015
Description Provided: Reduced activity at certain sites in the brain (called "voltage-gated potassium channels") has been linked to hearing problems, like age-related loss of hearing or tinnitus (a 'ringing' or buzzing noise in the ears). AUT00063 is an experimental new medicine that enhances the action of these specific channels and so may treat the brain component of these hearing problems.

The main purpose of this study is to try to demonstrate an improvement in a speech-in-noise deficit after 4 weeks of treatment with the study drug versus the placebo (dummy drug which does not contain the drug). Subjects will undergo a safety follow-up after the treatment period.
Safety and efficacy will be determined by looking at a number of assessments (physical examinations, blood sampling, hearing assessments, questionnaires, etc.).

The amount of drug in the blood will also be measured. It is expected that up to 100 people with age-related hearing loss may take part in the study. The study participants will be recruited at around 10-12 sites in the USA.

Title: Protective Effects of EPI-743 on Noise-Induced Hearing Loss
NCT Number: NCT02257983
Responsible Party: Edison Pharmaceuticals Inc
Conditions: Noise-induced Hearing Loss
Interventions: Drug: EPI-743; Drug: Placebo
Phases: Phase 2
Start Date: October 2014

Description Provided: If effective, administration of EPI-743 should have protective effects against temporary noise-induced hearing loss.

Title: Phase 3 Clinical Trial: D-methionine to Reduce Noise-Induced Hearing Loss (NIHL)
NCT Number: NCT01345474
Responsible Party: Southern Illinois University
Conditions: Noise-Induced Hearing Loss
Interventions: Drug: D-methionine, oral liquid suspension; Other: Placebo Comparator
Phases: Phase 3
Start Date: September 2013
Description Provided: Hearing loss can render a soldier less able to detect and identify the enemy, less able to understand commands, particularly in background noise typical on the battlefield, and may permanently reduce quality of life. In some cases, hearing loss may preclude redeployment or result in less optimal job assignment. Currently, no FDA approved pharmacological prevention exists for noise-induced hearing loss (NIHL). We have documented in animal studies that administration of D-methionine (D-met) can reduce or prevent NIHL. We now need to determine if it has similar efficacy in humans. Although we have not yet tested D-met on protection from noise-induced tinnitus in animals, this clinical trial would provide us the opportunity to also test for protection from noise induced tinnitus simultaneously.

Title: AM-111 in the Treatment of Acute Inner Ear Hearing Loss
NCT Number: NCT02561091
Responsible Party: Auris Medical, Inc.
Conditions: Hearing Loss
Interventions: Other: Placebo; Drug: AM-111 0.4 mg/ml; Drug: AM-111 0.8 mg/ml
Phases: Phase 3
Start Date: November 2015
Description Provided: This phase III study is assessing the drug's safety and is aiming to demonstrate efficacy of intratympanic AM-111 injections in the treatment of severe to profound idiopathic sudden sensorineural hearing loss (ISSNHL). The active pharmaceutical ingredient of AM-111 is the JNK inhibitor (D-JNKI-1), a synthetic peptide consisting of 31 D-amino acids, which acts as a c-Jun N-terminal kinase (JNK) ligand.

Title: AM-101 in the Treatment of Acute Tinnitus 2
NCT Number: NCT01803646

Responsible Party: Auris Medical, Inc.
Conditions: Tinnitus
Interventions: Drug: AM-101|Drug: Placebo
Phases: Phase 3
Start Date: February 2014
Description Provided: This phase III study is assessing the drug's safety and is aiming to demonstrate efficacy of repeated intratymanic AM-101 injections in the treatment of acute peripheral tinnitus (up to 3 months from onset).

Title: AM-101 in the Treatment of Acute Tinnitus 3

NCT Number: NCT02040194
Responsible Party: Auris Medical, Inc.
Conditions: Tinnitus
Interventions: Drug: AM-101; Drug: Placebo
Phases: Phase 3
Start Date: January 2014
Description Provided: This phase III study is assessing the drug's safety and is aiming to demonstrate efficacy of repeated intratymanic AM-101 injections in the treatment of acute peripheral tinnitus (up to 3 months (Stratum A), or between >3 and 6 months (Stratum B) from onset).

Title: Efficacy of Trans-tympanic Injections of a Sodium Thiosulfate Gel to Prevent Cisplatin-induced Ototoxicity

NCT Number: NCT02281006
Responsible Party: François Meyer, Centre Hospitalier Universitaire de Québec, CHU de Québec
Conditions: DDP; Head and Neck Cancer; Adverse Effect
Interventions: Drug: Trans-tympanic injection of a sodium thiosulfate gel
Phases: Phase 2
Start Date: January 2015
Description Provided: Cisplatin (cis-DiammineDichloridoPlatinum, DDP) is an antineoplastic agent used in the treatment of solid malignant tumors in adults and is also a key part of treatment for many children and adolescents with cancer. However, treatment with Cisplatin carries the risk of serious dose-limiting adverse effects. Ototoxicity is of major concern since the associated hearing loss greatly impairs patients' quality of life and no preventive treatment is presently available. Cisplatin ototoxicity is an important problem for patients treated for head and neck squamous cell carcinoma (HNSCC) who receive repeatedly high doses.

Cisplatin causes an accumulation of reactive oxygen species (ROS) in the cochlea, triggering damage to the outer hair cells of the organ of Corti. Sulfur-containing antioxidants can neutralize ROS following Cisplatin intoxication, and thus represent a potential preventive measure. A few sulfur-containing molecules have been studied. Experimental and human studies have shown that sodium thiosulfate (STS) can protect against Cisplatin-induced ototoxicity. However, when administered through the blood stream, STS interfere with Cisplatin treatment efficacy. To counter the ototoxic effects of Cisplatin treatment without impairing its efficacy, a local pharmacology approach directly aiming at the cochlea, would represent a powerful clinical strategy.

The proposed study is the first to test the efficacy of STS administered locally in the middle ear to prevent Cisplatin-induced ototoxicity in humans.

Title: Investigating the Neurobiology of Tinnitus
NCT Number: NCT01294124
Responsible Party: Jay F. Piccirillo, MD, Washington University School of Medicine
Conditions: Tinnitus; Traumatic Brain Injury; Post Traumatic Stress Disorder
Start Date: March 2015
Deswcription Provided: The investigators hypothesize that individual differences exist in resting-state cortical attention, control, sensory, and emotion networks prior to noise exposure and these differences predispose some to the development of bothersome tinnitus. Furthermore, the investigators hypothesize that these changes in functional connectivity of these vulnerable systems after noise exposure are responsible for tinnitus. The proposed study will use a case-control cohort study design. Cases will be those soldiers who develop tinnitus and controls will be those who do not. This will be the first prospective study of tinnitus and will provide important information about the neurobiology of tinnitus.

If a cortical neural network etiology for bothersome tinnitus is confirmed, it will be an astounding, powerful, paradigm shifting model for the diagnosis, prevention and, most importantly, treatment of tinnitus. Furthermore, if a battery of neurocognitive tests can identify soldiers at risk for the development of tinnitus then appropriate primary prevention strategies can be introduced.

Title: Sudden Hearing Loss Multi-center Clinical Trial
NCT Number: NCT02026479
Responsible Party: Li Sheng Yu, Peking University People's Hospital
Conditions: Full-frequency Sudden Hearing Loss

Interventions: Drug: Dexamethasone Phosphate; Drug: Dexamethasone Phosphate; Drug: Ginaton
Start Date: January 2014
Description Provided: The incidence of sudden hearing loss is rising obviously resent year, Glucocorticoids have obtained obvious effect in the treatment of sudden deafness. Postauricular hypodermic injection is the latest findings in clinical work and a new noninvasive way of administration which is gradually expanding research. The aim of this experiment is to verify and explore the efficacy and safety of the postauricular injection treatment with different doses of Glucocorticoids.

Title: Does Aspirin Have a Protective Role Against Chemotherapeutically Induced Ototoxicity?
NCT Number: NCT00578760
Responsible Party: University Health Network, Toronto
Conditions: Hearing Loss; Ototoxicity
Interventions: Drug: aspirin; Drug: placebo
Start Date: February 2008
Description Provided: Aspirin (ASA) has been shown, in an animal model, to attenuate the ototoxic properties of cisplatin. The researchers plan to investigate this in patients undergoing cisplatin chemotherapy.
The researchers hypothesise that low-dose aspirin can prevent cisplatin induced ototoxicity in the clinical setting.

Title: Efficacy, Safety, and Tolerability of Ancrod in Patients With Sudden Hearing Loss
NCT Number: NCT01621256
Responsible Party: Nordmark Arzneimittel GmbH & Co. KG
Conditions: Hearing Loss; Deafness; Hearing Loss, Sensorineural; Hearing Disorders; Ear Diseases
Interventions: Drug: Ancrod; Drug: Saline solution
Phases: Phase 1; Phase 2
Start Date: May 2013
Description Provided: The purpose of this study is to determine whether ancrod is effective and safe in the treatment of sudden sensorineural hearing loss (SSHL).

Title: Randomized Trial Comparison of Ototoxicity Monitoring Programs
NCT Number: NCT02099786
Responsible Party: VA Office of Research and Development
Conditions: Ototoxicity From Cisplatin Chemotherapy; Hearing Loss

Interventions: Other: COMP-VA; Other: Standard of care; Other: Program evaluation
Start Date: March 2014
Description Provided: This study involves research. Drugs can permanently reduce hearing are termed "ototoxic". One such drug is the chemotherapy called cisplatin. Currently, if a patient is receiving cisplatin, hearing is tested and monitored only when it is requested by their physician. Researchers think that hearing testing prior to each treatment with cisplatin may reduce the number of Veterans who get disabling hearing loss from treatment. The purpose of this study is to compare the current method of monitoring hearing (only when requested by the physician) with a new hearing monitoring program that tests hearing prior to each cisplatin treatment.

The proposed study tests this new approach for guideline-concordant ototoxicity monitoring implemented as a portable, comprehensive program of evidence-based protocols for VA healthcare (Comp-VA program). Research objectives are: to compare the effectiveness of ototoxicity monitoring implemented using Comp-VA and standard of care testing (SOC) with regard to (1) improving Veterans' hearing and quality of life outcomes and use of audiological rehabilitation services and (2) assisting Oncologists in chemotherapeutic planning and counseling. In order to achieve these objectives, we propose a randomized trial conducted at the Portland VA Medical Center. We plan to recruit a total of 320 Veterans undergoing cisplatin chemotherapeutic treatment over 4 years and 120 control subjects

Title: Commercial Lidocaine Patch as a Treatment for Ear-ringing
NCT Number: NCT02088866
Responsible Party: Rodney Diaz, MD, University of California, Davis
Conditions: Tinnitus
Interventions: Drug: Transdermal Lidocaine
Phases: Phase 0
Start Date: March 2014
Description Provided: The purpose of this investigation is to evaluate if topically applied lidocaine, in the form of lidocaine patches, reduces the burden of chronic subjective tinnitus in a consistent and measurable way.

Title: Fludrocortisone for Sudden Hearing Loss
NCT Number: NCT01186185
Responsible Party: Anh Nguyen-Huynh, Oregon Health and Science University
Conditions: Hearing Loss, Sensorineural
Interventions: Drug: Fludrocortisone

Start Date: August 2012
Description Provided: The standard of care treatment of sudden hearing loss uses a type of steroid called glucocorticoid. Examples of glucocorticoids are prednisone, methylprednisolone and dexamethasone. Not everybody recovers hearing with glucocorticoid treatment. Fludrocortisone is a different type of steroid called mineralocorticoid. Unlike glucocorticoids, which work by reducing inflammation, mineralocorticoids work by changing salt and fluid balance In animal studies, fludrocortisone is at least as effective as glucocorticoid in preserving hearing. Fludrocortisone is not approved for the treatment of sudden hearing loss. The purpose of this study is to test whether fludrocortisone can treat sudden hearing loss.

Title: Transtympanic Ringer's Lactate for the Prevention of Cisplatin Ototoxicity
NCT Number: NCT01108601
Responsible Party: McGill University Health Center
Conditions: Hearing Loss
Interventions: Drug: Ringer's Lactate (0.03% Ciprofloxacin)
Phases: Phase 1; Phase 2
Start Date: April 2008
Description Provided: Cisplatin and carboplatin induce ototoxicity manifested as sensorineural hearing loss, tinnitus, and/or vestibular disturbances. Ototoxicity is induced via damage to inner ear structures by reactive oxygen species. Previous animal studies demonstrated that transtympanic injection of Ringer's Lactate (RL) provided near complete otoprotective effect against cisplatin. The purpose of this study is to determine if transtympanic administration of Ringer's Lactate via a pressure equalising (PE) tube in patients undergoing platinum based chemotherapy treatment will prevent tinnitus, vestibular dysfunction and hearing loss especially at high frequencies. Pre- and post- chemotherapy treatment audiometry will be measured and statistically analysed for significance.

Title: Dexamethasone in Preventing Hearing Loss in Patients Receiving Cisplatin
NCT Number: NCT02382068
Responsible Party: Aaron Moberly, Ohio State University Comprehensive Cancer Center
Conditions: Malignant Neoplasm; Ototoxicity
Interventions: Drug: Dexamethasone; Other: Placebo; Drug: Cisplatin
Start Date: August 2014
Description Provided: This randomized pilot clinical trial studies dexamethasone in preventing hearing loss in patients receiving cisplatin. Injecting a steroid, such

as dexamethasone, behind the eardrum before chemotherapy may help protect against cisplatin-associated hearing loss.

Title: Preventing Nephrotoxicity and Ototoxicity From Osteosarcoma Therapy
NCT Number: NCT01848457
Responsible Party: Children's Hospital of Philadelphia
Conditions: Osteosarcoma; Nephrotoxicity; Ototoxicity
Interventions: Drug: Pantoprazole; Drug: High-dose methotrexate infusion duration
Phases: Phase 2
Start Date: April 2013
Description Provided: Osteosarcoma is the most common type of bone cancer in children, adolescents and young adults. Treatment with surgery and a combination of three conventional chemotherapy drugs can cure nearly two-thirds patients with osteosarcoma, but the treatment can also cause irreversible damage to the kidneys and cause permanent hearing loss. The purpose of this study is to evaluate new approaches to prevent these side effects without interfering with the beneficial effects of the chemotherapy drugs on the cancer by using our knowledge of how the drugs damage the kidney and cochlear hair cells in the ear to selectively block these side effects. Preventing these side effects without interfering with the anti-cancer effect of the drugs will improve the outcome in survivors and may also improve the effectiveness of the chemotherapy regimen by preventing treatment delays and dose reductions that are often caused by the side effects. Patients will be carefully monitored to ensure that the new interventions do not adversely affect response to the treatment and do not increase the other side effects of the chemotherapy. Specifically, we will monitor the nutritional status of the patients closely and ask patients to complete a survey describing the side effects after each treatment cycle. We will also collect a small sample of cancer tissue at the time of biopsy and surgery from each patient on this study for testing to determine new classes of anti-cancer drugs currently under development may have a role in treating osteosarcoma. If effective, these new approaches to prevent kidney damage and hearing loss will be applicable in other types of cancers treated with the same chemotherapy drugs.

Title: Effectiveness of Cannabis in the Treatment of Tinnitus Patients
NCT Number: NCT01969474
Responsible Party: Oron Yahav, Wolfson Medical Center
Conditions: Tinnitus
Interventions: Drug: Cannabis; Drug: Placebo

Phases: Phase 1

Start Date: December 2013

Description Provided: The hypothesis of the study is that the use of Cannabis will attenuate the tinnitus level as experienced by the patients.

Title: EMA-Defined Tinnitus Subgroups

NCT Number: NCT02191592

Responsible Party: Jay F. Piccirillo, MD, Washington University School of Medicine

Conditions: Tinnitus

Start Date: July 2014

Description Provided: The purpose of this research study is to test a new way of measuring the severity of tinnitus using a tool called Ecological Momentary Assessment (EMA) of Tinnitus. We will compare the relationship with this tool with another widely used questionnaire. Previous studies we have done suggest there are different patterns of tinnitus bother; we plan to explore how often these patterns occur, and how many patterns of tinnitus bother there are. And lastly we want to test how reliable this type of testing is for measuring the amount of bother people experience from their tinnitus.

Title: Prevention of Noise-induced Damage by Use of Antioxidants

NCT Number: NCT01727492

Responsible Party: Ethisch Comité UZ Antwerpen, University Hospital, Antwerp

Conditions: Noise-induced Tinnitus; Noise-induced Hearing Loss

Interventions: Drug: Antioxidantia

Start Date: November 2012

Description Provided: The current study is a dubble-blinde placebo-controlled cross-over study verifying the preventive effect of antioxidants on noise-induced hearing loss (NIHL) and noise-induced tinnitus (NIT). The antioxidants comprise of a mixture of magnesium and n-acetylcystein which should be taken 1h before leisure noise above 100dB for at least 30 minutes.

Title: Zinc to Treat Tinnitus

NCT Number: NCT00683644

Responsible Party: University of Iowa

Conditions: Tinnitus

Interventions: Dietary Supplement: Zinc sulfate

Phases: Phase 2

Start Date: January 2008

Description Provided: There is widespread belief and some evidence to indicate that zinc can successfully treat tinnitus. Zinc deficiency is more likely to occur in

the elderly. The primary objective of this study is to establish the effectiveness of zinc for the treatment of tinnitus in individuals 60 years of age and older. Subjects will be randomly assigned to either receive zinc daily or a placebo. After 4 months and a 1-month wash-out, the subjects will be crossed over to the other group.

Title: Efficacy of Internet and Smartphone Application-delivered Tinnitus Retraining Therapy
NCT Number: NCT01663467
Responsible Party: YOUNG HO KIM, Seoul National University Hospital
Conditions: Tinnitus
Interventions: Drug: Ginkgo biloba; Behavioral: modified tinnitus retraining therapy (TRT)
Start Date: September 2014
Description Provided: The purpose of this study is to prove the efficacy of the internet and smartphone application-delivered tinnitus retraining therapy (TRT).

Title: Applying Proton Pump Inhibitor to Prevent and Treat Acute Fluctuating Hearing Loss in Patients With SLC26A4 Mutation
NCT Number: NCT00789061
Responsible Party: National Taiwan University Hospital
Conditions: Hearing Loss
Interventions: Drug: Proton pump inhibitor
Phases: Phase 2; Phase 3
Start Date: August 2006
Description Provided: Disequilibrium between acid and base in the inner ear was suggested to be an important factor leading to hearing impairment associated with SLC26A4 mutations. For acid-base homeostasis in the inner ear, gastric-type proton pumps might demonstrate antagonistic effects to pendrin, the protein encoded by SLC26A4. To investigate whether proton pump inhibitors might prevent or treat acute fluctuating hearing loss related to SLC26A4 mutations, we launch the current double-blind randomized clinical trial.

Title: Bed Rest for Idiopathic Sudden Sensorineural Hearing Loss
NCT Number: NCT00416143
Responsible Party: Sheba Medical Center
Conditions: Sudden Loss of Hearing
Interventions: Procedure: bed rest; Drug: prednisone - oral corticosteroid 1mg/kg/D for 1 week
Phases: Phase 2; Phase 3

Start Date: June 2006
Description Provided: Sudden sensorineural hearing loss:
- idiopathic in most cases
- 5-20/100,000 new cases annually in the U.S
- no establishes pathogenesis
- treated with oral steroids in most cases
- ~50% improvement in hearing levels
- bed rest - acceptable treatment, not well investigated

Title: AM-101 in the Treatment of Post-Acute Tinnitus 2
NCT Number: NCT02040207
Responsible Party: Auris Medical, Inc. (Auris Medical AG)
Conditions: Tinnitus
Interventions: Drug: AM-101
Phases: Phase 3
Start Date: June 2014
Description Provided: The purpose of this research study is to test the safety and local tolerance of repeated treatment cycles of AM-101.

Title: AM-101 in the Treatment of Post-Acute Tinnitus 1
NCT Number: NCT01934010
Responsible Party: Auris Medical, Inc.
Conditions: Tinnitus
Interventions: Drug: AM-101
Phases: Phase 3
Start Date: June 2014
Description Provided: The purpose of this research study is to test the safety and local tolerance of repeated treatment cycles of AM-101.

Title: Aluminum and Auditory Function in ESRD
NCT Number: NCT00243958
Responsible Party: National Taiwan University Hospital
Conditions: End-Stage Renal Disease (ESRD)
Start Date: October 2005
Description Provided: Hearing impairment either clinical or subclinical is a characteristic of some renal disease patients. The hearing impairment could be result from specific etiologies or chronic renal failure itself. The causes of hearing impairment in renal disease patients ranged from drugs intoxication in both auditory and renal function, like gentamycin or isoniazid, congenital disease like

Alport syndrome or other collagen-defective renal disease, or just aging related. End-stage renal disease (ESRD) patients are special in many parts to general population who have hearing impairment. First, inflammation in ESRD patients is well-documented, second, they suffered from various underlying diseases which auditory function was potentially impaired, third, they need to undergo renal replacement therapy either hemodialysis (HD) or peritoneal dialysis (PD) to maintain their life. Dialysis itself was found to be a cause of hearing impairment, too. The biochemical change and constitutive inflammation status are thought to be implicated in the pathogenesis of hearing impairment in ESRD patients. Aluminum (Al) is a well-documented heavy metal, which predisposes to Alzheimer's disease, dementia or some neurologic diseases. Al intoxication is very rare in general health population but elevated serum Al level is easily found in ESRD patients since they can not excrete Al by damaged kidneys and dialyzers. Inner ear per se is a neurologic tissue, so if serum Al level in ESRD patients has any association in their haring function needs to be studied.

http://hearing.health.mil/EducationAdvocacy/Newsletters.aspx