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INVITED REVIEW

Hearing loss: The final frontier of pharmacology

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Abstract

Despite a prevalence greater than cancer or diabetes, there are no currently approved drugs for the treatment of hearing loss. Research over the past two decades has led to a vastly improved understanding of the cellular and molecular mechanisms in the cochlea that lead to hearing deficits and the advent of novel strategies to combat them. Combined with innovative methods that enable local drug delivery to the inner ear, these insights have paved the way for promising therapies that are now under clinical investigation. In this review, we will outline this renaissance of cochlear biology and drug development, focusing on noise, age-related, and chemotherapy-induced hearing dysfunction.

KEYWORDS
cochlea, hair cell, hearing loss, neurotrophin, ototoxicity, regeneration, synaptopathy

1 | INTRODUCTION

Hearing loss is a major global health problem. Data for 2015 indicate that almost half a billion people worldwide suffer from disabling hearing loss, constituting the fourth leading cause of global disability.[1] Moreover, hearing loss has been identified as a major risk factor for the development of dementia,[2] and is strongly associated with psychological disorders such as depression,[3] social isolation in the elderly,[4] and adversely impacts socioeconomic status.[5] In young children, hearing loss retards language acquisition and is associated with developmental delays,[6] impaired academic performance, and employment in adulthood.[7] Despite the significant impact of hearing loss on all segments of the population, there are currently no approved pharmacological treatments. Devices are available for hearing augmentation, although they have significant drawbacks. For patients with mild to moderate hearing loss, hearing aids can be beneficial when simple amplification of sound is required, although they are poorly effective for the perception of sounds in the presence of background noise ("speech-in-noise"; SIN[8,9]), and are associated with significant stigmas that result in low usage rates and adoption delays.[10,11] Cochlear implantation in patients with severe-to-profound hearing loss is of benefit but requires expensive and invasive surgery, and can provide only rudimentary sound perception. Consequently, the development of effective drug therapies that can halt hearing loss, prevent it or restore high-quality hearing comprehension would have a major impact on human health, and can truly be regarded as one of the "final frontiers" of pharmacology.

The past two decades have seen a remarkable increase in hearing research and a vast improvement in our understanding of the cellular and molecular mechanisms that contribute to different forms of hearing loss. This growing body of evidence has generated numerous ideas for therapies that are being assessed in new and improved preclinical hearing loss models, with several therapies already progressing into human clinical trials (Table 1; Figure 1). In this review, we will summarize the exciting data that have been generated concerning forms of hearing loss with high unmet clinical need:

Abbreviations: ABR, auditory brainstem response; BDNF, brain-derived neurotrophic factor; CIHL, cisplatin-induced hearing loss; CNS, central nervous system; HC, hair cell; HDAC, histone deacetylase; IHC, inner hair cell; MET, mechanoelectrical transduction; NAC, N-acetyl cysteine; NDA, new drug application; NT-3, neurotrophin-3; OHC, outer hair cell; P407, Poloxamer 407; SGN, spiral ganglion neuron; SIN, speech-in-noise; STS, sodium thiosulfate; Trk, tropomyosin receptor kinase family.

TABLE 1 Drugs in clinical development for hearing loss disorders

Name	Molecule	Mechanism	Route	Development phase	Patient population	Sponsor
Noise and age-related hearing loss						
CGF166	Adenovirus5-Atoh-1	Hair Cell Regen	IC	Phase 2 negative: minimal/no efficacy; Trial suspended[a]	Profound HL	Genvec/ Novartis
LY-3056480 (AUD-1001)	γ-secretase inhibitor	Hair Cell Regen	IT	Phase I REGAIN trial results '19[b]; Phase 2 REGAIN completed '19: "some benefit" reported[b]	Mild to moderate HL	Audion Therap
FX-322	GSK3 inhibito + Valproate	Hair Cell Regen	IT	Phase I/2: Improvement in word recognition scores in subset[c] Phase 2a: repeat dose—no benefit; Phase 1b: ARHL—no benefit; Phase 1b: severe HL results 4Q '21; Phase 2b: started Oct '21[c]	Mild to moderately severe HL; ARHL; Severe HL; noise and sudden sensorineural HL	Frequency Therap
OTO-413	BDNF	Restoration of ribbon synapses	IT	Phase 1/2 study completed: improvements in multiple WIN tests observed[d] Expansion study started June '21, results in mid-'22[d]	Subjects with SIN difficulties including moderate/severe HL	Otonomy
PIPE-505	γ-secretase inhibitor	Hair Cell Regen.; Ribbon synapse	IT	Phase 1/2 initiated July '20, results expected early '21[e]	Mild to moderate HL	Pipeline Therap
SPI-5557	CDK inhibitor	Hair Cell Regen.	Oral	Phase 1/2 est. '19 No updates	Target population?	Sound Pharma
Cisplatin-induced Hearing Loss						
Pedmark	Sodium Thiosulfate	Binds cisplatin; Antioxidant	IV	Phase 3 completed; NDA submitted, PDUFA date Nov '21[f]	1 mo–18 y; Localized, non- metastatic solid tumors	Fennec Pharma
DB-020	Sodium Thiosulfate	Binds cisplatin; Antioxidant	IT	Phase 1b, interim results in 1H '22[g]	18–50 y; any tumor type receiving high dose cisplatin in 21–28 d cycles	Decibel Therap
SPI-1005	Ebselen	Antioxidant; GSH-mimic; Anti-inflammatory	Oral	Phase 2: Status unknown.	19–80 y Advanced head/neck, lung cancer	Sound Pharma
SENS-401	R-azasetron	5-HT_3 antag.; Calcineurin antag	Oral	Phase 2 due to start 2H'21[h]	Adults	Sensorion
Lipitor	Atorvastatin	HMG CoA reductase inhibitor	Oral	Phase 3 started Nov '21[i]	Adults	NIDCD

Abbreviations: ARHL, age-related hearing loss; BDNF, brain-derived neurotrophic factor; CDK, cyclin-dependent kinase; HL, hearing loss; IC, intra-cochlear; IT, intratympanic; NIDCD, National Institute on Deafness and other Communicative Disorders; SIN, speech-in-noise.

[a]Novartis suspends CGF166 trials—HEARING LOSS JOURNAL.

[b]www.audiontherapeutics.com.

[c]www.frequencytx.com.

[d]www.otonomy.com.

[e]www.pipelinetherapeutics.com.

[f]www.fennecpharma.com.

[g]www.decibeltx.com.

[h]www.sensorion.com.

[i]ClinicalTrials.gov Identifier: NCT04915183.

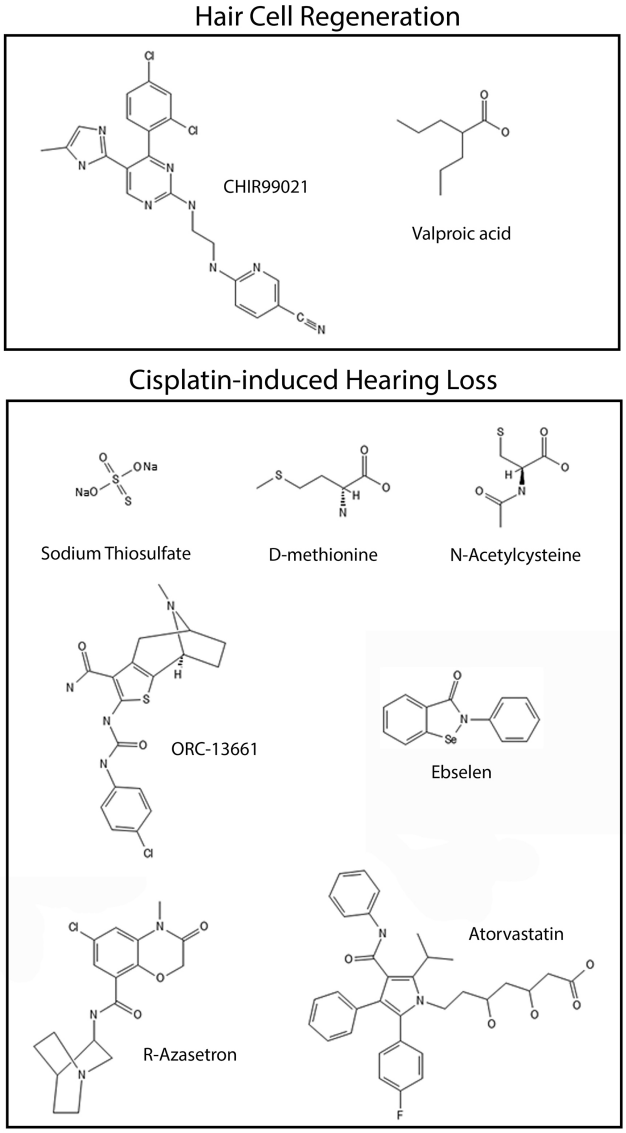

FIGURE 1 Chemical structures of small molecules in clinical development for hearing loss.

age- and noise-induced hearing loss resulting from cochlear hair cell degeneration and cochlear synaptopathy as well as chemotherapy-induced hearing loss.

2 | INNER EAR ANATOMY AND DISEASE MECHANISMS

The basic anatomy of the auditory sensory organ of the inner ear (the organ of Corti) is depicted in Figure 2A. External sound is transduced by the tympanic membrane and the middle ear ossicles to the oval window to produce motion of the inner ear fluids that fill the cochlea (the perilymph and endolymph). Consequently, cochlear hair cells (HCs) in the organ of Corti detect the fluid motion via their stereocilia, the deflection of which opens mechanoelectrical transduction (MET) channels, allowing an influx of potassium from the potassium-rich endolymph, depolarizing the HCs to induce release of the neurotransmitter glutamate at their ribbon synapses. Activation of the AMPA and NMDA receptor sub-types on the afferent terminals of the bipolar type I spiral ganglion neurons (SGNs) produces depolarization and generation of action potentials that carry the noise-evoked information to the auditory regions of the central nervous system (CNS) where sound is perceived.

The organ of Corti is a highly organized structure that contains two types of HCs, outer hair cells (OHCs) and inner hair cells (IHCs), arranged along a tonotopic axis on the basilar membrane that enables the fine discrimination of the range of audible frequencies. In placental mammals, the OHCs are arranged in three rows, and have motile properties which, in response to stimulation, amplify vibration of the basilar membrane; the single row of IHCs function as the primary "sound receptors" and are responsible for transducing the amplified basilar membrane vibration signal to the SGNs. Both types of HCs are also contacted by different efferent neurons that provide feedback loops from the CNS to the cochlea. Various types of support cells are also present in the organ of Corti, and play a role in maintaining HC function, the precise ionic environment, and other structural and homeostatic functions. Importantly, all of these cell types are susceptible to different kinds of external insult and the aging process, and damage to these cells can result in various degrees of hearing loss.

3 | OTIC DRUG DELIVERY

The recent renaissance in hearing biology is tremendously encouraging; however, a fundamental barrier to the development of hearing loss therapeutics has been the lack of an effective means of delivering drugs to the cochlea. Similar to the blood–brain barrier that protects the CNS, the blood–labyrinth barrier protects the cochlear and vestibular apparatus from blood-born agents, resulting in limited and highly variable drug exposure in the inner ear following systemic administration.[12]

This has provided the necessary impetus for the development of local delivery techniques to achieve effective drug levels in the cochlear fluids and tissues with the added advantage of low or undetectable drug exposure in systemic circulation (Figure 2B). This strategy has many of the benefits that are apparent with local drug delivery to another sensory organ, the eye, where intravitreal delivery has revolutionized the treatment of retinal disorders.[13] However, unlike the eye which is readily accessible for direct injection, the cochlea is encased within the dense temporal bone which poses an issue for direct access. A convenient solution is to inject drugs into the middle ear through the tympanic membrane, accessed via the external ear, and referred to as an intratympanic injection, a routine procedure which is easily performed in an ENT's office requiring only local topical numbing of the ear drum. Within the middle ear sits the round window (covered by a semi-permeable membrane) which allows direct diffusion of drug into the perilymph and endolymph of

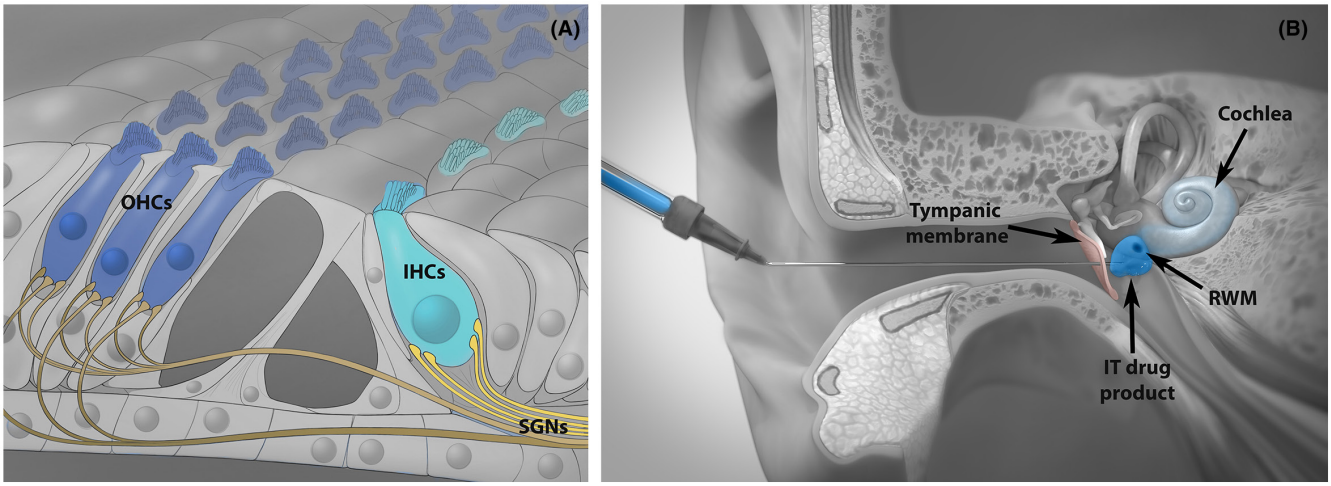

FIGURE 2 Auditory structures and cochlear anatomy. (A) Sound transmission within the cochlea occurs when fluid movement causes deflection of the basilar membrane upon which the mechanosensory inner and outer hair cells (IHCs and OHCs, respectively) sit. This produces deflections of the hair cell stereocilia to open spring-gated ion channels at their tips resulting in depolarization of the hair cells and neurotransmitter release onto the spiral ganglion neurons (SGNs) sending signals through the VIII cranial nerve to the brain. (B) Intratympanic (IT) injection is a non-invasive localized delivery strategy which targets the inner ear by injecting through the tympanic membrane to deliver drug to the surface of the permeable round window membrane (RWM) enabling drug to diffuse or move via active transport mechanisms into the cochlea to reach the sensory cells of the auditory periphery.

the cochlea. In addition, formulations of drugs have been specifically developed to ensure placement and stable retention of the injected material directly targeted to the round window niche itself.

For instance, the thermoreversible polymer, poloxamer, is a particularly effective and elegant means to provide sustained drug exposure to the cochlea. Under certain conditions, Poloxamer 407 (P407) is liquid at room temperature and can be injected easily using a syringe; at body temperature, it then rapidly transitions to a gel that is mucoadhesive and thus can hold drugs it contains in contact with the round window membrane for several days. With intratympanic injection of P407, preclinical studies have shown that therapeutic drug levels can be detected in the perilymph and cochlear tissue for weeks to months after a single injection.[12] This has proved to be a versatile means of minimally invasive, sustained delivery that is amenable to small molecule drugs, biologics, RNA/DNA-based molecules, and viral vectors, and whose benefits have now been demonstrated in clinical studies involving thousands of patients.[14–16] Additional delivery technologies that make use of other types of hydrogels, nanoparticles, magnetic beads, and oils have also been investigated.[17] For example, a lipid formulation of the NMDA receptor antagonist gacyclidine has demonstrated sustained cochlear exposure following intratympanic administration and initial clinical proof-of-concept for the treatment of tinnitus.[16]

Local administration to the inner ear provides the opportunity to target therapies to the site of the hearing loss pathologies and avoid unwanted side effects that could result from body-wide drug exposure following systemic administration. There are several examples, among the current clinical candidates, for hearing loss (Table 1). γ-Secretase inhibitors, that are under investigation for their ability to regenerate cochlear hair cells through Notch inhibition (see below), were previously studied as potential therapeutics for Alzheimer's disease. When given systemically, serious side effects were observed, including cognitive decline, gastrointestinal problems, and increased incidence of skin cancers and infections.[18,19] Notch inhibition was suspected to play a role in at least some of these unwanted effects.[20] Valproic acid, which is also being investigated for cochlear hair cell regeneration (see below), has a black box warning on its label for hepatotoxicity, pancreatitis, and fetal abnormalities (www.depakote.com), and in general, histone deacetylase (HDAC) inhibitors used in cancer therapy have significant side effects.[21] Consequently, local delivery to the inner ear can circumvent the toxicity and tolerability issues caused by systemic drug administration and this has facilitated drug repurposing for hearing loss.

The advent of minimally invasive local drug administration to the inner ear has the potential to revolutionize not only the treatment of hearing loss, but also the associated unmet medical needs of tinnitus and balance disorders, in the same way that intravitreal administration of anti-VEGF therapies has revolutionized the treatment of retinal disorders of the eye.

4 | HEARING LOSS MECHANISMS AND THERAPEUTIC STRATEGIES

Hearing loss can result from several types of insult that affect multiple cochlear cell types. Here, we will focus on the primary pathologies that have been considered for clinical intervention and the corresponding therapeutic strategies that have been considered for clinical intervention. For noise and age-related hearing loss, insults to the HCs (in particular OHCs) have been a major focus; however, a growing body of evidence now points toward degeneration of the neuronal components of the cochlea as a key factor, and one that

may underlie the SIN deficits that are the primary complaint of hearing loss sufferers. Chemotherapeutic agents are known to damage multiple cochlear cell types, and several approaches are being investigated to prevent cisplatin-induced hearing loss.

4.1 | Hair Cell Regeneration

Loss of mechanosensory HCs of the cochlea is common in moderate to severe hearing loss in humans.[22] This HC loss is believed to be a primary source of audiometric threshold elevation in presbycusis, noise-induced hearing loss, sudden sensorineural hearing loss, and ototoxicity (reviewed by[23]). In mammals, auditory HC loss due to either a chemical or noise-induced insult is permanent and HCs never recover spontaneously. However, since the discovery in the 1980s that birds can regenerate lost HCs via the proliferation and transdifferentiation of supporting cells into new HCs,[24–26] regeneration has been a key focus of research aimed at hearing restoration. The gene Atoh1 was shown to be necessary and sufficient for HC formation during development and many subsequent studies have identified the potential of virally mediated Atoh1 gene delivery to cochlear support cells as a means of HC regeneration.[27] Given the early therapeutic potential of Atoh1, an adenovirus 5-mediated Atoh1 gene therapy (CGF166) was evaluated in the first clinical trial for severe hearing loss (see Table 1). Rather than an intratympanic injection, this virally mediated gene delivery strategy necessitated direct intracochlear injection via a cochleostomy. While this trial failed to show a significant impact on hearing outcomes, such as improvement in pure tone averages or other measures, it helped reveal some of the challenges of surgical drug delivery to the cochlea.[28] Importantly, this study also represented the first ever clinical attempt at virally mediated gene delivery to the human cochlea as well as the first clinical trial aimed at cochlear HC regeneration.

Currently, most research into mammalian HC regeneration places a heavy emphasis on several key signaling pathways upstream of Atoh1 that have been shown to be critical for HC development and regeneration in fish and birds. Some of these pathways and genes include Wnt/β-catenin, Notch, $P27^{kip1}$, Gfi, MYC, Hippo/YAP, and most recently, epigenetic regulation by histone deacetylase (HDAC) inhibitors and others[29–32] (Figure 3). Small molecule inhibitors of the enzyme γ-secretase, originally developed for Alzheimer's disease, have been repurposed as potential hearing loss therapeutics due to their ability to modulate Notch signaling, a critical pathway in HC development and non-mammalian regeneration.[30] Similarly, other small molecules or siRNA-based approaches to Notch pathway modulation are being investigated as potential therapeutics to restore HC numbers.[33] However, given some of the challenges of directly accessing the cochlea via surgical approaches, many strategies now being considered for clinical HC restoration involve intratympanic delivery of drugs to the middle ear.

The first clinical trial utilizing an intratympanic approach for HC regeneration, involving the γ-secretase inhibitor LY3056480 (AUD1001), completed a Phase 1/2a study in 2019, and was shown

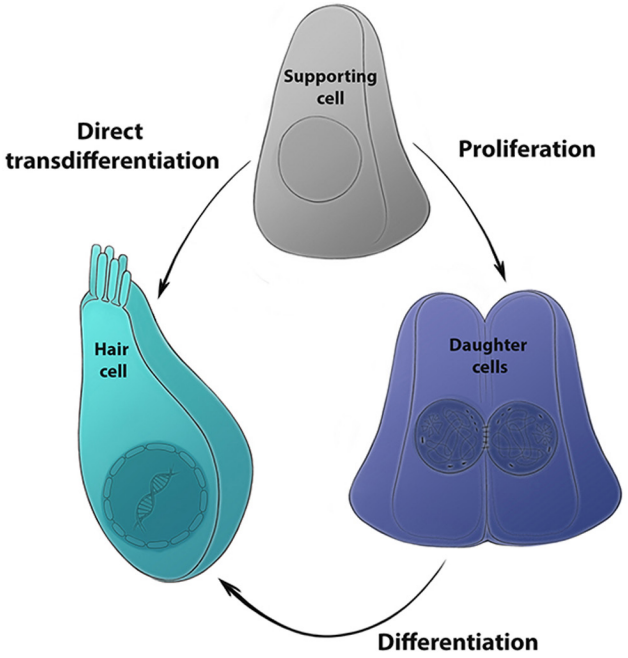

FIGURE 3 Key mechanisms in hair cell regeneration. Hair cell regeneration occurs by one of two complimentary mechanisms: direct transdifferentiation, in which a support cell directly converts into a new hair cell, and mitotic proliferation, in which support cells divide producing two daughter cells, one or more of which can then differentiate into a new hair cell. Some of the key pathways and genes known to play a role in either proliferation or differentiation of HCs during regeneration and which have been targets of therapeutic strategies include Wnt/β-catenin signaling, the Notch signaling pathway, P27kip1, Gfi, MYC, and most recently epigenetic regulation by HDAC inhibitors and others.

to be safe and well tolerated in patients with adult onset mild to moderate sensorineural hearing loss, with some indication of benefit in SIN hearing tests (www.audiontherapeutics.com). However, the mechanism of this potential improvement in hearing is currently unknown. In rodents, the utility of the Notch pathway to induce HC transdifferentiation is limited, as this pathway appears to shut down during postnatal stages, as early as P6 in mice,[34] suggesting it may have limited applicability in treating patients. However, another possible therapeutic role for the Notch pathway is in neuronal restoration/protection, as it is known to function in neural development and degeneration.[35] PIPE-505 is another small molecule γ-secretase inhibitor in development which aims to capitalize on this potential dual function of Notch inhibition. A Phase I/IIa trial of PIPE-505 was recently completed (June 2021) in 28 human subjects with hearing loss with the goal of inducing both HC regeneration and synaptic repair through the Netrin/DCC pathway[36]; results from this trial were still pending at the time of this review.

Growing evidence in the auditory field suggests that HC regeneration may require combinations of multiple key compounds or pathway targets. Some of the most efficacious proof-of-concept laboratory approaches to date using chimeric mouse models and viral vectors have involved the combination of 2–5 different pathway

targets.[37] One of these key regenerative pathways is Wnt/β-catenin signaling which is currently under clinical evaluation as a combination product. Small molecule GSK3-β inhibitors act to enhance β-catenin signaling and have been shown to promote regeneration in birds and fish as well as in ex-vivo mammalian models (reviewed by[29]). FX-322 is a combination of the well-known GSK3 inhibitor CHIR99021 and valproic acid, which has been suggested to have HDAC inhibitory properties potentially impacting the Notch pathway.[38]

In its first Phase 1/2 clinical trial, intratympanic FX-322 showed variable improvement in word recognition scores in a quiet background for a small subset of subjects (5 of 15 patients) with mild to moderately severe hearing loss, and potential improvement in hearing thresholds at a single frequency (8 kHz) in a limited number of patients when administered as a single dose.[39] However, a follow-on Phase 2a study, which evaluated single and multiple doses of FX-322 in an attempt to overcome the short duration of cochlear exposure to the drug combination,[39] failed to show any improvement in similar audiologic endpoints. A concurrent open-label single-administration FX-322 study in patients with mild to moderately severe hearing loss showed an improvement in word recognition scores in a subset of patients although a study in age-related hearing loss showed no evidence of benefit. A further trial is ongoing in subjects with severe hearing loss, and a phase 2b study in patients with noise and sudden sensorineural hearing loss was recently initiated (frequencytx.com). While these multi-component strategies remain of interest, their clinical translation to date remains equivocal, and they also face significant formulation and regulatory hurdles for drug approval.

Several more recently identified pathways of regenerative interest include the Lin28/Let7 axis,[40,41] and modulation of the Hippo/YAP pathway via LATS inhibitors.[42,43] These pathways are expected to either promote stemness in support cells, enabling them to potentially transdifferentiate into HCs,[40] or promote supporting cell proliferation by relaxing the mechanical restraints that limit cellular movements,[44] respectively. However, the efficacy of these approaches in preclinical animal models remains to be determined.

While cochlear HC regeneration has been a key focus of auditory research, the sensory epithelia that comprise the vestibular balance organs may be more amenable to HC regeneration.[45] The supporting cells of the utricle have been shown to have some limited endogenous capacity for regeneration, greater than that of the cochlea,[46,47] and many strategies that have failed to induce new cochlear HCs were able to promote some vestibular HC regeneration, such as small molecule LATS modulators.[42,48] Gene therapy approaches are currently being employed to target the vestibular epithelia for patients with bilateral vestibulopathy (www.decibeltx.com). These early discovery phase programs purportedly involve an Atoh1-AAV approach, or a combination of Atoh1 with a "reprogramming factor." The true clinical value of regenerative strategies aimed at vestibular targets remains unknown considering the central compensation that is known to occur in the vestibular system.

While understanding the multiple pathways that are required to elicit significant HC regeneration is a fascinating research endeavor, it also presents a major challenge for drug development. Alternatively, strategies focused on the repair or functional restoration of damaged rather than missing HCs may be a fruitful avenue for future research. In addition, there is emerging evidence (reviewed below) that damage to the neuronal elements of the cochlea plays a significant role in the SIN deficits that are a cardinal complaint of those with hearing difficulties. This has challenged the traditional focus on HC dysfunction as the primary cause of hearing loss and is providing new and potentially more facile treatment possibilities.

4.2 | Cochlear Synaptopathy

The ribbon synapses that connect IHCs and SGN afferent fibers are vulnerable to ototoxic agents, noise trauma, and aging (Figure 4A). This was first shown in animal models where a noise insult that produced no permanent change in auditory threshold resulted in a preferential and permanent loss of a sub-population of IHC afferent synapses, those that give rise to the so-called high threshold, low spontaneous activity fibers.[49,50]

A preferential loss of IHC afferent synapses is a consequence of the sudden and excessive release of glutamate from the presynaptic ribbons of HCs during loud noise producing an excitotoxic process caused by overactivation of AMPA and NMDA receptors present on afferent nerve terminals.[51,52] Preferential vulnerability of ribbon synapses has also been revealed in human subjects through post-mortem analysis in temporal bone specimens, where during aging the loss of type I afferent fibers and IHC synapses markedly precedes the loss of the IHCs themselves.[53,54] A similar analysis was extended to noise-exposed human cochleae and revealed substantial loss of both OHCs and auditory nerve fibers with a correlation analysis indicating that the loss of neuronal afferents contributes to poor word discrimination.[55]

Damage to ribbon synapses was originally recognized as "hidden hearing loss," an impairment of hearing quality that occurs despite relatively normal audiometric hearing thresholds. Growing evidence in the field suggest this loss of neuronal connectivity as a basis for SIN difficulties, characterized by an inability to hear meaningful sounds such as a conversation, in the presence of background noise.[49,50] In this respect, SIN difficulties represent a "real-world" situation and a common experience of hearing loss sufferers that is not remedied by hearing aids that simply amplify sound. Indeed, SIN tests have been characterized as a "stress test" for the auditory system, providing a more relevant indication of the difficulty a subject with hearing loss has with understanding speech, in contrast to word recognition in quiet that represents an optimal listening condition.[56] Consequently, the ability of a therapeutic to improve SIN deficits is highly relevant for the day-to-day experience of those suffering from hearing loss.

SIN difficulties with normal hearing thresholds (hidden hearing loss) may affect up to 3% of the adult population in the United States.[57] Given the more recent appreciation that peripheral afferents and their synapses are lost across a wide range of frequencies

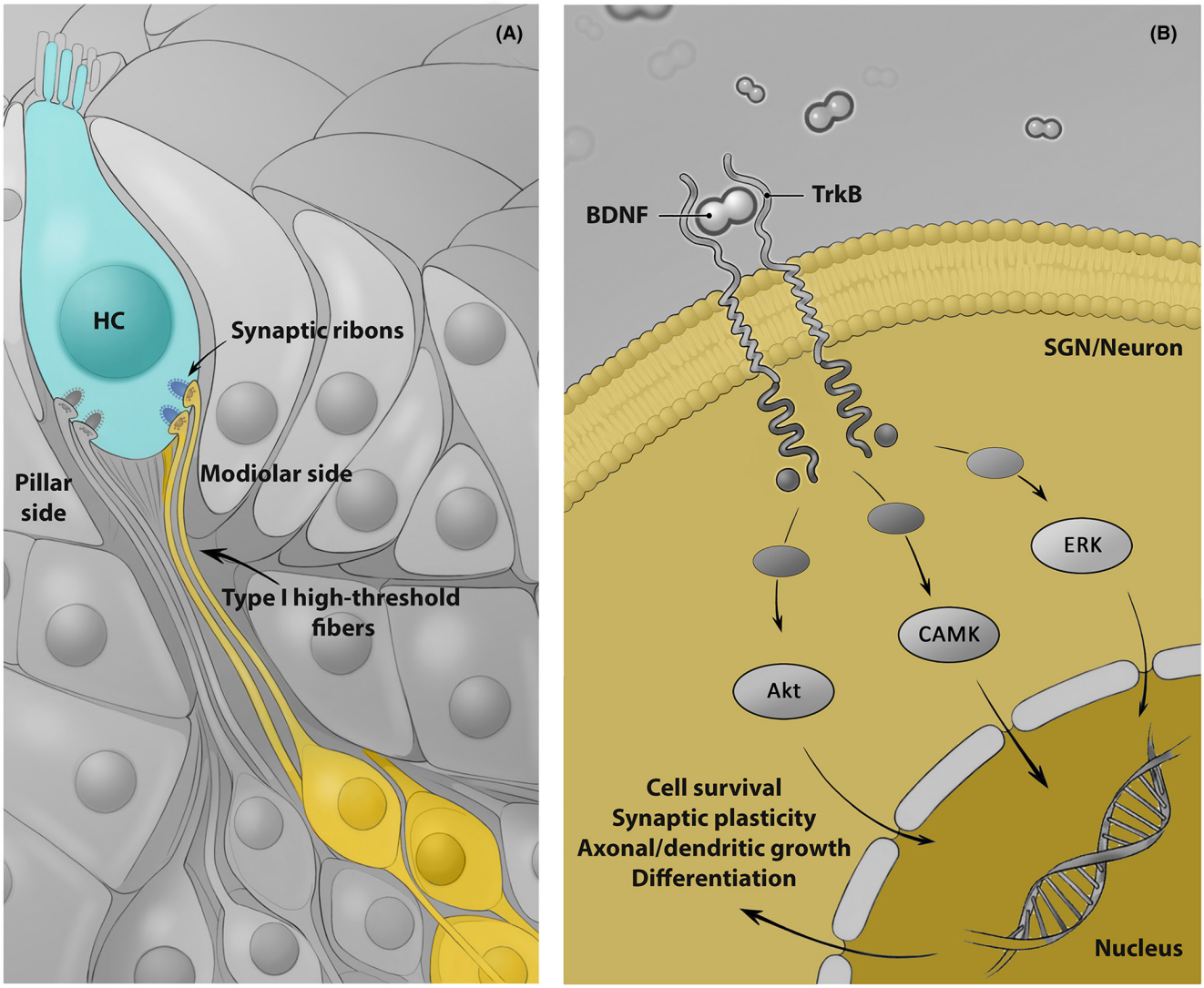

FIGURE 4 Cochlear synaptopathy and therapeutic approaches for restoring ribbon synapses using neurotrophic modulators. (A) Ribbon synapses that connect IHCs (turquoise) with SGN afferent fibers are vulnerable to ototoxic agents, noise trauma, and aging. Specifically, the high-threshold modiolar fibers (yellow) are most susceptible to these insults and show early degeneration and retraction from the IHCs resulting in speech-in-noise hearing difficulty. (B) Binding and homodimerization of Trk receptors (TrkB or C) with their neurotrophic ligands (BDNF, or NT-3, respectively) results in downstream activation of the AKT, CAMK, and ERK signaling pathways which play important roles in cell survival, synaptic plasticity, axonal/dendritic growth, and neural differentiation during development and repair, making them key targets for therapeutic intervention.

in subjects that have OHC loss due to noise exposure and aging,[55] we can now extend the contribution of these neuronal deficits to include SIN deficits that occur in moderate to severe hearing loss, a substantially larger group.

Consequently, the reconnection of afferent fibers to IHCs has the potential to provide benefit to a broad population of hearing loss sufferers. The fact that in both animal and human studies, the SGN cell bodies and central axons appear to be resistant to noise and the aging process[49] indicates that reconnection of the peripheral terminals should result in restoration of a full range of listening experiences, since the intricate connections between the peripheral and central auditory system that were established during development remain in place.

A recent study has provided persuasive evidence that cochlear synaptopathy leads to the equivalent of SIN difficulties in rats.[58] While the evidence that cochlear synaptopathy occurs in human subjects seems well established based on human post-mortem studies,[53,54] whether this directly leads to hearing problems in humans, such as SIN difficulties, has been more difficult to discern.[59] In animal studies, loss of IHC afferent synapses caused by noise trauma results in a reduction in the amplitude of the wave I component of the auditory brainstem response (ABR), a measurement that reflects activity at these synapses and in the cochlear nerve, and shows a strong correlation with the loss of IHC ribbon synapses.[49,50] Consequently, changes in the ABR wave I in human subjects have been intensively investigated, typically in younger populations with a history of noise

exposure, but with mixed results.[59–61] Interpretation of wave I ABR amplitude changes in older populations that have threshold elevations is compromised by OHC loss. However, based on the most recent human postmortem study[55] showing more substantial afferent fiber decrements along with OHC loss with age, it is possible that this is precisely where the effects of cochlear synaptopathy would be most evident, and so would not be revealed by wave I ABR amplitude measurements. Overall, it is reasonable to expect that a loss of IHC afferent synapses due to noise trauma or aging underpins SIN difficulties. Ultimately, interventional studies with therapeutics aimed at restoring these synapses and their function may provide the most compelling evidence for this hypothesis.

Neurotrophins and their receptors are a primary focus of therapeutic approaches to restore the cochlear afferents and ribbon synapses (Figure 4B). Neurotrophins are a family of soluble growth factors that are key to neuronal development, neuronal selection and survival, maintenance of neuronal phenotype and synapses, and neuronal function.[62–64] Two neurotrophic factors, brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), are critical for the establishment of type I afferent synapses during development, and genetic deletion of the neurotrophins or their receptors (TrkB and TrkC, respectively) disrupts SGNs and their afferent connections. During development, BDNF and NT-3 appear to play complementary roles in establishing the tonotopic gradient in the cochlea and both have been shown to protect SGNs against ototoxic insults.[65]

In animal models of cochlear synaptopathy, local administration of BDNF or NT-3 to the cochlea has been shown to restore ribbon synapses and their function.[66–68] In addition to the endogenous neurotrophins, other molecules that act as agonists for TrkB or TrkC receptors have been evaluated for their ability to restore IHC ribbon synapses. These include monoclonal antibodies that selectively activate TrkB or TrkC, engineered chimeric neurotrophins with dual agonist activity for both TrkB and TrkC, and small molecule receptor agonists.[69–71]

Other factors with neurotrophic activity, such as insulin-derived growth factor-1 (IGF-1) and glial-derived growth factor (GDNF), [72,73] have also been considered as potential therapeutics for cochlear synaptopathy, as well as compounds that interact with the Netrin/DCC pathway, that plays a role in axon guidance.[36]

From a pharmacological perspective, biologics that act as TrkB and TrkC agonists are potent molecules that produce neurotrophic effects often in the sub-nanomolar range and are therefore well-suited to local administration at the round window membrane. In addition to effects that result from an initial activation of cell surface Trk receptors, there is substantial evidence that receptor signaling continues after internalization of the neurotrophin-Trk complex in the so-called "signaling endosome," that travels to the nuclei of neurons and can promote changes in gene regulation that mediate long-term neurotrophic effects.[74,75] Recent and future studies in this area may shed more light on whether the pharmacodynamic effects of neurotrophins in the cochlea will outlast their presence in cochlear fluids and the extracellular matrix.

OTO-413 is a formulation of BDNF in P407 for intratympanic administration onto the round window membrane that provides extended exposure of BDNF to the cochlea.[68,76,77] In a phase 1/2a clinical trial in subjects with SIN difficulties, OTO-413 demonstrated clinically meaningful improvements in multiple SIN tests at both 8 and 12 weeks following a single intratympanic administration and had a favorable safety profile.[78] The improvements occurred in subjects with relatively normal hearing thresholds as well as those with moderate-to-severe hearing loss. These promising early-stage clinical data warrant further investigation in a larger number of subjects with hearing loss, and additional clinical work is now underway (www.otonomy.com).

The advent of cochlear synaptopathy as an important contributor to hearing deficits, particularly those that center on the most common complaint involving difficulty hearing in a noisy environment, is challenging traditional notions of hearing loss mechanisms and potential treatments that have focused solely on HCs. Indeed, recent studies have aimed at restoring cochlear neuronal connections rather than HC regeneration, and the preliminary data showing improvements in SIN difficulties with an intratympanically administered neurotrophin holds promise for alleviation of this cardinal complaint of the hearing impaired.

4.3 | Cisplatin-induced Hearing Loss

Cisplatin is a potent chemotherapeutic agent that is widely used to treat a variety of cancers in adults and children. Each year, in the United States alone, approximately 500,000 patients receive platinum-based chemotherapy. However, the administration of cisplatin is commonly associated with severe adverse effects including nephrotoxicity, peripheral neuropathy, and ototoxicity. Cisplatin-induced hearing loss (CIHL) has a high prevalence ranging from 20 to 80% in children undergoing cisplatin treatment[79] and manifests as sensorineural hearing loss and tinnitus, with the hearing loss being progressive, bilateral, and irreversible.[80] Children are at greater risk of developing hearing loss than adults, with dire consequences for speech development and social integration. Cisplatin ototoxicity results from high doses and/or multiple treatment cycle regimens that lead to significant and lasting platinum accumulation in the cochlea. Recently, studies of mouse and human temporal bones revealed that platinum remains in the cochlea for months to years following treatment, and could explain the delayed progression of cisplatin-induced hearing loss observed clinically.[81]

Since there are no approved treatments for CIHL prevention to date, management of the ototoxicity risk, when considered, primarily relies on dose adjustment or discontinuation of cisplatin therapy, with a potential significant negative impact on cancer progression.[82] Therapeutic approaches aimed at preventing cisplatin-induced ototoxicity need first to preserve the antitumor activity of the chemotherapy, or at the very least minimize interference. Consequently, different approaches have been considered depending on the route of administration. Systemic administration by oral or intravenous

routes faces significant challenges in reaching therapeutic drug levels in the inner ear, while minimizing systemic drug exposure to the neoplastic tissues targeted by cisplatin chemotherapy. An alternate and more effective approach would be local delivery to the ear. As described above, delivering a therapeutic agent via intratympanic injection into the middle ear can ensure that adequate exposure of otic tissues is achieved, while systemic levels are negligible.[12]

The ototoxicity of cisplatin encompasses a number of cellular tissues in the cochlea (Figure 5A). In particular, sensory HCs are severely affected with a more pronounced susceptibility of OHCs versus IHCs.[83] Evidence of damage to the SGNs and degeneration of the stria vascularis has also been noted.[83] Cellular uptake of cisplatin by passive diffusion and active transport mechanisms (such as copper transporter CTR1, organic cation transporter OCT2[84]) leads to oxidative stress (via generation of reactive oxygen species and depletion of the antioxidant defense system), inflammatory responses, and eventually apoptosis and cell death.[79] These underlying mechanisms of cisplatin's ototoxicity have been the subject of efforts to develop effective otoprotective therapies (Figure 5B).

Recent studies point to the role of the MET channel as an uptake mechanism for cisplatin entry into HCs. MET channel blockers such as ORC-13661[85] and berbamine[86] have been shown in preclinical models to protect against cisplatin-induced hearing loss. Another approach has been to use agents that specifically sequester cisplatin through covalent binding. Interestingly, most of these molecules, namely D-methionine, N-acetyl cysteine (NAC) and sodium thiosulfate (STS), also exhibit antioxidant properties. D-methionine[87,88] and NAC have shown promise based on preclinical studies conducted in animal models of CIHL. To date, however, clinical translation of these beneficial effects into patients undergoing cisplatin chemotherapy is limited, and the demonstration of significant otoprotection has remained elusive,[89] possibly due to dose limitation constraints. In contrast, clinical trials conducted with intravenously administered STS (Pedmark™) have demonstrated protection against CIHL in pediatric patients with localized, non-metastatic solid tumors.[90] However, in a patient population with metastatic tumors, mortality in the STS-treated group was greater, probably due to the systemically delivered STS directly interfering with the anti-tumor properties of cisplatin.[91] Given these results, intravenous STS administration must follow a very specific dosing protocol where it is administered between 4 and 6 h following cisplatin infusion, to maximize hearing preservation, while limiting any abrogation of the benefits of cisplatin for tumor shrinkage and may only be suitable for use in non-metastatic disease. Such approaches highlight the limitations of therapeutic agents that antagonize cisplatin function when given systemically.

Nevertheless, a new drug application (NDA) for Pedmark™ has been submitted to the FDA and is expected to be reviewed in late 2021 (www.fennecpharma.com). Additional systemically administered agents are being evaluated clinically on the basis of their antioxidant/anti-inflammatory properties (ebselen)[92] or anti-immune properties (R-azasetron).[93] Recently, a reduction in the incidence and severity of cisplatin-induced hearing loss in adults with head and neck cancer was shown to be associated with the use of atorvastatin, an HMG-CoA reductase inhibitor with reported anti-inflammatory and antioxidant properties.[94] On the basis of these encouraging findings, a Phase 3 interventional study is being initiated (ClinicalTrials.gov Identifier: NCT04915183) (Table 1).

More promising approaches focus on the direct delivery of a therapeutic agent to the otic compartment via intratympanic administration. As mentioned above, local administration has the advantage of maximizing delivery of the therapeutic agent to the

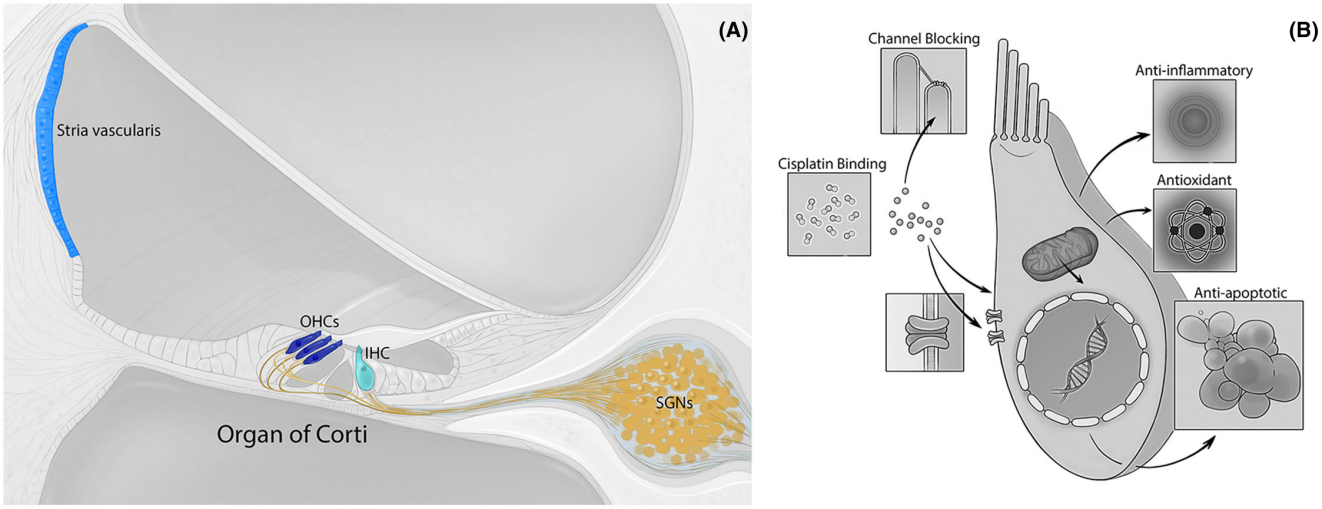

FIGURE 5 Cellular targets and therapeutic strategies for cisplatin-induced ototoxicity in the cochlea. (A) Within the cochlea, platinum-based chemotherapeutic agents can induce damage or cell death within cells of the stria vascularis (bright blue), the inner (dark blue), and outer hair cells (turquoise), as well as the spiral ganglion neurons (yellow) that innervate the hair cells, damage to any of which can contribute to hearing loss. (B) Many strategies have been evaluated to mitigate this ototoxic hearing loss, some of the mechanisms reported in the literature which have shown promise include channel blockers to prevent cisplatin from entering vulnerable cell types, anti-inflammatory agents, antioxidants, anti-apoptotic agents, and cisplatin binding/scavenging compounds.

otic compartment while minimizing systemic exposure that could compromise the anti-tumor effects of cisplatin. For instance, an otic formulation of STS (DB-020) is currently being evaluated for hearing preservation in adult patients undergoing chemotherapy.[95] Recently, a novel class of molecules has emerged that has optimized cisplatin binding properties in addition to antioxidant benefits. A lead compound was formulated into OTO-510 for sustained release after intratympanic administration, which demonstrated significant protection in preclinical models of CIHL.[96–98] These local delivery approaches are attractive since they preclude any interference with the chemotherapeutic benefits of cisplatin.

As treatment regimens for chemotherapeutics have been optimized and improved to provide greater survival benefits for cancer patients, the need to provide protection from ototoxicity has become increasingly relevant, particularly in pediatric and young adult populations that can most benefit from healthy hearing. This was highlighted in a 2018 conference on childhood cancer hearing loss as part of the FDAs Patient-focused Drug Development initiative (https://www.flipsnack.com/childrenscause/pfdd-final-report-_-5-17-2019/full-view.html). The experimental therapies described above could pave the way for new strategies to combat this considerable unmet need.

5 | CONCLUSIONS

According to the World Health Organization, 466 million people suffer with disabling hearing loss worldwide, a number that could grow to 900 million by 2050 (https://www.who.int/deafness/estimates/en/). The renaissance in cochlear biology that has occurred over the past two decades, combined with innovations in drug delivery to the inner ear, provides an opportunity to address this growing unmet clinical need. The current efforts reviewed here provide hope that effective pharmacological treatments are on the way to ameliorate hearing loss due to cochlear malfunction caused by noise, aging, and ototoxicity. There are also pharmacological developments in the associated areas of balance disorders[99] and initial proof-of-concept data in tinnitus.[16] Local gene therapy for the inner ear is also under investigation as a means to restore hearing function in monogenetic hearing disorders.[100] With the promise of hearing loss therapies now on the horizon, it seems likely that the next decade will yield meaningful inroads into this “final frontier” of pharmacology and provide much needed relief for those suffering from hearing loss.

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AUTHOR CONTRIBUTION

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DISCLOSURE

The authors are employees of and shareholders in Otonomy, Inc.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[101] and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[102–106]

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES

1. Wilson BS, Tucci DL, Merson MH, O'Donoghue GM. Global hearing health care: new findings and perspectives. *Lancet*. 2017;390(10111):2503-2515. doi:10.1016/S0140-6736(17)31073-5
2. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734. doi:10.1016/S0140-6736(17)31363-6
3. Mener DJ, Betz J, Genther DJ, Chen D, Lin FR. Hearing loss and depression in older adults. *J Am Geriatr Soc*. 2013;61(9):1627-1629. doi:10.1111/jgs.12429
4. Shukla A, Harper M, Pedersen E, et al. Hearing loss, loneliness, and social isolation: a systematic review. *Otolaryngol Head Neck Surg*. 2020;162(5):622-633. doi:10.1177/0194599820910377
5. Emmett SD, Francis HW. The socioeconomic impact of hearing loss in U.S. adults. *Otol Neurotol*. 2015;36(3):545-550. doi:10.1097/MAO.0000000000000562
6. Tomblin JB, Harrison M, Ambrose SE, Walker EA, Oleson JJ, Moeller MP. Language outcomes in young children with mild to severe hearing loss. *Ear Hear*. 2015;36(suppl 1):76S-91S. doi:10.1097/AUD.0000000000000219
7. Jarvelin MR, Maki-Torkko E, Sorri MJ, Rantakallio PT. Effect of hearing impairment on educational outcomes and employment up to the age of 25 years in northern Finland. *Br J Audiol*. 1997;31(3):165-175. doi:10.3109/03005364000000019
8. Bronkhorst AW. The cocktail party phenomenon: a review of research on speech intelligibility in multiple-talker conditions. *Acta Acustica United Acustica*. 2000;86(1):117-128.
9. Bronkhorst AW. The cocktail-party problem revisited: early processing and selection of multi-talker speech. *Atten Percept Psychophys*. 2015;77(5):1465-1487. doi:10.3758/s13414-015-0882-9
10. Chien W, Lin FR. Prevalence of hearing aid use among older adults in the United States. *Arch Intern Med*. 2012;172(3):292-293. doi:10.1001/archinternmed.2011.1408
11. Simpson AN, Matthews LJ, Cassarly C, Dubno JR. Time from hearing aid candidacy to hearing aid adoption: a longitudinal cohort study. *Ear Hear*. 2019;40(3):468-476. doi:10.1097/AUD.0000000000000641
12. Piu F, Bishop KM. Local drug delivery for the treatment of neurotology disorders. *Front Cell Neurosci*. 2019;13:238. doi:10.3389/fncel.2019.00238
13. Hurley B. Therapeutic revolution in the management of diabetic retinopathy. *Can J Ophthalmol*. 2017;52(suppl 1):S1-S2. doi:10.1016/j.jcjo.2017.06.006

14. Park AH, White DR, Moss JR, Bear M, LeBel C. Phase 3 trials of thermosensitive ciprofloxacin gel for middle ear effusion in children with tubes. *Otolaryngol Head Neck Surg*. 2016;155(2):324-331. doi:10.1177/0194599816645526
15. Lambert PR, Carey J, Mikulec AA, LeBel C; Otonomy Meniere's Study G. Intratympanic sustained-exposure dexamethasone thermosensitive gel for symptoms of Meniere's disease: randomized phase 2b safety and efficacy trial. *Otol Neurotol*. 2016;37(10):1669-1676. doi:10.1097/MAO.0000000000001227
16. Maxwell KS, Robinson JM, Hoffmann I, et al. Intratympanic administration of OTO-313 reduces tinnitus in patients with moderate to severe, persistent tinnitus: a phase 1/2 study. *Otol Neurotol*. 2021;42(10):e1625-e1633. doi:10.1097/MAO.0000000000003369
17. Rybak LP, Dhukhwa A, Mukherjea D, Ramkumar V. Local drug delivery for prevention of hearing loss. *Front Cell Neurosci*. 2019;13:300. doi:10.3389/fncel.2019.00300
18. Coric V, van Dyck CH, Salloway S, et al. Safety and tolerability of the gamma-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. *Arch Neurol*. 2012;69(11):1430-1440. doi:10.1001/archneurol.2012.2194
19. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369(4):341-350. doi:10.1056/NEJMoa1210951
20. Doody RS, Raman R, Sperling RA, et al. Peripheral and central effects of gamma-secretase inhibition by semagacestat in Alzheimer's disease. *Alzheimers Res Ther*. 2015;7(1):36. doi:10.1186/s13195-015-0121-6
21. Li G, Tian Y, Zhu WG. The roles of histone deacetylases and their inhibitors in cancer therapy. *Front Cell Dev Biol*. 2020;8:576946. doi:10.3389/fcell.2020.576946
22. Wu PZ, O'Malley JT, de Gruttola V, Liberman MC. Age-related hearing loss is dominated by damage to inner ear sensory cells, not the cellular battery that powers them. *J Neurosci*. 2020;40(33):6357-6366. doi:10.1523/JNEUROSCI.0937-20.2020
23. Wagner EL, Shin JB. Mechanisms of hair cell damage and repair. *Trends Neurosci*. 2019;42(6):414-424. doi:10.1016/j.tins.2019.03.006
24. Cotanche DA. Regeneration of hair cell stereociliary bundles in the chick cochlea following severe acoustic trauma. *Hear Res*. 1987;30(2-3):181-195. doi:10.1016/0378-5955(87)90135-3
25. Cruz RM, Lambert PR, Rubel EW. Light microscopic evidence of hair cell regeneration after gentamicin toxicity in chick cochlea. *Arch Otolaryngol Head Neck Surg*. 1987;113(10):1058-1062. doi:10.1001/archotol.1987.01860100036017
26. Atkinson PJ, Huarcaya Najarro E, Sayyid ZN, Cheng AG. Sensory hair cell development and regeneration: similarities and differences. *Development*. 2015;142(9):1561-1571. doi:10.1242/dev.114926
27. Shibata SB, West MB, Du X, Iwasa Y, Raphael Y, Kopke RD. Gene therapy for hair cell regeneration: review and new data. *Hear Res*. 2020;394:107981. doi:10.1016/j.heares.2020.107981
28. Staecker H. Optimizing delivery of molecular therapeutics to the inner ear. Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2020; San Jose, California, USA.
29. Samarajeewa A, Jacques BE, Dabdoub A. Therapeutic potential of Wnt and Notch signaling and epigenetic regulation in mammalian sensory hair cell regeneration. *Mol Ther*. 2019;27(5):904-911. doi:10.1016/j.ymthe.2019.03.017
30. Daudet N, Zak M. Notch signalling: the multitask manager of inner ear development and regeneration. *Adv Exp Med Biol*. 2020;1218:129-157. doi:10.1007/978-3-030-34436-8_8
31. Zheng F, Zuo J. Cochlear hair cell regeneration after noise-induced hearing loss: does regeneration follow development? *Hear Res*. 2017;349:182-196. doi:10.1016/j.heares.2016.12.011
32. Borse V, Barton M, Arndt H, Kaur T, Warchol ME. Dynamic patterns of YAP1 expression and cellular localization in the developing and injured utricle. *Sci Rep*. 2021;11(1):2140. doi:10.1038/s41598-020-77775-8
33. Du X, Cai Q, West MB, et al. Regeneration of cochlear hair cells and hearing recovery through Hes1 modulation with siRNA nanoparticles in adult guinea pigs. *Mol Ther*. 2018;26(5):1313-1326. doi:10.1016/j.ymthe.2018.03.004
34. Maass JC, Gu R, Basch ML, et al. Changes in the regulation of the Notch signaling pathway are temporally correlated with regenerative failure in the mouse cochlea. *Front Cell Neurosci*. 2015;9:110. doi:10.3389/fncel.2015.00110
35. Ho DM, Artavanis-Tsakonas S, Louvi A. The Notch pathway in CNS homeostasis and neurodegeneration. *Wiley Interdiscip Rev Dev Biol*. 2020;9(1):e358. doi:10.1002/wdev.358
36. Lorrain D, Poon M, Stebbins KJ, et al. Discovery of PIPE-505, a small molecule therapeutic for the treatment of sensorineural hearing loss (SNHL) associated with cochlear synaptopathy. Presented at: Society for Neuroscience; 2019; Chicago, Illinois, USA.
37. Lee S, Song JJ, Beyer LA, et al. Combinatorial Atoh1 and Gfi1 induction enhances hair cell regeneration in the adult cochlea. *Sci Rep*. 2020;10(1):21397. doi:10.1038/s41598-020-78167-8
38. McLean WJ, Yin X, Lu L, et al. Clonal expansion of Lgr5-positive cells from mammalian cochlea and high-purity generation of sensory hair cells. *Cell Rep*. 2017;18(8):1917-1929. doi:10.1016/j.celrep.2017.01.066
39. McLean WJ, Hinton AS, Herby JTJ, et al. Improved speech intelligibility in subjects with stable sensorineural hearing loss following intratympanic dosing of FX-322 in a phase 1b study. *Otol Neurotol*. 2021;42(7):e849-e857. doi:10.1097/MAO.0000000000003120
40. Li XJ, Doetzlhofer A. LIN28B/let-7 control the ability of neonatal murine auditory supporting cells to generate hair cells through mTOR signaling. *Proc Natl Acad Sci USA*. 2020;117(36):22225-22236. doi:10.1073/pnas.2000417117
41. Golden EJ, Benito-Gonzalez A, Doetzlhofer A. The RNA-binding protein LIN28B regulates developmental timing in the mammalian cochlea. *Proc Natl Acad Sci USA*. 2015;112(29):E3864-E3873. doi:10.1073/pnas.1501077112
42. Rudolf MA, Andreeva A, Kozlowski MM, et al. YAP mediates hair cell regeneration in balance organs of chickens, but LATS kinases suppress its activity in mice. *J Neurosci*. 2020;40(20):3915-3932. doi:10.1523/JNEUROSCI.0306-20.2020
43. Gnedeva K, Wang X, McGovern MM, et al. Organ of corti size is governed by Yap/Tead-mediated progenitor self-renewal. *Proc Natl Acad Sci USA*. 2020;117(24):13552-13561. doi:10.1073/pnas.2000175117
44. Kozlowski MM, Rudolf MA, Corwin JT. EGF and a GSK3 inhibitor deplete junctional E-cadherin and stimulate proliferation in the mature mammalian ear. *J Neurosci*. 2020;40(13):2618-2632. doi:10.1523/JNEUROSCI.2630-19.2020
45. Burns JC, Stone JS. Development and regeneration of vestibular hair cells in mammals. *Semin Cell Dev Biol*. 2017;65:96-105. doi:10.1016/j.semcdb.2016.11.001
46. Warchol ME, Lambert PR, Goldstein BJ, Forge A, Corwin JT. Regenerative proliferation in inner ear sensory epithelia from adult guinea pigs and humans. *Science*. 1993;259(5101):1619-1622. doi:10.1126/science.8456285
47. Forge A, Li L, Corwin JT, Nevill G. Ultrastructural evidence for hair cell regeneration in the mammalian inner ear. *Science*. 1993;259(5101):1616-1619. doi:10.1126/science.8456284
48. Sayyid ZN, Kim GS, Cheng AG. Molecular therapy for genetic and degenerative vestibular disorders. *Curr Opin Otolaryngol Head Neck Surg*. 2018;26(5):307-311. doi:10.1097/MOO.0000000000000477

49. Kujawa SG, Liberman MC. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. *J Neurosci*. 2009;29(45):14077-14085. doi:10.1523/JNEUROSCI.2845-09.2009
50. Kujawa SG, Liberman MC. Synaptopathy in the noise-exposed and aging cochlea: primary neural degeneration in acquired sensorineural hearing loss. *Hear Res*. 2015;330(Pt B):191-199. doi:10.1016/j.heares.2015.02.009
51. Ruel J, Wang J, Rebillard G, et al. Physiology, pharmacology and plasticity at the inner hair cell synaptic complex. *Hear Res*. 2007;227(1-2):19-27. doi:10.1016/j.heares.2006.08.017
52. Liberman MC. Noise-induced and age-related hearing loss: new perspectives and potential therapies. *F1000Res*. 2017;6:927. doi:10.12688/f1000research.11310.1
53. Viana LM, O'Malley JT, Burgess BJ, et al. Cochlear neuropathy in human presbycusis: confocal analysis of hidden hearing loss in post-mortem tissue. *Hear Res*. 2015;327:78-88. doi:10.1016/j.heares.2015.04.014
54. Wu PZ, Liberman LD, Bennett K, de Gruttola V, O'Malley JT, Liberman MC. Primary neural degeneration in the human cochlea: evidence for hidden hearing loss in the aging ear. *Neuroscience*. 2019;407:8-20. doi:10.1016/j.neuroscience.2018.07.053
55. Wu PZ, O'Malley JT, de Gruttola V, Liberman MC. Primary neural degeneration in noise-exposed human cochleas: correlations with outer hair cell loss and word-discrimination scores. *J Neurosci*. 2021;41(20):4439-4447. doi:10.1523/JNEUROSCI.3238-20.2021
56. Wilson RH. Clinical experience with the words-in-noise test on 3430 veterans: comparisons with pure-tone thresholds and word recognition in quiet. *J Am Acad Audiol*. 2011;22(7):405-423. doi:10.3766/jaaa.22.7.3
57. Tremblay KL, Pinto A, Fischer ME, et al. Self-reported hearing difficulties among adults with normal audiograms: the Beaver Dam Offspring Study. *Ear Hear*. 2015;36(6):e290-e299. doi:10.1097/AUD.0000000000000195
58. Resnik J, Polley DB. Cochlear neural degeneration disrupts hearing in background noise by increasing auditory cortex internal noise. *Neuron*. 2021;109(6):984-996 e4. doi:10.1016/j.neuron.2021.01.015
59. Bramhall N, Beach EF, Epp B, et al. The search for noise-induced cochlear synaptopathy in humans: mission impossible? *Hear Res*. 2019;377:88-103. doi:10.1016/j.heares.2019.02.016
60. Prendergast G, Guest H, Munro KJ, et al. Effects of noise exposure on young adults with normal audiograms I: electrophysiology. *Hear Res*. 2017;344:68-81. doi:10.1016/j.heares.2016.10.028
61. Liberman MC, Epstein MJ, Cleveland SS, Wang H, Maison SF. Toward a differential diagnosis of hidden hearing loss in humans. *PLoS One*. 2016;11(9):e0162726. doi:10.1371/journal.pone.0162726
62. Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci*. 2003;4(4):299-309. doi:10.1038/nrn1078
63. Saragovi HU, Galan A, Levin LA. Neuroprotection: pro-survival and anti-neurotoxic mechanisms as therapeutic strategies in neurodegeneration. *Front Cell Neurosci*. 2019;13:231. doi:10.3389/fncel.2019.00231
64. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci*. 2001;24:677-736. doi:10.1146/annurev.neuro.24.1.677
65. Green SH, Bailey E, Wang Q, Davis RL. The Trk A, B, C's of neurotrophins in the cochlea. *Anat Rec (Hoboken)*. 2012;295(11):1877-1895. doi:10.1002/ar.22587
66. Sly DJ, Campbell L, Uschakov A, Saief ST, Lam M, O'Leary SJ. Applying neurotrophins to the round window rescues auditory function and reduces inner hair cell synaptopathy after noise-induced hearing loss. *Otol Neurotol*. 2016;37(9):1223-1230. doi:10.1097/MAO.0000000000001191
67. Suzuki J, Corfas G, Liberman MC. Round-window delivery of neurotrophin 3 regenerates cochlear synapses after acoustic overexposure. *Sci Rep*. 2016;6:24907. doi:10.1038/srep24907
68. Piu F, Tsivkovskaia N, Fernandez R, et al. A sustained-exposure formulation of the neurotrophic factor BDNF protects against noise-induced cochlear synaptopathy in young adult and aged rats. Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2018; San Diego, California, USA.
69. Szobota S, Mathur PD, Siegel S, Black K, Saragovi HU, Foster AC. BDNF, NT-3 and Trk receptor agonist monoclonal antibodies promote neuron survival, neurite extension, and synapse restoration in rat cochlea ex vivo models relevant for hidden hearing loss. *PLoS One*. 2019;14(10):e0224022. doi:10.1371/journal.pone.0224022
70. Szobota S, Mathur PD, Siegel S, Brahimi F, Saragovi U, Foster AC. Modified versions of NT-3 enable enhanced activation of TrkB and TrkC responses in ex vivo models relevant to cochlear synaptopathy. Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2019; Baltimore, Maryland, USA.
71. Tsivkovskaia N, Fernandez C, Altmann T, et al. Characterization of a TrkB mAb agonist for the treatment of speech-in-noise hearing difficulties (cochlear synaptopathy). Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2021; virtual.
72. Euteneuer S, Yang KH, Chavez E, et al. Glial cell line-derived neurotrophic factor (GDNF) induces neuritogenesis in the cochlear spiral ganglion via neural cell adhesion molecule (NCAM). *Mol Cell Neurosci*. 2013;54:30-43. doi:10.1016/j.mcn.2012.12.004
73. Yamahara K, Asaka N, Kita T, et al. Insulin-like growth factor 1 promotes cochlear synapse regeneration after excitotoxic trauma in vitro. *Hear Res*. 2019;374:5-12. doi:10.1016/j.heares.2019.01.008
74. Howe CL, Mobley WC. Signaling endosome hypothesis: a cellular mechanism for long distance communication. *J Neurobiol*. 2004;58(2):207-216. doi:10.1002/neu.10323
75. Bronfman FC, Escudero CA, Weis J, Kruttgen A. Endosomal transport of neurotrophins: roles in signaling and neurodegenerative diseases. *Dev Neurobiol*. 2007;67(9):1183-1203. doi:10.1002/dneu.20513
76. Jacques BE, Tsivkovskaia N, Fernandez R, et al. Development of intratympanically administered neurotrophic factor BDNF for the treatment of speech-in-noise hearing difficulties (cochlear synaptopathy). Presented at: Society for Neuroscience; 2018; San Diego, California, USA.
77. Tsivkovskaia N, Wang X, Fernandez C, et al. Characterization of OTO-413, an intratympanic sustained-exposure formulation of the neurotrophic factor BDNF, in preclinical models of cochlear synaptopathy. Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2020; San Jose, California, USA.
78. Anderson JJ, Robinson J, Blaj A, et al. A first-in-human study of OTO-413, an intratympanic sustained-exposure formulation of BDNF, for the treatment of speech-in-noise hearing impairment. Presented at: Association for Research in Otolaryngology Mid-winter Meeting; 2021; online.
79. Sheth S, Mukherjea D, Rybak LP, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and otoprotection. *Front Cell Neurosci*. 2017;11:338. doi:10.3389/fncel.2017.00338
80. Waissbluth S, Peleva E, Daniel SJ. Platinum-induced ototoxicity: a review of prevailing ototoxicity criteria. *Eur Arch Otorhinolaryngol*. 2017;274(3):1187-1196. doi:10.1007/s00405-016-4117-z
81. Breglio AM, Rusheen AE, Shide ED, et al. Cisplatin is retained in the cochlea indefinitely following chemotherapy. *Nat Commun*. 2017;8(1). 10.1038/s41467-017-01837-1
82. Avan A, Postma TJ, Ceresa C, et al. Platinum-induced neurotoxicity and preventive strategies: past, present, and future. *Oncologist*. 2015;20(4):411-432. doi:10.1634/theoncologist.2014-0044

83. Nakai Y, Konishi K, Chang KC, et al. Ototoxicity of the anticancer drug cisplatin. An experimental study. *Acta Otolaryngol*. 1982;93(1-6):227-232. doi:10.3109/00016488209130876
84. Gentilin E, Simoni E, Candito M, Cazzador D, Astolfi L. Cisplatin-induced ototoxicity: updates on molecular targets. *Trends Mol Med*. 2019;25(12):1123-1132. doi:10.1016/j.molmed.2019.08.002
85. Kitcher SR, Kirkwood NK, Camci ED, et al. ORC-13661 protects sensory hair cells from aminoglycoside and cisplatin ototoxicity. *JCI Insight*. 2019;4(15). doi:10.1172/jci.insight.126764
86. Kruger M, Boney R, Ordoobadi AJ, Sommers TF, Trapani JG, Coffin AB. Natural bizbenzoquinoline derivatives protect zebrafish lateral line sensory hair cells from aminoglycoside toxicity. *Front Cell Neurosci*. 2016;10:83. doi:10.3389/fncel.2016.00083
87. Campbell KC, Meech RP, Rybak LP, Hughes LF. D-Methionine protects against cisplatin damage to the stria vascularis. *Hear Res*. 1999;138(1-2):13-28. doi:10.1016/s0378-5955(99)00142-2
88. Campbell KC, Rybak LP, Meech RP, Hughes L. D-methionine provides excellent protection from cisplatin ototoxicity in the rat. *Hear Res*. 1996;102(1-2):90-98. doi:10.1016/s0378-5955(96)00152-9
89. Hamstra DA, Lee KC, Eisbruch A, et al. Double-blind placebo-controlled multicenter phase II trial to evaluate D-methionine in preventing/reducing oral mucositis induced by radiation and chemotherapy for head and neck cancer. *Head Neck*. 2018;40(7):1375-1388. doi:10.1002/hed.25115
90. Brock PR, Maibach R, Childs M, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. *N Engl J Med*. 2018;378(25):2376-2385. doi:10.1056/NEJMoa1801109
91. Freyer DR, Chen LU, Krailo MD, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(1):63-74. doi:10.1016/S1470-2045(16)30625-8
92. Lynch ED, Gu R, Pierce C, Kil J. Reduction of acute cisplatin ototoxicity and nephrotoxicity in rats by oral administration of allopurinol and ebselen. *Hear Res*. 2005;201(1-2):81-89. doi:10.1016/j.heares.2004.08.002
93. Petremann M, Tran Van Ba C, Broussy A, Romanet C, Dyhrfjeld-Johnsen J. Oral administration of clinical stage drug candidate SENS-401 effectively reduces cisplatin-induced hearing loss in rats. *Otol Neurotol*. 2017;38(9):1355-1361. doi:10.1097/MAO.0000000000001546
94. Fernandez KA, Allen P, Campbell M, et al. Atorvastatin is associated with reduced cisplatin-induced hearing loss. *J Clin Invest*. 2021;131(1). doi:10.1172/JCI142616
95. Viglietta V, Shi F, Hu Q-Y, et al. Phase 1 study to evaluate safety, tolerability and pharmacokinetics of a novel intra-tympanic administered thiosulfate to prevent cisplatin-induced hearing loss in cancer patients. *Invest New Drugs*. 2020;38(5):1463-1471. doi:10.1007/s10637-020-00918-1
96. Mathur PD, Uribe P, Szobota S, et al. Ex vivo evaluation of the therapeutic potential of several drug classes to prevent cisplatin mediated ototoxicity in the rat cochlea. Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2020; San Jose, California, USA.
97. Tsivkovskaia N, Fernandez R, Fernandez C, Jacques BE, Piu F. Evaluation of various therapeutic classes in protection against cisplatin-induced hearing loss (Preclinical models). Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2020; San Jose, California, USA.
98. Tsivkovskaia N, Fernandez C, Fernandez R, et al. Identification and characterization of a novel therapeutic class for protection against cisplatin-induced hearing loss. Presented at: Association For Research in Otolaryngology Mid-winter Meeting; 2021; virtual.
99. Venail F, Attali P, Wersinger E, Gomeni R, Poli S, Schmerber S. Safety, tolerability, pharmacokinetics and pharmacokinetic-pharmacodynamic modelling of the novel H4 receptor inhibitor SENS-111 using a modified caloric test in healthy subjects. *Br J Clin Pharmacol*. 2018;84(12):2836-2848. doi:10.1111/bcp.13744
100. Omichi R, Shibata SB, Morton CC, Smith RJH. Gene therapy for hearing loss. *Hum Mol Genet*. 2019;28(R1):R65-R79. doi:10.1093/hmg/ddz129
101. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Res*. 2018;46(D1):D1091-D1106. doi:10.1093/nar/gkx1121
102. Alexander SPH, Kelly E, Mathie A, et al. The concise guide to pharmacology 2021/22: transporters. *Br J Pharmacol*. 2021;178(suppl 1):S412-S513. doi:10.1111/bph.15543
103. Alexander SPH, Christopoulos A, Davenport AP, et al. The concise guide to pharmacology 2019/20: G protein-coupled receptors. *Br J Pharmacol*. 2019;176(suppl 1):S21-S141. doi:10.1111/bph.14748
104. Alexander SPH, Kelly E, Mathie A, et al. The concise guide to pharmacology 2019/20: introduction and other protein targets. *Br J Pharmacol*. 2019;176(suppl 1):S1-S20. doi:10.1111/bph.14747
105. Alexander SPH, Mathie A, Peters JA, et al. The concise guide to pharmacology 2019/20: ion channels. *Br J Pharmacol*. 2019;176(suppl 1):S142-S228. doi:10.1111/bph.14749
106. Alexander SPH, Fabbro D, Kelly E, et al. The concise guide to pharmacology 2021/22: enzymes. *Br J Pharmacol*. 2021;178(suppl 1):S313-S411. doi:10.1111/bph.15542

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