Original Article

# An Overview of Nanoparticle Drug Delivery for Ototoxin and Noise Mediated Hearing Loss Treatment

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## ABSTRACT

Efficient delivery of therapeutic material to target site of the inner ear is considered as the most challenging process due to their poor blood flow and inaccessibility sensitivity towards chemical stimuli, inability of drug to be delivered as well. Novel nanoparticle-based drug transport approaches have emerged for overcoming the restriction associated with inner ear therapeutic material delivery. The main focus of this article is to highlight the potential benefits, pre-clinical level otoprotective effect of different types of NPs based payload delivery strategies in mitigating sensorineural hearing impairment resulting from medication (cisplatin and antibiotic treatment) and noise exposure. This review converses about advantage of nanocarrier assisted targeted cell specific inner ear drug delivery approach and demonstrates that targeted NPs delivery systems have the capability to be utilized as vehicle to transport therapeutic materials into the OHCs within the cochlea in controlled and sustained way and maximize following therapeutic effects. Efficacy of systemic and minimally invasive intratympanic and RWM approach for delivering steroids/ genetic material to the inner ear has also been compared in this article. Understanding the importance (design, formulation, cochlear biocompatibility and cell specific binding efficiency of NPs, mechanistic pathways, route of delivery, positive therapeutic outcomes) and hitches (adverse effects after treatment, negative therapeutic outcome) of currently available NPs based drug delivery systems offer new opportunity to develop best treatment methods for sensorineural hearing dysfunction.

**Keywords:** Nanocarriers, Otoprotective agents, Sensorineural heating loss, Ototoxicity, Noise trauma, Ototoxin.

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## INTRODUCTION

Otitis media, sudden sensorineural hearing loss (SSHL), tinnitus, presbycusis, autoimmune inner ear ailment, serious inner ear infections caused by bacteria and virus and Meniere's disease affect substantial portion of world population at any stage of life cycle/regardless of their age.[1-4] Heredity.[5-6] age factors,[7-8] autoimmune disorders,[9-10] pathogen (viral, bacterial, and fungal),[11-15] environmental factors (exposure to excessive noise and radiation),[16-17] increase in life expectancy, chemotherapeutic drugs induced ototoxic[18-19] are the main cause for the most of the disorders in the otic region. Despite ear disorders have not been considered as life-threatening issue, sometimes they lead to some form of mild to irreversible hearing impairment. Since

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the auditory function plays a major role in our day-to-day lives, occurrence of hearing loss can impact social, mental and economic well-being, educational and employment development.[7,20-22] Contemporarily utilized strategies for the delivery of drug into the otic region have been confronting/ many challenges owing to the complicated anatomical features, mechanistic and physiological blockades of the ear along with instability and poor bioavailability of drugs at the site of action.[8,23-26] Hearing function is usually tested by means of auditory brainstem response (ABR) and distortion product otoacoustic emission (DPOAE) techniques. Many otoprotective agents, namely dexamethasone (DEX), antioxidants, sodium thiosulfate (STS), acetylcysteine, genetic materials, d-methionine, and amifostine have been formulated and studied their inner ear therapeutic efficacy.[27-31] It was also noted that treatment to reverse cochlea insults by otoprotective agents is inadequate and therapeutic results of these clinical otoprotective agents are also highly unreliable. In the past few decades, several NPs with particle size of 100 nm to 1µm have been employed as carriers for treating and or preventing various disorders with better results.[25,32,41-48,33-40]

Nanoparticles (NPs) have been proved to avoid poor solubility, distribution stability, permeability and off target cell activity of pharmacotherapies, rapid drug clearance from inner ear cavity, these are precondition for achieving therapeutic amount of drug in the target site of the inner ear and effective pharmaceutical treatments for otic diseases in preclinical level. Because of these advantages, biocompatible NPs have been involved in otology imaging.[49-53] cochlear implantation[54-60] and carrying drug to the specific location of inner ear.[24,35,61-64] Recently, several reports have attempted to review different topics related to inner ear drug delivery. In this article, we aim to exclusively summarize *in vitro* and *in vivo* therapeutic outcome and pharmacokinetics of pharmaceutical molecules delivered into the cochlea with NPs to alleviate medication and noise induced sensorineural hearing dysfunction. Brief synopsis about route of administration inner ear drug delivery and ear anatomy are presented. Defense mechanistic pathway of pharmacotherapies loaded NPs drug delivery system against ototoxic drug and noise induced trauma are also discussed.

## Anatomy and Route of Administration

Ear consists of three main parts such as the outer or external ear, middle, and inner ear with limited accessibility, in which cochlea and the vestibule positioned in the inner ear are responsible for two main functions including hearing and balance. The

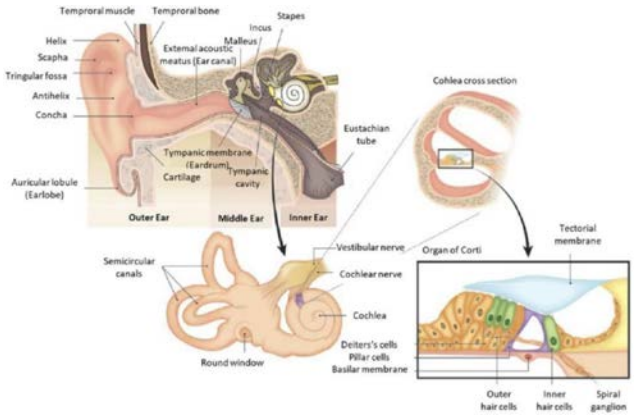


**Figure 1: Detailed Anatomy of ear and organ of Corti. Reproduced with permission from CC BY-NC.[166]**

complex anatomy of ear is depicted in Figure 1. The cochlea is organ of hearing and their delicate hair cells and epithelial tissue are secured by the otic capsule bone, RWM and blood-labyrinth barrier from the hazardous external and internal environment. Various types of cell (inner and outer hair cells, stria vascularis, spiral ganglion neurons and supporting cells) present within the cochlea are sensitive to hazardous local environment, which lead to sensorineural related hearing disorders in the clinical setting. Due to the low blood flow, isolated position, complicated structure and their associated barriers including, eustachian tube, RWM, oval window, cerebrospinal fluid, blood-labyrinth barrier and blood-perilymph barriers of inner ear, it's difficult for therapeutic concentration of drug to reach inner ear, which make pharmacotherapy ineffective.

Roles of these barriers in the therapeutic molecule transport to the inner ear are briefly outlined here.

Eustachian Tube-drug can be quickly discharged due to mucociliary flow of the middle ear RWM-Soft membrane on the scala tympani, primary interface between the middle and inner ear, thickness varies from patient-to-patient hence drug absorption varies.

Oval Window-situated on the scala vestibuli, prohibit the penetration of larger molecules into the cochlea.

Blood-labyrinth Barrier-main physical barriers to entry for systemic drug administration Blood–perilymph Barrier-decreases exchange of systemically administrated drug from plasma to inner ear fluids.

Selecting an apt route of administration is indispensable for the efficient pharmacotherapy to inner ear disease with attenuating any adverse effects. Researchers have investigated different administration strategies, including systemic, intracochlear and intratympanic methods to find better solution for improving therapeutic concentrations of drugs to enter inner ear. Traditional

systemic administration route (Oral, intravenous and intramural) are predominantly used clinical method to treat some type of ear disorder, despite it has low therapeutic carriage ability and related hostile effects due to inadequate blood supply in the inner ear's and the insufficient dispersion of the blood–inner ear barrier (BLB).[35,65-68] Intracochlear route thru cochleostomy seems to be the most implicit approach for transporting drug loaded nanoparticles to cochlear tissues,[24,26,69-71] but this is recognized to be more invasive and traumatic to inner ear (Damage the cochlea, worsen or destroy hearing function) than alternative strategies.[68,72,73] Intratympanic (IT) delivery has been manifested to retain higher local drug level in the perilymph as compared to systemic administration due to their dearth of intervention from the blood–labyrinth barrier and systemic reactions. Round and oval window membranes are another possible way to enter into the inner ear and presumed to be the least traumatic approach. Thickness of three-layered structure RWM of human inner ear is 70 microns, which can permeable small molecules up to 1 μm in size. Round window membrane is considered as bridge between the inner and middle ear, act as elite drug administration route.[74-77] Unique properties of NPs enable them to across the RWM without creating surgical demolition to the delicate inner ear region. It's reported that NPs with smaller particle size can easily penetrate through RWM than bigger size particles.[24,78] Besides, other factors (Charge, nature of drug and lipid solubility) also influence crossing mechanism and speed of diffusion. Among the various routes of administration of otoprotective therapies, local drug delivery techniques including intratympanic and RWM routes have particularly reduced systemic exposure, offered less invasive treatment and promisingly increased the therapeutic drug concentration level in the inner ear.

Inner and outer hair cells in the cochlea are called as mechanical transduction cells, which are fragile and almost has no regeneration capacity, thus formation and progression of inflammation in the inner part of the ear can greatly impact the endurance of hair cell.[79-82] Prevention of hair cells damage from ototoxic drug and noise is the crucial part to the treatment of hearing loss.[79,81,83] Nanoparticle based therapeutic molecule delivery procedures have been found to enrich high loading capacity and drug availability in the inner ear, targeting specific site by surface modification, magnetically and cell penetrating peptides, drugs release in sustained manner into cochlear region and capable of transport across RWM. Advantages of NPs have made them emerging and effective candidates for non-invasive and targeted otoprotective material delivery to the complicated structure of the otic region.

## Drug Induced Hearing Loss

Medication mediated hearing impairment stems from deprivation or injury of outer hair cells in subregion of cochlea tissues and sensorineural structures of cochlea. Clear mechanism for toxicity induced by ototoxin in the ear has not been completely explicated but substantial formation of reactive oxygen species in the region of cochlea is commonly recognized reason in addition to some other pathways for hearing loss. Study design and results of nanocarrier drug delivery against ototoxin and noise-traumatized hearing loss are summarized in Table 1.

## Cisplatin-induced Hearing Loss (CIHL)

Cisplatin has been used as antineoplastic drug for many types of cancer in both adult and pediatric patients.[84-87] However, cisplatin chemotherapy often cause dose-related short-term and/or long-term undesirably effects, including nausea, ototoxicity, ulcers, neurotoxicity, renal dysfunction and nephrotoxicity.[84,88-90] According to reported studies, chemotherapy drug induced permanent hearing loss mostly affects the pediatric groups (77%) than adult (23– 50%) groups.[84,88,90-92] Cisplatin toxicity causes sensory cells damage in the inner ear as a result of the formation reactive oxygen species (ROS) and inflammation on the cochlear tissue, leading to irreversible to severe hearing loss. But mechanisms associated with cochlear impairment are still being scrutinized.[93] Glucocorticoids have been reported to minimize cisplatin-induced auditory sensory cells death, probably by offsetting the reactive oxygen species triggered by cisplatin treatment.[94-95] Nevertheless, systematically administrated cytoprotective drugs have interrupted with antitumor efficacy of cisplatin and multidose of systemic steroids have also instigated additive toxicities,[96-98] whereas cytoprotective drugs are rapidly eliminated through the eustachian tube from otic region when dispensed intratympanically.[74] Since FDA has not approved any drug to evade cisplatin caused ototoxicity and connected hearing loss, signifying the need for suitable drug with best delivery method to prevent and repair the hearing loss in cancer patients, particularly young children.

DEX provides otoprotective effect against drug induced (cisplatin, gentamycin) ototoxicity thru various kind of mechanisms, viz. impeding apoptosis and pro-inflammatory cytokines, and upregulating antioxidant enzymes.[99-100] Systemic multidose and frequent administration of dexamethasone (DEX) have only moder-

**Table 1: Study design and results of nanoparticle-based drug delivery system against ototoxin and noise traumatized hearing loss. [IO]**

| Nanocarrier (size nm) | Drug/ Conc. | Ototoxin | *In vitro* model | *In vivo* model | Findings | Days on ABR measured | Route of delivery |
|---|---|---|---|---|---|---|---|
| DEX- PEG-PLA (130±4.78 nm) | DEX 10 mg/kg Dexamethasone (50 µg, 8%) | Cisplatin (12 mg/kg) | artificial perilymph and rat plasma. | Guinea pig | induced hearing Improvement at 4 and 8 kHz and protect hair cells (65%) at 6 kHz and no effect at high frequencies 16 kHz and 32 kHz. | 3 days after drug administration. | RWM - 1 hr before CDDP injection [102] |
| DEX- PEG-PLA (130±4.78 nm) | DEX 10 mg/kg (50 µg, 8%) | Cisplatin (12 mg/kg) | artificial perilymph | Guinea pig | Enhanced functional and histological protection against cisplatin-induced ototoxicity | 3 days after drug administration. | Intra-peritoneal -1hr prior to IO[101] |
| NP-MVE-15 and NP-MTOS-15 | 15%6α-methylprednisolone-(2 mg/ml) | Cisplatin (10 mg/kg) | HEI-OC1 auditory cell line | Wistar rats | NP-MVE-15 showed effective hearing and OHCs protection at all frequencies against CDDP toxicity 3 days after treatment | 3 days after drug administration. | Intratympanic right before IO[104] |
| Methacrylic derivatives of tocopheryl succinate or tocopherol (120–140) | Tocopheryl succinate (10%) or DEX (15%) | Cisplatin (10 mg/kg) | HEI-OC1 auditory cell line | Wistar rats | 15 dB of hearing improvement observed with better hair cell recovery at all frequencies by DEX- NPs Tocopheryl succinate-loaded NPs persuaded 10 dB improvement with hair cell recovery at 12, 20 and 32 kHz | 3 days after drug administration. | Intratympanic right before IO[78] |
| Poly(VI-*co*-HEI)-poly(VP-*co*-MTOS) NP | DEX (15%) | Cisplatin (10 mg/kg) | HEI-OC1 auditory cell line | Wistar rats | DEX-loaded Poly(VI-*co*-HEI)- poly(VP-*co*-MTOS) NP activated 10 dB of improvement at all measured frequency ranges. | 3 days after drug administration. | Intratympanic right before IO[103] |
| LPN (DMPC/mPEG-PLA 1:2) (90) | 1% ATX (50 µg/ml) | 60 µM Cisplatin for 24 hr | HEI-OC1 | zebrafish and guinea pigs | release profile in vitro (15 d) in vivo (24 hr). decreased ROS, | 3 days after drug. | RWM 4 hr prior to IO[127] |
| Silk-PEG-mDEX hydrogel | mDEX (2.5% w/v loading) | cisplatin (12 mg/kg) | HEI-OC1 | C57/BL6 mice | Auditory function was minimally protected | 5 days after drug administration. | RWM- 2 h prior to IO[110] |
| 15% SILK-PEG-8000 hydrogel NP | 8% w/v of DEX | Cisplatin (12 mg/kg) | Cultured cells organ of Corti culture | Mice model (C57/BL6) | Controlled and Longer drug release time. Reduced the cisplatin induced ototoxicity, organ of corti damage, and hearing loss at 4, 8, and 16 kHz. | 5 days after drug administration. | RWM- 2 hr prior to IO[114] |
| PEGylated PLGA -A666 peptide (158 ± 14 nm) | DEX (0.6 µg) | Cisplatin (12 mg/kg) | HEI-OC1 cells of transgenic mouse Immortomouse | Guinea pig | Subdued the cisplatin induced apoptosis by increasing antiapoptotic protein and Bcl-2, and cleaving caspase-3 formation. 20 and 10 dB of auditory enhancement at low and high frequencies. | 3 days after drug administration. | RWM - 4hr before IO[123] |

continued...

**Table 1: Cont'd.**

| Nanocarrier (size nm) | Drug/ Conc. | Ototoxin | *In vitro* model | *In vivo* model | Findings | Days on ABR measured | Route of delivery |
|---|---|---|---|---|---|---|---|
| Nanoencapsulated curcumin and dexamethasone, | Dexamethasone 10 and 20 mg/kg per day over 9 consecutive days | Cisplatin -total dose of 13 mg/kg for 7 consecutive days | HEI-OC1 cells | Hartley guinea pigs | Prevent hearing loss and damage to auditory cells by decreasing Cisplatin Ototoxicity | 1 day after the last cisplatin treament | Intraperitoneally - 24 hr before first day of cisplatin exposures[124] |
| Chitosan-SPION NPs (300 nm) | Methylprednisolone (0.15 µg) | 4 mg/kg of cisplatin for 4 days on and 10 days off (14-day cycles for the first 2 cycles) and 3rd cycle for 16-day (2 days on and 14 days off) | NA | Mouse (4 mg/kg for 1½ months) | Improvement in hearing loss and outer hair cell density by magnetic drug delivery method. | 1 day after the third cycle cisplatin injection | Intratympanic A day prior to second and third cisplatin cycle.[125] |
| Dex-Cat-PEG NPs (280) | Dexamethasone 0.14 mg/mL | kanamycin (500 mg/kg; furosemide (120 mg/kg) IP | human mucosal layer, HEI-OC1 | C57/BL6 mice | ABR test done on day 7, showed hearing protection (20 dB) and greater anti- inflammatory effect. | 7 days after treatment | intratympanic 2 h prior to IO[140] |
| NUFS B (250) | Dexamethasone 5mg/mL and | kanamycin (1000 mg/kg) and furosemide (180 mg/kg) IP | HEI-OC 1 | male BALB/c mice | Exhibited significantly better hearing by upregulating phosphorylated glucocorticoid receptors (P-GRs) in cochlear region at 8 kHz and 16 kHz. than the other two groups | *in vitro* 100 mg/mL and in vivo 20mg/mL ABR Two weeks after drug injection | Intratympanic 2 hr prior to IO[133] |
| SS31-PEG-PLGA -GGA (115) | Geranylgeranylacetone 27 µM | Gentamicin 200 µM -Acute(1h) Gentamicin 2 µM -Chronic(6h) | NA | zebrafish model | Accumulating in mitochondrial hair cells and diminished the activity of mechanoelectrical transduction (MET) channel | NA | 1 hr before IO[134] |
| Pluronic F-127 NP | Alpha-lipoic acid (5.0 mg/mL) | 5 mM kanamycin | artificial mucosa created from human | C57/BL6 mice | ameliorates hearing problem at four different frequencies | 4th and 7th day | Intratympanic 4 hr prior IO[141] |
| mPEG-PCL-GelMA hydrogel (220) | Artemisinin 4 mg/mL | Gentamicin intramuscular (120 mg·kg−1-d−1) for 14 days | NA | guinea pig | Reversing auditory function and cochlea pathomorphological change | 14th day | Intratympanic right after gentamycin[142] |
| PLGA nanocarriers | siRNA 100-500 pmol per mg of NPs. | 125 dB SPL centered at 4 kHz for 3 hr | Cochlear tissue explant | $p27^{kip1}$/-GFP transgenic of mouse pup | Inhibited HES1 mRNA levels and promote the regeneration of hair cells | 1 day after drug injection | RWM 24 hr after trauma[158] |
| PEG-coated PLA nanoparticles (116 nm) | betamethasone phosphate (BP) | 8 KHz at 120 dB for 2hr | NA | Male CBA/N mice | Glucocorticoid receptor (GR) activated in hair cells. Significantly improved auditory function on day 14th | 5 min 4, 7 and 14 days | Intravenously. (immediately after noise trauma)[156] |

continued...

**Table 1: Cont'd.**

| Nanocarrier (size nm) | Drug/ Conc. | Ototoxin | *In vitro* model | *In vivo* model | Findings | Days on ABR measured | Route of delivery |
|---|---|---|---|---|---|---|---|
| SLNs (93) | Edaravone 0.1 ml | 110 dB for 4 days at 2 h/d | NA | Guinea pigs | Intratympanic injection showed better protection than systematic use and | 1, 4 and 6 th day | intratympanic or intravenous (1st day after noise trauma )[17] |
| polyvinylpyrrolidone NPs(100-500) | hydrocortisone 5 mg/kg | 110 dB for 2 hr | NA | Rat | Notably change in auditory function within 1 day after treatment with single dose of hydrocortisonepovidone NPS | 1 and 24 hr and 7 days | Intravenous – (immediately after noise trauma) [163] |
| Hyaluronic acid gel containing PEGylated liposomes (146) | Dexamethasone phosphate (1.5 mg) | 5 kHz pure tone, 100 dB SPL for 1 hr | NA | Guinea pig | HA-DexP-Lip attained prolonged residence time without apparent histological changes and hearing recovery in the inner ear on day 7. | 0, 7 and 30 days | Intratympanic (2 days post noise trauma)[165] |
| Chitosan-hydrogel-PEGylated liposomes conjagated prestin peptide-1(87) | c-Jun kinase inhibitor-1, D-JNKi-1 | 115–120 dB broadband white noise between 6.3 kHz and 20 kHz for 4 hr | NA | Mouse | targeted D-JNKi-1 loaded tMFNP induced greater and consistent changes in hearing threshold shift after 14 days at all frequencies. | 1, 3, 7 and 14 days after noise | RWM -2 days before trauma [120] |

IO- Induced ototoxicity

ately rescued hearing functions that lost by the cisplatin ototoxicity in guinea pigs due to poor biocompatibility and rapid clearance from blood circulation. On the other hand, intraperitoneally administered (1 hr before cisplatin administration) single dose of polyethylene glycol-encapsulated polylactic acid nanoparticles encapsulated dexamethasone (PEG-PLA-DEX-NPs) encouragingly preserved the auditory function at 4, 8, 16, and 24 kHz frequencies and structural features of the cochlea in cisplatin pretreated guinea pig models, which were more effective than multidose (3 days) NP free DEX injection. This results clearly showed the sustained and target drug, DEX releasing ability of nanoparticles formulation.[101] PEG-PLA-DEX-NPs have also been directly administrated onto RWM, which is established as minimally invasive method to distribute drugs to the cochlea, to fight the chemotherapeutic drug toxin in guinea pigs.[102] Notably, single-dose administration of PEG-PLA-DEX-NPs have effortlessly penetrated RWM and accrued on the inner ear region, such as organ of corti, ganglion cells and stria vascularis and also continuously released DEX in the cochlear region of guinea pigs for up to 2 days, 1 day and 5 days in rat plasma and artificial perilymph respectively, which were considerably longer than free DEX. Furthermore, PEG-PLA-DEX-NPs hoarded outer hair cells from cisplatin toxicity and improved auditory function of inner ear at 4 kHz and 8 kHz frequencies. The observed negligible protection by PEG-PLA-DEX-NPs at the high frequencies (16 kHz and 32 kHz) was may be due to severe OHCs damage at basal (high frequency) than apex (lower frequency) turns of cochlea following cisplatin treatment.

Martín-Saldaña group developed pH-sensitive self-assembled polymeric nanocarriers for transporting antioxidant and anti-inflammatory drugs into the cochlea tissues by intratympanic route, exhibited some degree of efficiency for acute hearing loss.[78,103-104] Drug-loaded-polymeric NPs were able to release the payload when acidic environment triggered within the cochlea by increasing ROS and inflammation due to the cisplatin toxicity. Amphiphilic copolymers (CO-MVE and CO-MTOS) were prepared from N-vinyl pyrrolidone (VP) and methacrylic derivative of Vitamin E (MVE) and methacrylic derivative of α-tocopheryl succinate (MTOS) by free radical polymerization process in which, 6α-methylprednisolone was encapsulated into their inner core by surfactant free nanoprecipitation techniques to acquire spherical shaped (96 and 220 nm) self-assembled polymeric micelle NPs due to the presence of hydrophilic (VP) and hydrophobic segment ((MVE) or (MTOS) stability of these amphiphilic

polymers. MP-loaded polymeric NPs intratympanically administered in the middle ear of Wistar rat model followed by slow intraperitoneal injection of cisplatin (10 mg/kg) to study their otoprotection effect. ASSR were tested 3 days after cisplatin treatment, NP-MVE-15 and NP-MTOS-15 (15% w/w of drug to polymer ratio) resulted active in reversing hearing loss at all frequencies and cochlear toxicity of cisplatin. NP-MVE-15 nanoparticles highly reduced *in vitro* ototoxicity because of their free radical scavenging ability and higher encapsulation efficiency, which in turn greatly restore outer hair cells of the cochlea and deafness from cisplatin damage than other tested groups.[104] The MAPK pathway is assumed to be cause for apoptotic effect of cisplatin in the cochlea of inner ear. Spherical shaped (183.88 ± 6.26 nm) biocompatible *si*RNA-*MAPK1* loaded PLGA NPs have silenced the MAPK signaling against cisplatin triggered ototoxicity in sensory HEI-OC1 epithelial cells and protected hair cell loss in cochlear of murine organotypic culture by interminable release of siRNA payload.[105]

In another study, pH responsive amphiphilic copolymers with antioxidant and anti-inflammatory properties have been used as nanocarriers to improve therapeutic efficiency of anti-inflammatory drug, dexamethasone against ototoxicity ensuing the administration of high doses of cisplatin. Poly(VI-*co*-HEI) has been incorporated to poly(VP-*co*-MVE) or poly(VP-*co*-MTOS) by means of free radical polymerization process to fabricate the amphiphilic copolymeric nanocarriers, which was then precipitated with DEX to obtain the pH-sensitive NPs sizes of 179-210 nm. Encapsulation efficiencies (36-59%), isoelectric points that closely match the pH of infected tissue and precise hydrodynamic properties of DEX loaded pH sensitive nanoparticle system alleviated hearing loss in murine *in vivo* model, declined the caspase 3/7 expression, IL-1β release in hair cells on organ of corti, and intracellular ROS accumulation *in vitro* HEI-OC1 cells.[103] Adequate amount of dexamethasone and α-tocopheryl succinate loaded self-assembled micellar NPs have been successfully administered into the middle ear of Wistar rats by bullostomy to treat cisplatin ototoxicity. These cargos eased the ototoxicity, protected ABR threshold changes at 12, 20, and 32 frequencies and improved 15 dB of hearing function at all frequencies by downregulating caspase 3/7 and IL-1β release pathway.[78] Interestingly, nanoparticles were detected predominantly in the IHC basal turn of the cochlea than OHC by fluorescence microscope, after 2 hr post injection. Moreover, gradient decreased from basal, which is related with higher frequency hearing to apical turn.[78,103-104]

Taking advantages of solution to gel transformation and high affinity towards RWM of silk fibroin (SF) hydrogel, silk-polyethylene glycol (PEG) hydrogel has been tested as vehicles to deliver the drug in target site by RWM.[106-110] Administration of solution form of drugs were rapidly cleared through middle ear mucosa, which significantly reduces the interaction of drug to cochlea ear, whereas hydrogel formulations have provided longer exposure time to drug in the inner ear.[111-113] Yu and co-workers reported that optimized hydrogel formulation, silk-PEG-mDEX hydrogel (4% w/v loading) maintained the DEX quantity (100 ng/ml) in perilymph of guinea pigs for at least 10 days following thru round window membrane administration. Poor distribution of DEX in the inner ear was overcome by affixing ability of hydrogel to RWM, which aided to penetrate the sufficient concentration of DEX from the outermost layers into the inner ear. Auditory brainstem response technique results showed that the observed transient hearing threshold shift was successfully eliminated after 14 days, which was revealed by slight inflammatory reactions on the round window membrane and perilymph-filled tympanic duct in guinea pigs model.[110]

In order to achieve better drug loading, protract retention of DEX-loaded SILK-PEG hydrogel on RWM of ear, preparation of SILK-PEG-DEX hydrogel was optimized by altering concentration of polymers and silk in nanocarrier and DEX. In this study, 8% w/v of DEX loaded on the 15% SILK-PEG-8000 hydrogel to attain optimized DEX-SILK hydrogel formulation, in which concertation of silk was primary factor to determine the gelation time, DEX distribution, morphological characteristics, mechanical properties and viscosity of hydrogel formulation.[114] Only small number of nanospheres with homogeneous pores were unveiled for 10% of silk hydrogel formulation but many nanospheres with more dense pores were shown in 15% and 20% SILK-PEG-DEX hydrogels formulation, however, gelation time was negatively influenced in the case of 20% SILK-PEG-DEX hydrogel. *In vitro* (HEI-OC1 cells, mouse cochlea corti cultures) and *in vivo* (ototoxicity mouse model) DEX distribution and therapeutic result against cisplatin-induced tone deafness of water-soluble DEX-SILK-PEG hydrogel and lipid-soluble DEX -SILK-PEG hydrogel were evaluated and compared with previous report.[110] Notable difference *in vitro* and *in vivo* release profiles were found for 8% w/v of water-soluble DEX and for 8% w/v of lipid-soluble DEX released from 15% SILK-PEG8000 hydrogel nanocarrier. The detected sustainable release of DEX (168 hr for *in vitro* cells and 21 d for in mouse model) from lipid-soluble DEX-

SILK-PEG hydrogel was superior than release of DEX (less than 24 hr both *in vitro* and *in vivo*) from water-soluble DEX-SILK-PEG nano vehicle, which might be linked to the poor drug loading proficiency of water-soluble DEX in the hydrogel formulation. Moreover, low concertation of PEG (72%), high concentration of DEX loading (8%) on the silk hydrogel matrix and additional β-sheet structures with more homogeneous pore in the nanospheres could be the reason for longer and sustained release as compared to previous study (PEG 84%, DEX 2.5%). In addition, drug loaded nano vehicle, DEX-SILK-PEG hydrogel (8%, 15%, 72%) was injected directly onto the RWM of hearing-impaired animal model to examine the otoprotective efficiency of DEX after cisplatin exposure. Remarkably, end results of this study exhibited substantial protection against ototoxicity at 4, 8, and 16 kHz by inhibiting production of reactive oxygen species (ROS).[114]

Surface of lipid core nano capsules was grafted using peptides mimicking TrkB to deliver rolipram into tyrosine kinase B positive cells of cochlea for inhibiting cisplatin-induced apoptosis in murine inner ear. In the structure of LNC core-shell nano capsule, lipidic core of triglycerides and mineral oil was enclosed by polyethlenglycol (PEG) amphiphilic shell of lecithin and stearate.[115] Expectedly, versatile amendment to NP surfaces extensively changes the desirable properties of nanocarriers.[116-119] Prestin is well-known OHC-specific protein with extracellular domain and it is only found on outer hair cell and not found in any other cells present in cochlea. Currently, researcher has utilized prestin to transport otoprotective molecules in a cell-specific targeted way to the OHCs of the cochlea.[120-122] For example, surface of PEG -PLA modified with A666 peptide to effectively target prestin in outer hair cells (OHCs), which afford substantial protection against ototoxicity associated with use of cisplatin.[123] As shown in Figure 2, A666 molecules were conjugated at the distal end of PEG surface of amphiphilic polymers, Mal-PEG-PLA and mPEG-PLA to prepare A666-DEX-NP in which, ~3490 A666 peptide fragment had found on the exterior portion of each NP with mean distance of 4.85 nm between two adjacent PEG chains by CBQCA-based fluorescence techniques. Release profile of drug (DEX) in the perilymph and *in vivo* circulating time of DEX-NP and A666-DEX-NP indicated that decoration of A666 peptide did not improve aforementioned activity of DEX-NP, but A666 peptides on the outside of the NP unambiguously facilitated the accumulation of drug in the *in vitro* and *in vivo* outer hair cells (HEI- OC1) by interacting with prestin receptors which was predominantly upregulated

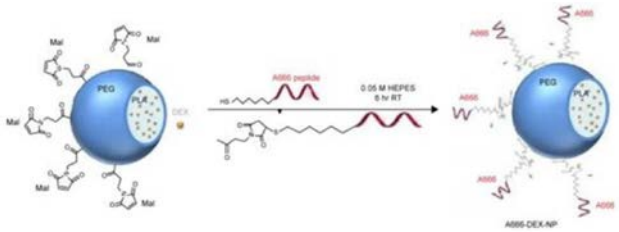

**Figure 2: Preparation of A666-DEX-NP. Adapted with permission from CC BY-NC.[123]**

in the plasma of HEI-OC1 tissues. Moreover, round window membrane route of infusion of A666-DEX-NP (4 hr before cisplatin treatment) delivered the DEX *in vitro* perilymph for 14 d and *in vivo* perilymph for 2 d in a long and sustained way. 80 ng/mL of A666-DEX-NP effectively rescued the OHCs from cisplatin damage and reversed the hearing loss associated with cisplatin at 4, 8, and 16 kHz by reducing the caspase-3 activity and apoptotic properties, and concentration of reactive oxygen species in cells in contrast to DEX and DEX-NP. In another study, effectiveness of combination (synergistic effects) of nanoencapsulated curcumin and dexamethasone in improving hearing loss caused by cisplatin were investigated. ABR test results identified that morphologic integrity protection and partial cochlea auditory function protection were found in guinea pig due to the synergistic action of nanoencapsulated curcumin and dexamethasone.[124]

In another study, prednisolone has been transported into the round window membrane of inner ear by using magnetic delivery approach with support of magnetic nanoparticles, chitosan nanocarriers encapsulated SPION (300 nm) to guard the inner ear of mice from systemic cisplatin-induced ototoxicity.[125] The observed slight loss of 9% of outer hair cells in the basal area of cochlear, better release of drug to the cochlea and prolonged drug exposure have evidenced the superiority of magnetic delivery method over drug-loaded nanoparticles alone and intratympanic free drug administration. Overall, magnetically delivered prednisolone have mitigated cisplatin mediated hearing loss damage at high frequencies by achieving high concentration of otoprotective agent in the perilymph and high circulation time of otoprotectant loaded nanoparticles in cochlea which in turn effectively preserving outer hair cells. Dexamethasone and salvianolic acid B (SAL) were covalent linked to form amphiphilic drug-drug conjugates thru an ester or amide bond, which were self-assembled into biocompatible nanoparticles (NPs). *In vitro* and *in vivo* otoprotection ability of conjugates NPs were notably greater than free

drugs and their physical mixture. Moreover, conjugates NPs predominantly have improved hair cell damage in HEI-OC1 cells and hair cells of zebrafish and reversed hearing loss in cisplatin pretreated guinea pig model by triggering the glucocorticoid receptor.[126] Glucocorticoid receptor pathway may be major mechanisms for otoprotective effects of DEX in DEX-SAL conjugates NPs and PEG-PLA-DEX-NPs.[102] Since ATX does not has ability to across membrane of round window, lipid-polymer hybrid nanoparticles (LPN) were used as vehicle for facilitating penetration, distribution, high concentration level of ATX in perilymph region. Remarkably, cisplatin mediated mitochondrial membrane potential change and cell apoptosis were successfully reversed by ATX-LPN, which were evidenced in JC-1 and Mito Tracker Green staining results. Percentage of survived OHCs (*in vitro* and *in vivo*) at the basal, middle and apex turns were measured by confocal microscope and fluorescence microscope. Pretreatment of AST-LPN rescued 32% of OHCs in zebrafish, approximately 30.33%of OHCs in cultured organ of corti and greatest number of OHCs in guinea pig model and blocked mitochondrial fragmentation, expression of caspase-3 and cytochrome-c (mitogen-activated protein kinase signaling route) as well. The resulting protective effect at all detected ABR threshold frequencies (2 kHz ,2.8 kHz, 4 kHz, 5.6 kHz, 8 kHz, 11.3 kHz, 16 kHz and 22.6 kHz) have verified that ATX-LPN moderately reversed hearing damage induced by cisplatin on the day 3 after RWM administration.[127] Damage of OHCs mainly resulted in the activation of caspase dependent pathway. The results clearly demonstrated that A666-DEX NPs[123] and ATX[127] formulations had reduced pro-apoptotic protein, cascade of caspases-3 activity and consequently attenuated apoptosis in animal model that induced from cisplatin ototoxicity.

## Aminoglycosides Induced Hearing Loss

Intravenously injected antibiotics, including aminoglycosides (tobramycin, neomycin, gentamicin, amikacin, and kanamycin) and the glycopeptide vancomycin and platinum containing chemotherapeutic drugs, namely cisplatin and carboplatin are the most commonly involved in causing ototoxicity followed by non-mechanical hearing loss.[128-129] Clinically, aminoglycosides can enter thru the stria vascularis, accumulate in the inner ear and absorbed either by endocytosis or transduction channels.[130] These drugs persuade cell necrosis and apoptosis in the ear, which in turn destroy mechano-sensory hair cells, resulting to hearing loss or even deafness.[131-132]

To circumvent low penetration competence of dexamethasone sodium phosphate (Dex-SP) into the site of location, three different types of dexamethasone nanosuspensions (NUFS A, NUFS B and, NUFS C) with approximately 250 and 350 nm size were fabricated by merging PEG-40 stearate polymer, surfactant (fat and supercritical fluid (NUFS$^{TM}$)), saccharide, poloxamer 188 and PVP. Of these, NUFS B nanosuspension was selected based on their size, higher dissolution rate and stability for further studies. DEX loaded nanosuspensions were prevail in suspension state for more than eight hours, which avoids quick elimination of DEX from middle ear cavity, as opposed to solution formulations. Nanosuspension, NUFS B steadily released the drug for up to 6 hr in the perilymph and cochlear tissues and showed safety (no inflammatory reaction and damage in the inner ear tissue and tympanic membrane) up to 20 mg/ml and 100 µg/mL concentration range under both *in vivo* and *in vitro* conditions respectively. NUFS B intratympanically injected 2h prior to induction of ototoxicity (intraperitoneal injection of kanamycin) in the middle ear of BALB/c mice model. As the otoprotective results of NUFS B nanosuspension and it provided greater hearing protection to cochlear tissue of mice against kanamycin ototoxicity than free Dex-SP. Figure 3 indicated that NUFS B group showed considerably better hearing at 8 kHz and 16 kHz and very less damage on the organ of corti, because of superior cell membrane permeation and absorption in the tissue than Dex-SP group.[133]

Xiao and co-workers synthesized mitochondrial targeting SS31 peptide functionalized GGA loaded poly(lactic-co-glycolic acid) (PLGA) nanocarrier to defend inner hair cell injury caused by gentamicin in zebrafish model. The drug, GGA release profiles of SS31-PEG-PLGA-GGA NPs and PEG-PLGA- GGA NPs specified that amendment of PLGA NPs surface with SS31 peptide did not evocatively change drug release pattern. GGA loaded SS31-PEG-PLGA NPs improved zebrafish lateral outer and inner hair cell endurance from 63.7 ±14.2% to 92.8 ±6.14% and 50.5 ±17.2% to 84.9 ±9.6% for acute gentamicin exposure (1hr) and chronic gentamicin exposure (6hr) respectively than unmodified GGA loaded PLGA NPs, which proved the mitochondrial specific accumulation of SS31-PEG-PLGA-GGA NPs in hair cells.[134] Similarly, SS-31 peptide were used to modify minocycline loaded liposomes NPs for recovering mechano transduction channels in the hair cells and hair cell survival after gentamicin induced toxicity in a zebrafish model.[135] In another study, triphenylphosphonium (TPP) cation was coupled with poly(lactic-*co*-glycolic acid) nanoparticles (PLGA NPs) to generate 145 nm mitochondria-

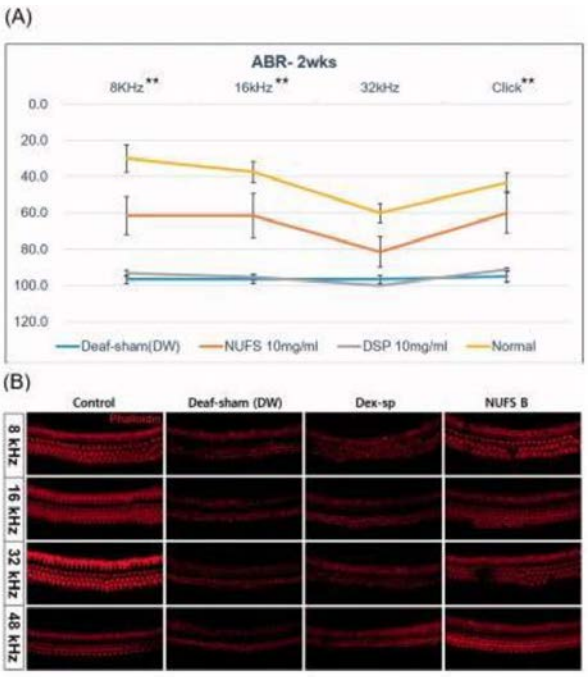


**Figure 3: The therapeutic results of NUFS B in an ototoxic preclinical model. (A) The auditory brainstem response (ABR) thresholds of the three groups were detected 14 days after aminoglycoside induced toxicity. Only the 10 mg/mL NUFS B group unveiled better hearing function than the other two groups at two different frequencies (8 and 16 kHz and the click sound). (B) We observed the whole organ of Corti using confocal microscopy, the stereocilia of the deaf-sham group and the Dex-SP group were highly hurt at all frequency, whereas those of NUFS B group displayed less hurt than those of the other two groups. Adapted with permission from CC BY-NC.[133]**

targeting NPs for shutting down hair cell injury of gentamicin ototoxicity in zebrafish animal model by releasing GGA successfully into the site of action. Mitochondria-targeting platform augmented the hair cells survival from 36% to 69% and 20% to 62% under acute exposure and chronic exposure of gentamycin respectively. These results indicated that alteration of NPs with mitochondrial targeting TTP cations or SS31 peptide promisingly alleviated gentamycin mediated hearing loss as contrast to free drugs and untargeted NPs.[136]

Four different phospholipid nanoparticles (neutral, anionic, cationic, and cationic-PEG nanoparticles) were prepared to examine the distribution proficiency of drug loaded phospholipid nano emulsions in the inner ear in terms of their surface charges, in which three dimensional human mucosal 100 mm thick layer model, comparable with the human RWM (about 70 mm) was used as *in vitro* model. Based upon multiple *in vitro* and *in vivo* screening results, Cat-PEG nanoparticles were evinced to be highly absorbed in hair cells, organ of corti and perilymph. It is well documented that positively charged particles have high tendency to bind with negatively charged glycoproteins cell surface.[32,137-139] Dex-Cat-PEG NPs and free Dex were injected to middle ear cavity of mouse 2 hr before to the induction of ototoxicity (500 mg/kg of kanamycin and 120 mg/kg of furosemide injected subcutaneous and intraperitoneal respectively) to observe *in vivo* otoprotection effect. Dex-Cat-PEG NP absorbed in the spiral ganglion, spiral lamina and medial portion of modiolus slightly more than free DEX but not statistically different, whereas, Deaf-Cat-PEG-Dex highly secured stereocilia, inner ear tissues and hair cells and showed only slight damage on organs of corti at the 16 kHz site as compared to free Dex.[140]

Antioxidant, Alpha-lipoic acid (ALA) conjugated within the pluronic F127 NPs and conserved kanamycin induced hearing impairment and outer hair cells located in the organ of corti by rising Nrf2, HO-1, SOD-1, and SOD-2 antioxidant proteins levels. *In vitro* mucosal permeation and *in vivo* NPs distribution capability of ALA-NPs were greater than free ALA. 190 nm sized ALA-NPs intratympanically inoculated into cavity of the mice middle ear 4 hr prior to 5 mM kanamycin treatment, exhibiting better hearing protection on the 7$^{th}$ day at 4 kHz, 8 kHz, 16 kHz and 32 kHz by activating NRF2/HO1 antioxidant pathway.[141] Like, 210 nm artemisinin-loaded mPEG-PCL-based GelMA hydrogel, mPEG-PCL-ART-GelMA-NPs was synthesized by double emulsion process and its efficiency on restoring auditory function and inner ear morphology from gentamicin induced ototoxicity was also explored. Histological evaluation of guinea pig cochlea demonstrated that intratympanic administration of mPEG-PCL-ART-GelMA-NPs significantly improved the inner ear damages such as vessels fracture, structure helical primary zone, vascular morphology and basement membrane structure, evidencing controlled ART release and high cumulative skin penetration activity of hydro gel nanocarrier. ABR was measured 14 days after administration, thus resulting better auditory function in gentamycin toxicity mediated guinea pig ear damage model.[142]

## Noise-induced Hearing Loss (NIHL)

Generally, the noise above 85 dB is regarded as harmful to auditory nerve system,[143] which is characterized by high-frequency auditory threshold shift.[144] Mild or acute noise trauma can be accountable for temporary hearing threshold shift (TTS),[145-146] which can be reversed by regeneration of two different types of hair cell and hearing nerve fiber using glucocorticoid treatment,[147-148]

whereas overexposure and/ or strong sound vibrations of harmful noise can trigger permanent threshold shift (PTS), resulting to the irreversible HCs regeneration and auditory nerve deterioration,[143,149] Hair cells, especially outer hair cells (OHCs), auditory nerve deterioration, synaptic ribbon reduction and tympanic membrane perforation are the crucial targets of acoustic trauma.[150-152] Various studies have evidenced that necrosis and apoptosis detected in the sensory epithelium after exposed to harmful noise trauma,[150,153-155] thus target specific nanoparticle-based drug delivery system is needed to targeting TNF-*a* inhibition, oxidative stress, inflammation, or noise-induced neuropathy. It is noted that decrease of blood flow and excessive free radical production are closely related pathogenesis of NIHL.

Surface of PEG-DSPE NP was altered with prestin-targeting peptide2 (PrTP2), which support for accumulation of drug loaded NPs in outer hair cell zones and poly(propylene sulfide)$_{120}$ (PPS$_{120}$), which scavenges ROS to form ROS responsive nano carrier PL-PPS/BBR. In the ROS milieu, drug, berberine (BBR) expertly released from nanoparticle when poly(propylene sulfide)$_{120}$ transformed to poly(propylene sulfoxide)$_{12}$ by means of scavenging reactive oxygen species. As expected, drug loaded ROS responsive PL-PPS/BBR retained morphological integrity of OHCs as a result of high absorption rate in basal, apex, middle areas of OHCs, evidencing the OHC targeted delivery. The auditory brainstem response (ABR) was tested on day 14, hearing impairment was greatly reduced in noise-induced hearing loss (NIHL) murine model by onsite release of antioxidant barbering from ROS responsive PL-PPS/BBR.[121] FDA approved polyethylene glycol (PEG) based poly lactic acid (PLA) NPs was fabricated with betamethasone phosphate (BP) to release BP in the cochlea for 24 hr in a sustained way, (enhancing survival of hair cell in mouse model after exposure to traumatic noise by improving therapeutic potential of BP. Increase of GR nuclear translocation in OHCs of cochleae indicated that drugs distributed from NPs rescued hearing activity by activating GRs in hair cells. This PEG-coated PLA nanoparticles attenuated cochleae damage by nuclear GR signaling pathway.[156] Metal organic framework-based zeolitic imidazolate (ZIF) nano system encapsulated methylprednisolone (MP), MP@ZIF-90 NP was used first time for the treatment of noise-traumatized hearing impairment in preclinical animal model. Intraperitoneal injected 120 nm of MP@ZIF-90 NP protected the drug from entering peripheral blood circulation, displayed negligible nephrotoxicity and damage to the inner ear structure than free drug during treatment.[157]

Du and colleagues used biocompatible poly(lactide-*co*-glycolide acid) nano vehicle to deliver *Hes1* siRNA for regenerating the damaged hair cells *in vitro* (cultured cochlea tissue) and mouse pup models pre-treated with hair cell toxins (4-hydroxy-2-nonenal or neomycin) by knocking down the Notch-responsive activators, *Hes1* and *Hes5* mRNA levels.[158] Previous reports have indicated that rejuvenation of new hair cells (HCs) in animal models cochleae can be accelerated by using the notch signaling route,[159-162] which plays a key role in defining specification and succeeding cell fate of otic sensory region. Results presented in this work demonstrating the appearance of new outer hair cells in organ of corti and vestibular maculae of mouse pup by hindering of notch signaling and up-regulating *Atoh1* expression and PLGA polymeric based NPs may be better nanocarrier to distribute siRNA specific inner ear regions and suitable approach to treat noise mediated hearing damage.

Since the reduction of excessive reactive oxygen species and inflammation in the cochlea are two important objectives for attenuates noise-induced injury in the cochleae, solid-lipid nano carrier entrapped edaravone was synthesized with 76.7% drug loading efficiency by ultrasound technique to upsurge the free radical scavenging ability of edaravone. 2 hr/d for 4 days, animals were pre-treated with 110 dB noise (SPL) at 0.25–4.0 kHz and edaravone SLNs was intratympanically or intravenously administrated after the 1st day of noise treatment. Considerable ROS and hearing thresholds reduction without changing ratio of outer hair cell (OHC) damage were observed for intratympanic delivery of edaravone SLNs to the inner ear than intravenous delivery method. Results determined that local application of SLNs might effectively protect cochlea from noise exposure due to the sustained drug release.[17] Likewise, otoprotective result of steroid, hydrocortisone was also investigated on the Wister rat with acute noise damaged auditory system. In this case, hydrocortisone entrapped povidone (polyvinylpyrrolidone) NPs were injected intravenously subsequent acoustic stimulation at 110 dB noise for 2 hr at 5 kHz frequency and the amplitude of otoacoustic emission was recorded on 1 and 24 hr and 7 days after the noise trauma at 4-6.4 kHz frequency resulted in relatively better otoprotective effect of single injection hydrocortisone-povidone NPs within 1 day than those of free drug.[163] Liposomes NPs particles have been extensively used as drug transport vehicle for a variety of payloads. Hyaluronic acid gel conjugated PEGylated liposomes NPs (HA-Lip) have been used to deliver the dexamethasone phosphate (DexP) into middle

ear of noise-induced guinea pig model for evaluating otoprotection ability. In the previous study, this liposome based hyaluronic acid specific gel formulation released the high dexamethasone phosphate content in the perilymph of guinea pigs for at least 30 days in a sustained manner.[164] Despite the formulation has maintained therapeutic drug concentration level in target site and promoted sustained drug release for 30 days due to the longer residence time of gels and controlled drug release profile of liposome part of NPs respectively, no hearing regain was observed at all recorded frequency on day 0 and 7 when HA-DexP-Lip NP injected transtympanically 48 hr after moderate noise-exposure.[165]

It is important to develop nanocarrier that offer controlled and sustainable drug or biomaterial discharge profile to circumvent inconsistent therapeutic results. Highly versatile chitosan glycerophosphate (CGP)-hydrogel system, which can transform the liquid (at room temperature) into semi-gel state (at physiological temperature 37°C). This temperature responsive transition permits the hydrogel, chitosan glycerophosphate (CGP)- to sticky on the RWN and distribute payloads exclusively into the inner ear. Kayyali and co-workers constructed chitosan glycerophosphate (CGP)-hydrogel based targeted multifunctional nanocarrier (tMFNP) strategy by means of thin-film hydration technique to release payloads (c-Jun N-terminal kinase (JNK) inhibitor and D-JNKi-1) into OHCs of the inner ear, in which PrTP1 (Prestin Targeting Peptide 1) was used to target extracellular domains of prestin that solely expressed in OHCs. Flow cytometry and fluorescence microscopy studies were performed to determine *in vivo* binding capability of tMFNPs to prestin on OHCs, demonstrating the tMFNPs enormously bound to OHCs than untargeted NPs due to the presence of conjugated targeting PrTP1 in the former one. It was clearly shown that tMFNPs were found in both mid-basal (high frequency) and apical (low frequency) region of the cochlea while untargeted MFNPs were observed only in the mid-basal region. Apical area is important for speech perception and not easily accessible by means of currently existing drug delivery techniques. Thus, it was obvious that PrTP1-conjugated MFNPs carrier could effectively release the payloads into the specific cell type of cochlea. D-JNKi-1 loaded chitosan-gel coated PEGylated liposomes conjugated prestin targeting PrTP1 NPs (tMFNPs) and D-JNKi-1 loaded untargeted MFNPs were accommodated on the round window niche of mice 2 days prior to noise trauma and ABR test were recorded at various time-intervals (2 days prior noise induction, 1, 3, 7 and 14 days after noise) to compare the therapeutic efficacy of D-JNKi-1 loaded targeted tMFNPs and D-JNKi-1 loaded untargeted MFNPs, resulted in reasonable concentrations of JNK inhibitor on the outer hair cells because of the prestin targeting peptide of tMFNPs and subsequent protection of the hearing function from the noise insult than untargeted MFNPs . As illustrated in Figure 4 A targeted D-JNKi-1 tMFNPs greatly amended the hearing threshold at 4 and 8 kHz frequencies, in contrasts with minimal threshold shift observed for untargeted D-JNKi-1 MFNPs (Figure 4 C and D), which was consistent with binding of more tMFNPs on the apical OHCs compared to untargeted MFNPs. Both targeted and untargeted D-JNKi-1-MFNPs have achieved almost comparable partial preventive effect at 16, 24 and 32 kHz (Figure 4 E–G), but targeted D-JNKi-1 tMFNPs consistently improved the hearing threshold shift compared to inconsistent results acquired by untargeted d-JNKi-1 MFNPs.[120]

## CONCLUSION

Stress stimulators like cisplatin, aminoglycoside antibiotics and exposure to loud noise are key source for provoking auditory nerve deterioration, oxidative imbalance, injuries and inflammation in cochlear hair cells and spiral ganglion neurons, leading to sensorineural hearing

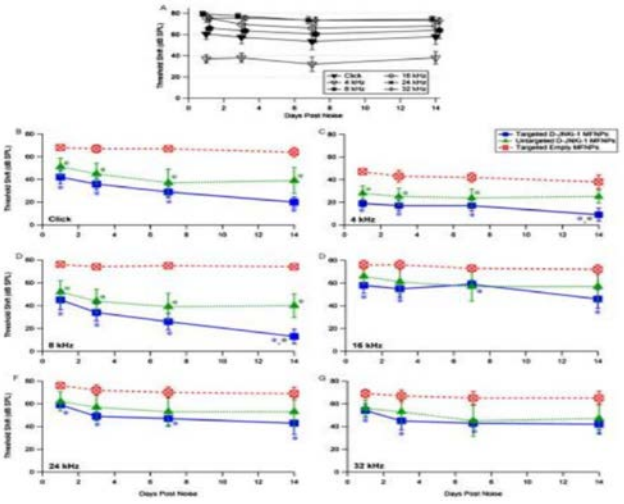

**Figure 4: A) Acoustic trauma paradigm cause a permanent stable threshold shift over 14 days (n = 10). Mice were treated with 115–120 dB noise for 4 hr. Data for 4, 8, 24 and 32 kHz are offset for clarity. Pretreatment with D-JNKi-1 2 d prior to noise trauma provides partial defense activity to mice from acoustic trauma up to 14 d post noise for almost all frequencies measured. Hearing threshold shifts for targeted empty (red), targeted D-JNKi-1 (blue) and untargeted D-JNKi-1 (green) MFNPs are manifested for responses to (B) Click, (C) 4, (D) 8, (E) 16, (F) 24 and (G) 32 kHz. Adapted with permission from; Copyright 2018 Elsevier.[120]**

disorder in both adult and young population. Therefore, conservation of leftover hair cells and restoration of damaged hair cell from ototoxicity and noise trauma are one of the crucial tasks for pharmacotherapy. NPs have greatly improved antioxidant, anti-inflammatory and genetic material delivery to the inner ear and thereby proceeding virtuous therapeutic outcome. It is proved that membrane accessibility, high loading capacity, specific targeting and small size, biotherapeutic stability of NPs enabled the pharmaceuticals magnificently enter RWM than free drugs and thus offer better noninvasive treatment for hearing loss without side effects. Different types of inner ear biocompatible NPs with promising alteration such as surface modification, ROS responsive, hydrogel, magnetic targeted, and functional targeting treatment have provoked the degeneration of cell damage and/or reverse hair cell loss in preclinical models. However, specific action of the nanocarrier drug delivery approach in recuperating sensorineural hearing loss is still ambiguous. In some studies, NP loaded therapy were introduced before trauma was triggered to increase the content of therapeutic materials easily obtainable in the inner ear and this study paradigm is mostly suitable for drug (cisplatin and aminoglycoside) mediated hearing impairment treatment. Further extensive studies are needed to verify efficacy and cochlea safety of these nanoparticle-based treatment.

When comparing intratympanic, systemic application of drugs were ineffective for SNHL treatment may be due to the off-target effects. Furthermore, surface modification by specific molecules on NPs endows targeting capability for precise homing and following better treatment. Cell specific proteins inside the cochlea cells (e.g., hair, supporting and spiral ganglion cells, and stria vascularis) can be used as targets for site specific inner ear otoprotective materials delivery. Preclinical therapeutic outcomes of different type of nano carriers (ROS responsive, PEGand hydrogel NPs etc.) loaded with various pharmaceuticals have been tested against various degrees of noise traumatized hearing impairment. It should be noted that hearing capacity have been reinstated in most of the case following drugs transported into noise trauma animal models either before or after noise exposure, but some NPs systems did not show any positive effects or showed small hearing gain. Some drug loaded nanocarriers discussed in this review did not show substantial *in vivo* hearing recovery, despite they have inhibited free radical production in the cochlea, persevered in the inner ear for longer time. Hence, interaction between the drug and vehicle, biosafety of nonvehicle and the causative mechanisms inducing sensorineural hair cell death and cochlea injury should be further assessed. Understanding the potential benefits, advancement and hitches of NP drug delivery strategies in preventing or treating stress stimulators (sound exposure, cisplatin and aminoglycosides) induced sensorineural hearing disorders will enable to select future therapeutic options and convert preclinical findings to clinical settings.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATION

**ASSR:** auditory steady-state responses; **FDA:** Food and Drug Administration; **Cisplatin:** (cis-diamminedichloroplatinum); **MAPK:** mitogen-activated protein kinase; **siRNA:** Small interfering RNA; **PEG-PLA:** polyethylene glycol-coated polylactic acid; **VI:** 1-vinylimidazole; **VP:** *N*-vinylpyrrolidone; **HEI:** methacrylic derivatives of ibuprofen; **MVE:** α-tocopherol; **MTOS:** α-tocopheryl succinate; **ABR:** auditory brainstem response; **Silk-PEG:** hydrogel, silk fibroin-polyethylene glycol; **mDEX:** micronized dexamethasone; **SF:** Silk fibroin; **DMPC:** 1,2-Dimyristoyl -sn-glycero-3-phos- phocholine; **mPEG-PLA:** methoxy (polyethylene glycol)- poly(lactide); **HEI-OC1:** House Ear Institute Organ of Corti-1; **PVP:** polyvinylpyrrolidone; **GGA:** geranylgeranylacetone; **OHC:** outer hair cells, IO- Induced ototoxicity.

## SUMMARY

Stress stimulants such as cisplatin, aminoglycoside antibiotics, and loud noise exposure are all known to cause auditory nerve deterioration, oxidative imbalance, injuries, and inflammation in cochlear hair cells and spiral ganglion neurons, resulting in sensorineural hearing loss in adults and children.

It should be highlighted that hearing capacity was restored in the majority of cases after medicines were administered to noise trauma animal models either before or after noise exposure, although some NPs systems exhibited no or only minor hearing gain.

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