Expert Opinion

Intracochlear drug delivery systems

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Introduction: Advances in molecular biology and in the basic understanding of the mechanisms associated with sensorineural hearing loss and other diseases of the inner ear are paving the way towards new approaches for treatments for millions of patients. However, the cochlea is a particularly challenging target for drug therapy, and new technologies will be required to provide safe and efficacious delivery of these compounds. Emerging delivery systems based on microfluidic technologies are showing promise as a means for direct intracochlear delivery. Ultimately, these systems may serve as a means for extended delivery of regenerative compounds to restore hearing in patients suffering from a host of auditory diseases.

Areas covered: Recent progress in the development of drug delivery systems capable of direct intracochlear delivery is reviewed, including passive systems such as osmotic pumps, active microfluidic devices and systems combined with currently available devices such as cochlear implants. The aim of this article is to provide a concise review of intracochlear drug delivery systems currently under development and ultimately capable of being combined with emerging therapeutic compounds for the treatment of inner ear diseases.

Expert opinion: Safe and efficacious treatment of auditory diseases will require the development of microscale delivery devices, capable of extended operation and direct application to the inner ear. These advances will require miniaturization and integration of multiple functions, including drug storage, delivery, power management and sensing, ultimately enabling closed-loop control and timed-sequence delivery devices for treatment of these diseases.

Keywords: computational models, drug delivery, hair cells, intracochlear, microelectronics, microfluidics, regeneration

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1. Introduction

Disorders of the inner ear comprise the largest and most serious class of diseases responsible for hearing loss, with 250 million people worldwide suffering from disabling hearing loss [1]. In the US alone, 28 million patients suffer from sensorineural hearing loss (SNHL), a condition that currently causes an irreversible decline in cochlear function, and profound deafness remains the most prevalent serious medical condition at birth, with 3 in 1000 newborns suffering from this condition. In addition to these auditory disorders, a host of vestibular conditions such as Meniere's disease affect millions of patients, and tinnitus remains an intractable problem for many patients and the most common and expensive condition for the US Department of Defense treating Armed Forces personnel who have suffered a blast-related injury [2] with tympanic membrane [3]. A partial list of inner ear diseases potentially amenable to intracochlear drug delivery is provided in **Table 1**.

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Article highlights.

- Local drug delivery systems represent a very high priority for next-generation clinical approaches for treatment of diseases of the inner ear
- Diseases of the inner ear affect the lives of hundreds of millions of patients worldwide
- Passive delivery systems have been explored as a means to overcome barriers to delivery of compounds to the inner ear
- Active delivery systems capable of extended, programmable delivery are emerging in response to needs related to specific inner ear diseases
- Further miniaturization and integration of delivery and sensing functions will be required for the development of implantable intracochlear drug delivery systems

This box summarizes key points contained in the article.

Spurred by the rising incidence of inner ear diseases, researchers have made significant advances in understanding the basic mechanisms and molecular biology of diseases of the inner ear and have identified potential pathways for regeneration and restoration of hair cell and neural cell function in the inner ear [1]. These approaches encompass the use of stem cells, gene therapy as well as neurotrophin- and RNA-interference-based systems. While significant hurdles remain before these therapies become available for human clinical use, they hold promise as avenues for restoration of hearing and other inner ear functions for patients with no currently available treatment for these devastating diseases [4]. The principal challenge in treatment of inner ear diseases remains the inaccessibility of targets for therapy, due largely to the presence of the blood–cochlear barrier. Oral medications are typically blocked by the blood–cochlear barrier and, therefore, clinicians have resorted to delivering drugs intratympanically for a range of auditory and vestibular conditions [5]. Intratympanic delivery of compounds for treatment of inner ear diseases relies on diffusion through the round window membrane (RWM), a structure with widely disparate transport properties depending on the patient and disease state. This variability results in poor dosage control, and coupled with the reliance on passive diffusion mechanisms to transport drugs along the length of the cochlea, has limited the effectiveness of intratympanic delivery. Recent efforts have, therefore, shifted toward intracochlear drug delivery approaches, the subject of this review, as a means to directly and controllably deliver medications to specific targets in the inner ear [6].

Intracochlear delivery systems typically comprise micropumps with active or passive control systems, either as a standalone device or in combination with a cochlear implant. Initial efforts have focused on the use of osmotic pumps [7,8], passive devices that are sufficiently small to enable implantation but have limited lifetime and lack control over delivery parameters [9,10]. More recently, microfluidic systems have emerged, providing either constant drug infusion [11-14] or reciprocating delivery using a micropump [15-18]. These approaches offer the opportunity to provide precise control over delivery, for extended periods of treatment, and with the potential for combination therapies in a timed-sequence fashion. In addition to demonstrating efficacy, these systems must be proven safe, with a low risk of infection and avoidance of repeated surgical procedures or damage to hearing structures with associated further hearing loss. Further, they may be combined with sensors for real-time measurement of drug concentration, flow rate and bioactivity. One avenue for clinical introduction of these delivery systems is the integration of a delivery device with a cochlear implant, thus providing regenerative therapy as well as restoring hearing [19-21]. These emerging technologies and the intracochlear systems will enable having the potential to revolutionize treatment of diseases of the inner ear.

2. Inner ear diseases and therapeutic approaches

2.1 Cochlear physiology and function: considerations for drug delivery systems

The cochlea, the organ of hearing, resides along with the vestibular organ in the inner ear and is responsible for converting mechanical signals from the middle ear into electrical signals that are transmitted along the auditory nerve toward the brainstem. It is the small size and remote location of the cochlea that renders direct drug delivery to the organ so difficult. The cochlea, roughly 32 mm in length in humans, comprises three coiled fluid-filled tubes, the scala tympani (ST), scala vestibuli and scala media [22]. The ST terminates at the RWM, a structure that may be used for direct intracochlear delivery as is described later. The scala vestibuli terminates at the oval window, which houses the stapes or footplate that transmits mechanical signals from the middle ear. The scala vestibuli and tympani connect to each other at the apex of the cochlea via the helicotrema. Sound from the outer ear causes motion of the eardrum or tympanic membrane, which in turn generates motion of the fluids in the inner ear. The cochlea contains the Organ of Corti, which comprises three rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs) along a basilar membrane. The IHCs respond to the waveform of a sound stimulus by releasing neurotransmitters to activate auditory nerve fibers. Loss of function of the hair cells and auditory neurons results in hearing loss, and one of the prevailing goals of intracochlear drug delivery systems is to provide therapeutic agents directly to the cochlea to effect regeneration of these sensorineural cells [23].

The two principal fluids present in the cochlea are perilymph and endolymph. Perilymph bears some similarities to cerebrospinal fluid (CSF), but its protein concentration is roughly an order of magnitude higher than CSF and its composition is slightly different [24,25]. Perilymph is in direct contact with the basolateral surface of the hair cells and auditory neurons; its composition is of importance in

Table 1. Partial list of inner ear diseases potentially amenable to intracochlear drug delivery along with salient comments regarding the patient population and broad requirements for each condition.

Inner ear disease	Considerations for drug delivery
Sensorineural hearing loss	Largest patient population May require extended delivery of multiple compounds for regeneration
Noise-induced hearing loss	Large and rapidly growing patient population May require timed-sequenced delivery High priority for Department of Defense
Sudden sensorineural hearing loss	Rapid intervention required Therapeutics suitable for local delivery may already exist
Autoimmune inner ear disease	Small patient population but urgent need Therapeutics suitable for local delivery may already exist
Meniere's disease	Relatively large patient population May require patient-controlled burst delivery
Tinnitus	Very large patient population with complex spectrum
Cisplatin ototoxicity protection	Very important for pediatric population Therapeutics suitable for local delivery may already exist Duration of delivery weeks to months
Radiation-induced ototoxicity protection	Occurs in large percentage of patients with a range of head and neck tumors Duration of delivery weeks to months
Cranial nerve schwannoma	Potential alternative to surgery May require extended delivery

understanding drug delivery kinetics in the cochlea [26]. Endolymph, the fluid contained within the scala media, bathes the apical surface of hair cells and has an ionic composition similar to the intracellular fluid environment. The cochlea contains a highly vascularized region known as the stria vascularis that maintains a unique electrochemical environment which supports transduction of sound by the IHC.

Surgical access to the inner ear is perhaps the most critical aspect of direct intracochlear drug delivery. As mentioned earlier, one potential route of administration is directly through the RWM, thereby eliminating the challenge intratympanic delivery methods encounter related to compound diffusion across the membrane. Another potential access point for intracochlear drug delivery is through a cochleostomy, a hole drilled surgically through the cochlear bone [27]. A cochleostomy into the ST has been established as the preferred entry technique for insertion of multi-electrode cochlear implants [28]. Minimization of surgical trauma associated with this technique is important for preservation of residual hearing structures in cochlear implant recipients. For drug delivery applications, preservation of hearing structures and minimization of surgical trauma are paramount. Other important aspects of the surgical procedure and placement of drug delivery devices that are beyond the scope of this review are the establishment of a robust, leak-proof seal at the site of insertion of the delivery system and avoidance of foreign body rejection, inflammatory response and biofouling of the device by the patient's immune system.

Functional assessment of hearing utilizes a well-established set of electrophysiological parameters with known effects on specific hearing structures. These include distortion product otoacoustic emissions (DPOAE) and the auditory brainstem response [29], both of which are useful clinically but discussed here in the context of intracochlear drug delivery experiments. In addition, compound action potential (CAP) measurements are often used in drug delivery experiments to evaluate delivery kinetics. Each of these can be assessed at specific frequencies; the tonotopic arrangement of the cochlea provides a spatial map of hair cell function due to the correlation between particular frequency response and position along the length of the cochlea, as shown in **Figure 1**. Measurement of DPOAE is accomplished by introducing two tone pips with predetermined sound levels and frequencies into the ear canal; the inner ear generates acoustic emissions as a result of mechanical motion of the basilar membrane that provide a direct assessment of the function of the OHC. One particularly useful application of DPOAE measurements in drug delivery experiments is as a baseline measurement to assess surgically-induced trauma [30,31]. The CAP measurement is a far-field electrocochleographic technique that monitors nerve fiber response to tone pips, often by using a ball electrode positioned in the vicinity of the RWM [32]. This technique can be used as a measure of cochlear function at specific frequencies, providing a map of hair cell function through the cochlea during drug delivery experiments.

Assessment of pharmacokinetics and pharmacodynamics are critical aspects of the development of drug delivery systems [33]. For intracochlear delivery, these present particular challenges because of the remoteness and small size of hearing structures, and difficulties in imaging drug transport.

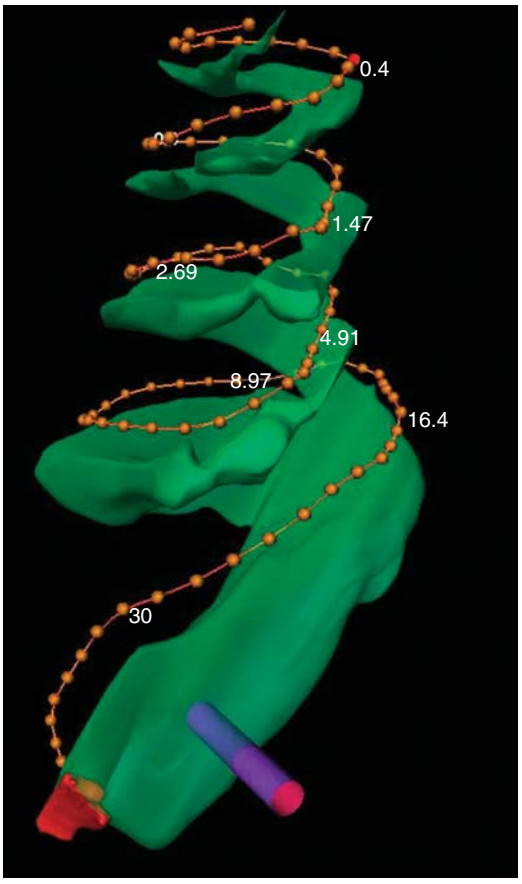

Figure 1. Cast of a guinea-pig cochlea, showing the locations along the length of the scala tympani where various frequencies are detected, along with a notional placement of a cannula for intracochlear drug delivery near the 30 kHz point.

Ultimately, development of drug delivery systems for specific clinical applications will require functional assessment of the mechanism and disease the drug–device combination is targeting. However, early stage drug delivery technology development can benefit significantly from the use of surrogate compounds with known, predictable and reversible effects on hearing [34]. Use of these surrogates has been invoked in the development of kinetic models describing drug delivery as a function of delivery parameters and the structural and biochemical environment of the cochlea [15].

2.2 Auditory diseases

Among auditory diseases, the most prevalent condition is SNHL, afflicting some 28 million individuals in the US and hundreds of millions worldwide [1]. Aging of the population is expected to double these numbers within the next 2 decades. Principal causes of SNHL include damage to, or death of hair cells as a result of noise, drug ototoxicity and aging, resulting in communication difficulties and social withdrawal and ultimately profound deafness. Current treatments are based on hearing assist devices including hearing aids and cochlear implants, neither of which arrests progressive hearing loss nor restores hair cell function. Therapeutic approaches for SNHL are emerging, as shown in **Table 2**, including pharmacologic compounds, growth factors and stem cells.

A number of more immediate auditory applications of intracochlear drug delivery are being pursued, many with significant patient populations and all in need of significant advances towards improved outcomes. Principal among these is noise-induced hearing loss (NIHL), brought about by either acute or chronic noise exposure [35]. Steroids, growth factors and antioxidants are being explored [36], but lack methods for direct intracochlear delivery and, therefore, provide limited benefit while in some cases causing significant side effects. Of particular urgency is the incidence of NIHL in members of the Armed Services exposed chronically to engine noise or acutely in the battlefield. Incidence of NIHL has also been a concern in younger patients due to exposure to personal music players.

Ototoxicity due to chemotherapy [37] and radiation therapy in cancer patients represents an urgent condition requiring advances in drug delivery technology [38]. Cisplatin, a commonly used chemotherapeutic agent, is known to cause significant and permanent hearing loss in a large proportion of the patient population [39]. Current systemic approaches involving platinum binders and antioxidants appear to mitigate the ototoxicity but may reduce the effectiveness of the anticancer action of the cisplatin [40]. Therefore, a local delivery approach that protects the cochlea without interfering with the therapeutic effect would be ideal. Similar effects are seen with radiation treatment of head and neck tumors, where approximately a third of the patients suffer severe and irreversible hearing loss [41,42]. A related opportunity exists with antibiotic-associated ototoxicity seen with aminoglycoside compounds [43], where high frequency hearing loss is frequently experienced.

Two less common but very severe causes of hearing loss potentially addressable by intracochlear drug delivery include autoimmune inner ear disease (AIED) [44-46] and sudden sensorineural hearing loss (SSNHL) [47]. Typically, AIED is treated with high-dose systemic steroids, but side effects are so severe that many patients terminate therapy and move to a cochlear implant. While the efficacy of locally delivered steroids is unknown, AIED represents a potential early path to the clinic for intracochlear delivery systems where alternatives that preserve hearing structures do not exist and safety can be assessed using known, approved compounds. Like AIED, SSNHL represents another very promising avenue for intracochlear delivery, because current clinical practice involves the use of high-dose systemic steroids with dangerous side effects. Intratympanic delivery and a catheter-based approach have been used to treat this condition with some success [48,49].

Table 2. Sampling of therapeutic compounds in development towards a range of diseases of the inner ear, including disease target, state of development and current status.

Company	Therapeutic	Developed for	Category	Description	Status
Quark Pharmaceuticals	AHLi	Acute hearing loss-apoptosis prevention	siRNA	Temporarily inhibits expression of p53 tumor repressor gene	Preclinical, IND Submission 2009
Sound Pharmaceuticals	SPL-128	Regeneration	siRNA	Temporarily inhibits expression of cyclin-dependent kinase inhibitor 1B	Preclinical
Merck & Co.	-	Apoptosis prevention	siRNA	Temporarily inhibits expression of Rb1	Preclinical
Kinex Pharmaceuticals	KX1 – 004	NIHL, cisplatin ototoxicity	Small molecule	Src inhibitor	Preclinical
Adherex	STS	Cisplatin ototoxicity	Antioxidant	Sodium thiosulfate	Orphan
GenVee	TherAtoh	Regeneration	Gene	Human atonal gene Hath1 vector	Preclinical
Auris Medical	AM-111	NIHL, aminoglycoside ototoxicity	Small molecule	Block JNK MAPK-mediated apoptosis from stress injury	Orphan. Phase IIb
Living Cell Technologies	Neurotrophin Cell	Degeneration prevention	Cell	Pig cells encapsulated in alginate beads (500 μm)	Preclinical
Otonomy	OTO-104	Meniere's disease	Steroid	Intratympanic injection	Phase Ib clinical trial
Neurosystec	NST-001	Tinnitus	NMDA antagonist	Osmotic pump	Phase Ib clinical trial

IND: Investigational new drug; NIHL: Noise-induced hearing loss.

2.3 Vestibular diseases

Transtympanic injections of gentamicin represented the first local drug delivery application in the inner ear, aimed at treating Meniere's disease, a debilitating condition involving sudden, severe attacks of vertigo often associated with hearing loss and other symptoms. Microcatheters, microwicks and hydrogels for RWM application have all been developed with the goal of treating Meniere's disease by providing a more uniform and well-controlled rate of delivery. Safety concerns regarding the transtympanic administration of gentamicin, due to hearing loss incurred in many cases, have led to a reduction in the dosage that has improved safety while preserving efficacy [50,51]. Intralabyrinthine delivery represents an opportunity to deliver the drug directly to the site of disease, bypassing potential barriers to drug transport such as the middle ear and the RWM. Further, the possibility of enabling burst delivery in response to an impending attack of vertigo would provide additional benefit to patients, potentially through an implanted intracochlear delivery system.

2.4 Tinnitus

Tinnitus affects ~ 10% of the US population and has been the focus of intensive efforts in delivery technologies due to the potentially debilitating nature of the disease. Retraining, biofeedback and masking approaches have met with limited success [52], but pharmacologic approaches, typically via transtympanic injections, have been underway for > 4 decades. Dexamethasone and steroid delivery have also been demonstrated with moderate success in mitigating tinnitus while preserving hearing. However, each approach suffers from potential issues in assessing efficacy and safety as a function of dosage and duration of treatment. A direct intracochlear approach, particularly with programmable and adjustable rates of delivery, has the potential of addressing some of these concerns and resulting in a safer and more efficacious avenue for therapy.

3. Passive intracochlear delivery systems

Intracochlear delivery systems may be broadly classified as either passive or active, depending on whether there is a requirement for power and electronic controls embedded within the device. The following discussion summarizes several of the intracochlear delivery methods that have been explored, primarily in research laboratories in animal models, but some of which have been tested clinically. **Table 3** provides a list of several of the intracochlear delivery methods investigated by researchers, along with relevant advantages and disadvantages for each approach.

Table 3. List of intracochlear delivery approaches and their perceived advantages and disadvantages.

Delivery method	Advantages	Disadvantages
Osmotic pumps	Flexible payload Small No power required	Cannot turn off or alter profile Limited delivery duration
Direct injection	Simple Already demonstrated clinically	Single administration Poor control over distribution
Micro-injector	Simple Already demonstrated clinically Range of infusion rates possible	Challenging surgically Issues with robustness Component-level approach Prone to fouling Poor distribution kinetics
Infusion with canalostomy	Provides superior distribution kinetics	Multiple surgical sites
Reciprocating system	Wide range of operating conditions May reduce fouling Capable of timed-sequence delivery	Issues with robustness Complex mechanism
Cochlear implant-mediated delivery	Integrated with well-established therapy Enhances clinical benefit of implant	Limits therapy to more severely impaired patients May involve complications due to interactions between implant operation and delivery device

3.1 Transtympanic routes

Direct intracochlear delivery, the subject of this review, entails the surgical placement of a delivery device in direct communication with cochlear structures and the cochlear fluid. Previous delivery approaches through an intratympanic route are briefly reviewed to provide a context for the development of direct intracochlear systems. The standard indirect approach for cochlear drug delivery is based on introduction of compounds to the middle ear, followed by absorption into the inner ear. Needle injection into the middle ear is the simplest approach, but a more involved procedure introduces drug through a myringotomy, sometimes through a tympanostomy tube [53]. A myringotomy has also been used to deliver drugs directly to the RWM through a Silverstein MicroWick® [11]; this technique has been used to treat SSNHL as well as Meniere's disease. Plontke *et al.* [54] have reported the use of an implantable microcatheter placed in the round window niche; this system has been tested on 25 patients for treatment of SSNHL. Recent progress in treatment of Meniere's disease has been reported using IT injections of a steroid (OTO-104) that has been shown to reduce the severity of symptoms in a Phase Ib trial without adverse events [55].

In order to improve dosage control during intratympanic delivery, several groups have explored the use of nanoparticles and hydrogels as delivery vehicles. A major advantage of these systems is the ability to provide sustained delivery for extended periods of time using controlled release matrices, thereby greatly increasing the period of performance over previous liquid delivery sources. Nanoparticles offer the potential for more sustained and well-controlled delivery, and various compositions including biodegradable and non-degradable nanoparticle delivery systems have been explored for intracochlear therapy. A bioresorbable nanoparticle composition based on poly(lactic co-glycolic) acid (PLGA) has been reported by Tamura *et al.* [56]. This investigation confirmed the beneficial effects of nanoparticles on pharmacokinetics by demonstrating a significant increase in the concentration of a fluorescent label attached to the nanoparticles in the cochlea relative to levels seen when the fluorescent label was introduced either systemically or by application as a free molecule to the RWM. Superparamagnetic nanoparticles represent another delivery modality; magnetic fields have been used to guide these particles down the chinchilla cochlea [57] as a means to enhance apical delivery, although evidence for increased penetration depth is not clear. Liposomal delivery has been used for gene therapy [58]; the liposomes can either be injected or delivered using an osmotic pump.

Hydrogels exhibit great versatility as drug delivery vehicles for a range of clinical applications [59]. Triggering mechanisms for release of the hydrogel's drug payload include temperature, pH, pressure, electrical stimulation and chemical means. Brain-derived neurotrophic factor (BDNF) has been delivered using a hydrogel matrix applied to the RWM [60], with protective effects seen in SGN cells. Siloxane-based hydrogel systems [61] have been reported, but much emphasis has been placed on biodegradable hydrogels including PLGA [62]. Recent clinical trials have shown that topical application of IGF-1 results in measurable hearing improvement in about 50% the patients, with no adverse events [63].

3.2 Osmotic pumps

Osmotic pumps provide a means to deliver drugs directly to tissues without the requirement for external connections or a power source. They operate by means of establishment of an

osmotic gradient that drives the drug out of a canister, and in the case of intracochlear delivery through a cannula into the inner ear, at a rate determined by the design of the device. Large molecules, proteins and peptides may be delivered by osmotic pumps and, therefore, these devices have been used for a variety of intracochlear applications. An early demonstration of intracochlear drug delivery was reported by Kingma *et al.* [64]; guinea pigs received surgical placement of a micro-injector near the basal turn of the ST. Animals received injections of either tetrodotoxin or saline solution as a control, and auditory brainstem response was monitored over periods of up to 2 weeks. Prieskorn and Miller [10] reported chronic intracochlear delivery using osmotic pumps (Alza Corp.), as well as chronically implanted cannulae for repeat drug infusions. Carvalho and Lalwani have reported a lentiviral vector as a gene delivery agent [65]. Ototoxicity protection during cisplatin-based chemotherapy represents another avenue of investigation for osmotic pumps; sodium thiosulfate infused through a glass cannula from an osmotic pump has been shown to protect hair cells from the damaging effects of cisplatin [66].

4. Active intracochlear delivery systems

Progress in the development of active intracochlear drug delivery systems has been spurred by parallel advances in surgical approaches to the inner ear and the development of miniaturized pumping systems based on microfluidics technologies. Surgical approaches for intracochlear delivery generally comprise either a cochleostomy (typically to the ST although both the scala media and scala vestibuli have been explored as routes for delivery) or directly through the RWM. One of the primary challenges in intracochlear delivery involves the establishment of a robust fluidic connection to the cochlea; difficulties have been encountered in realizing an initial seal that does not leak at the cochleostomy site as well as with rejection of the cannula due to a foreign body response.

4.1 Constant infusion systems

Constant infusion systems used for direct intracochlear drug delivery include direct injections and syringe pump delivery [67-69]. The former approach has been used for gene transfer, liposomal delivery and agents capable of reducing damage associated with cochlear implant placement. The latter approach has been utilized experimentally to establish kinetic models for drug transport in the ST as a basis for the development of miniaturized reciprocating delivery systems, as described in the next section.

An interesting intracochlear delivery system utilizing a constant infusion pump has been reported by Borkholder *et al.* [14]. This system utilizes a cochleostomy as a port for drug delivery using a constant infusion pump in combination with a canalostomy in the posterior semicircular canal designed to reduce concentration gradients and enhance drug transport and apical delivery. Salicylate delivery from a syringe pump was monitored using DPOAE and modeled using a computational approach developed by Salt and co-workers [70]. **Figure 2** illustrates the concentration gradients generated by constant infusion with and without the presence of the posterior canalostomy. These results clearly demonstrated that the canalostomy reduced the basal-to-apical concentration gradient, presumably by modulating fluidic resistance along the delivery path relative to clearance and other mechanisms.

4.2 Reciprocating microfluidic devices

The small space and fluid volume within the cochlea presents a particular challenge for drug delivery systems requiring adequate mixing and distribution to regions distant from the site of initial delivery. Constant infusion approaches as described in the previous section are hindered by the low rate of clearance of cochlear fluid and hence the limited volume of drug that can be introduced into the cochlea in a given time window. These difficulties are exacerbated by the relatively long, narrow passages within the cochlear tubes, and the increasing difficulty of surgically approaching more apical regions of the progressively narrowing and remote regions comprising the lower frequency hearing response. The aforementioned work of the Borkholder group, in which a canalostomy in the posterior semicircular canal was created to reduce concentration gradients, highlights this challenge related to moving drug apically through a long, narrow space with a severely limited maximum sustained flow rate. As a means to overcome this limitation, a reciprocating drug delivery system has been developed that provides zero net volume delivery by infusing and withdrawing a constant volume of drug in a cyclic fashion [15-18,71]. This approach is designed to enhance drug mixing and apical transport while limiting the maximum flow rate and maintaining the total volume of cochlear fluid. Typically, the infusion portion of the cycle lasts for several seconds using a total drug volume of roughly 1 µl, while the remainder of the cycle lasts for several minutes as a mixture of drug and endogenous perilymph is withdrawn back into the device. This process is repeated in a cyclic fashion using a programmable pump. Current development efforts are focused on integration of delivery components in a microfluidic chip of a size suitable for implantation [72]; a prototype of this device is shown in **Figure 3**.

Initial studies with reciprocating delivery systems have utilized commercially available micropumps or a syringe pump programmed to provide cyclic infusion and withdrawal steps. These investigations, conducted using 6,7-dinitroquinoxaline-2,3-dione, a glutamate receptor antagonist, along with monitoring of CAP as an assay for drug transport and concentration as a function of location in the ST, have been used to establish a basic kinetic model for intracochlear delivery based primarily on drug diffusion. The relationship between apical transport and delivery parameters has been explored, as shown

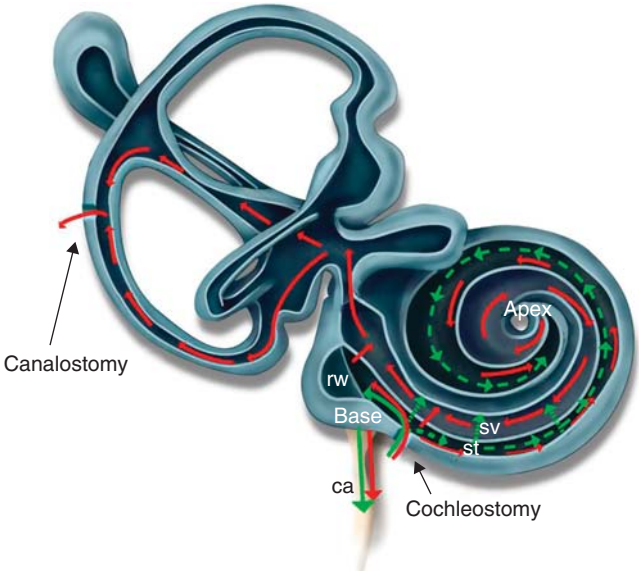

Figure 2. Image showing a drug delivery technique in which drug is infused into the scala tympani near the base, and a posterior canalostomy is opened to reduce concentration gradients by modulating the resistance along the delivery path.

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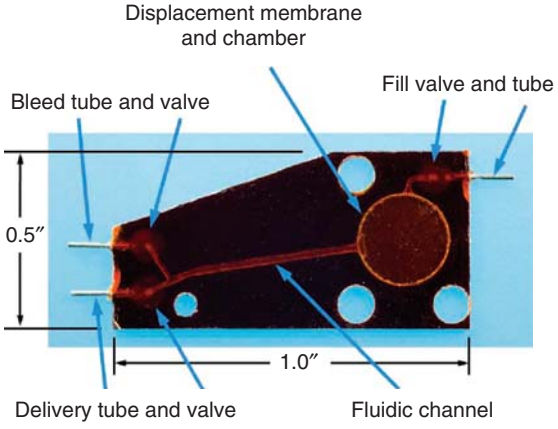

Figure 3. Photograph with dimensions of microfluidic intracochlear drug delivery chip developed by Draper Laboratory and the Massachusetts Eye and Ear Infirmary, containing a displacement chamber, valves and fluidic vials for delivery of compounds through a single cannula into the cochlea using a reciprocating delivery profile.

in **Figure 4**, as has the influence of instantaneous flow rate on hair cell damage. More complex mechanisms such as drug binding to proteins in the perilymph and clearance mechanisms through cochlear structures and tissues are being incorporated into next-generation kinetic models [18].

4.3 Cochlear prosthesis-mediated delivery

One of the most logical routes to intracochlear drug delivery is to integrate the delivery system with the placement of a cochlear prosthesis [19-21,73,74], a device that provides a sense of sound to patients with significant or profound hearing loss by directly stimulating the auditory nerve. These devices, which comprise a microphone, transmitter, speech processor and electrode array, contain elements that are implanted directly into the inner ear, either via a cochleostomy or through the RWM [75]. Because the device is implanted directly into the cochlea, it provides a convenient pathway to deliver drugs to the inner ears of patients for a variety of potential applications. Delivery approaches include the use of drug-eluting polymers coated onto the implant device and the integration of active infusion pumps with the device.

One of the most direct applications of intracochlear delivery with a cochlear implant is the use of neurotrophic factors capable of preserving spiral ganglion (SG) cells and thereby enhancing hearing in implanted patients [76]. Neurotrophic factors such as BDNF and fibroblast growth factor-1 have been investigated as a means to preserve SG cells; in the former case, survival and neurite outgrowth of SG cells in culture have been observed [77], while a combination of the two factors has been explored as a means to preserve SG cells in a guinea-pig model [78]. In addition, neurotrophin-3 has been incorporated in an electrically conducting polymer coating on cochlear implant electrodes in a guinea-pig model [79].

Active drug delivery in the context of a cochlear implant is being explored through the use of catheters and infusion pumps integrated with the implant device. One of the driving forces for this approach is the desire to limit the structural damage caused by the cochlear implant, thereby enabling the device to be used for patients with less severe hearing loss than those typically receiving a conventional implant. This approach utilizes either a shortened electrode or partial insertion of a conventional electrode, limiting the region of damage to hearing structures to the highest frequencies. Delivery of specific compounds such as steroids has been shown to minimize the effects of surgical trauma, and offers a potential route to providing cochlear implants to a far wider patient population than current practice allows. Implants have been combined with infusion pumps to deliver drug through a catheter; most recently, the implementation of a single-use catheter has been explored with a bolus injection from a syringe [80]. Laser machining of a cannula to provide numerous delivery ports is another method that has been explored as a means to improve apical distribution of drug in concert with a cochlear implant [81]. Approaches towards cochlear implant-mediated delivery through an integrated cannula are illustrated in **Figure 5** [82]. Finally, coating of cochlear implants using biodegradable materials such as polyvinyl alcohol has been shown to reduce insertion forces [83] and could potentially be used for drug delivery.

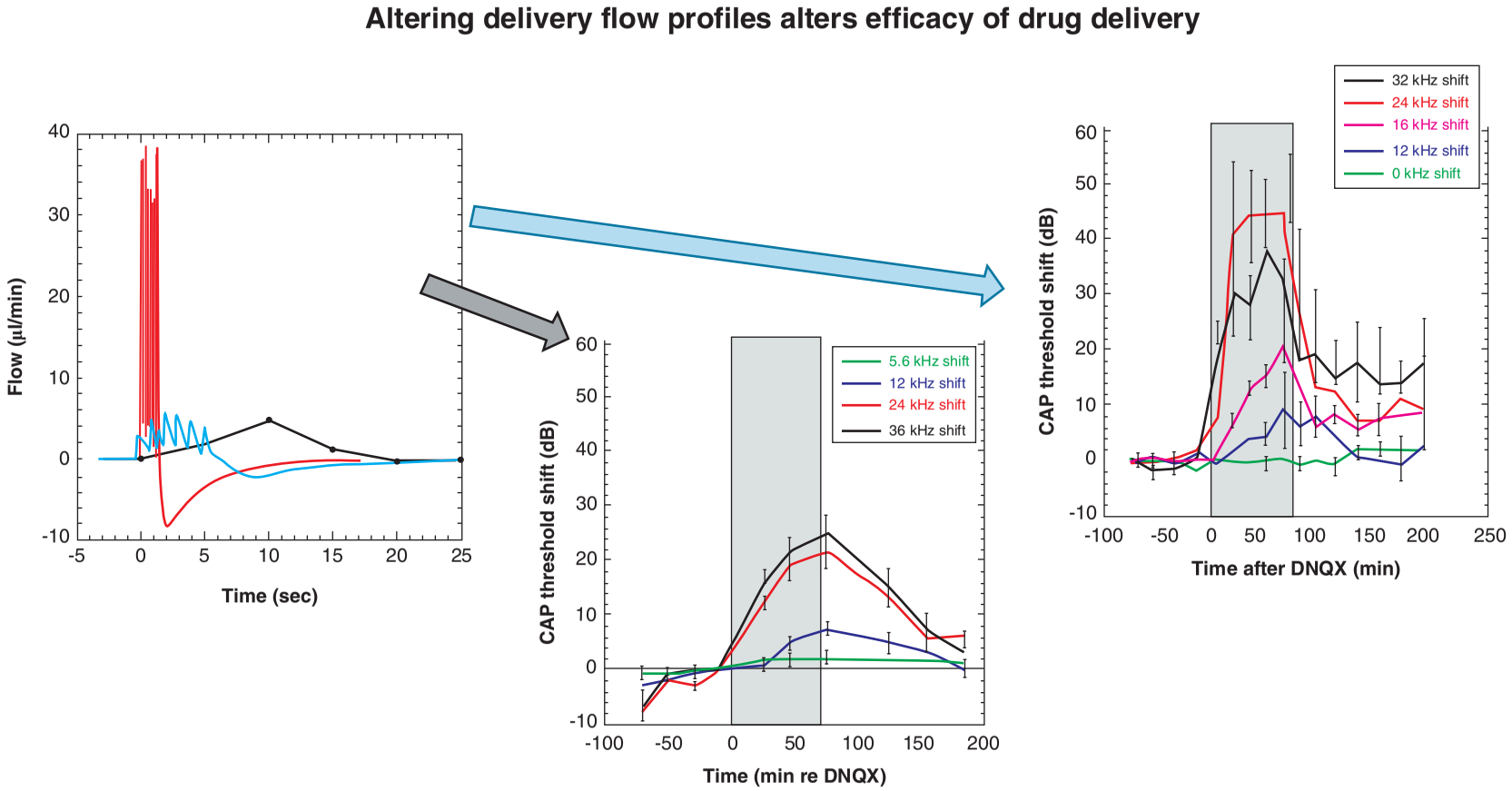

Figure 4. Three flow profiles are shown, all of which were used to deliver DNQX (300 µM), a glutamate receptor blocker that elevates thresholds for the CAP. Flow profiles from the early prototype [15], shown in black, produced threshold alterations (center) of around 25 dB at high CFs that built up slowly during the delivery period (shaded bar). (Right) Modification of the delivery profile (blue) produced larger and more rapid changes in CAP thresholds (around 40 dB for high CFs. Further modification (red) induced threshold changes unrelated to drug delivery (data not shown).

CAP: Compound action potential; CF: Characteristic frequency; DNQX: 6,7-Dinitroquinoxaline-2,3-dione.

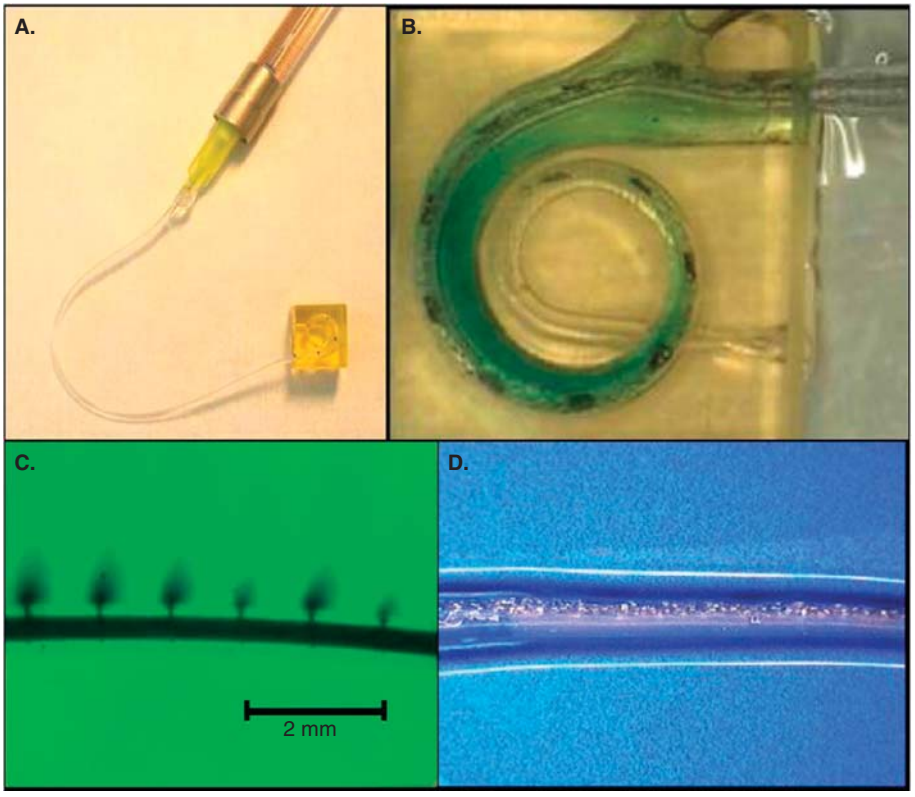

Figure 5. Illustration of two methods of drug delivery from a cochlear implant device is given. (**A**) Prototype of a catheter designed for atraumatic insertion into the cochlea, shown inserted into a model of the cochlea and attached to a syringe. The catheter can be up to 20 mm in length and has thin walls and a small wall diameter, resulting in a highly flexible construction. (**B**) Insertion of an electrode array highlighted by green dye infused from the catheter. (**C**) Drug delivery enabled by laser-drilled holes of 50 μm diameter to enable enhanced drug distribution in the cochlea. (**D**) Elution of pharmaceutical-grade dexamethasone mixed with medical-grade silicone elastomer; the drug is contained in the lower region (opaque).
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5. Conclusions

Intracochlear drug delivery systems represent a promising approach to treat a host of currently intractable diseases of the inner ear, ranging from auditory disorders such as severe hearing loss to vestibular conditions and tinnitus. Current approaches are severely limited by safety issues such as systemic side effects and adverse reactions and by the inaccessibility of inner ear targets to oral, intravenous and even intratympanic administration. The first generation of intracochlear delivery devices, comprised primarily by miniaturized osmotic pumps and constant infusion micropumps, have demonstrated the ability to reach targets such as inner ear hair cells, but the short operational life of these devices and the lack of programmable control have limited their usefulness. More recent generations of intracochlear delivery systems incorporate precision micropumps with miniaturized power and electronic controls. These systems will ultimately serve as fully implantable therapeutic devices for extended delivery of pharmacologic compounds for treatment of inner ear diseases. In the nearer term, they will find utility as wearable and implantable systems for animal models, accelerating the pace of drug development and enabling a deeper understanding of the mechanisms underlying inner ear diseases and regeneration.

6. Expert opinion

Intracochlear drug delivery systems are emerging in response to recent advances in molecular biology and understanding of the mechanisms underlying inner ear diseases, and as a means to overcome many of the barriers and limitations of conventional drug delivery approaches such as intratympanic administration. Inner ear diseases comprise an enormous and growing class of disorders affecting hundreds of millions of patients worldwide, and the aging population and increasing levels of exposure to noise are exacerbating the situation. Without a means to deliver drugs safely and efficaciously directly to the cochlea, the benefits of advances in discovery of regenerative compounds will not be realized, because of difficulties in reaching and targeting these sensitive and remote locations.

Current approaches rely on systemic delivery of steroids, antibiotics and other compounds as well as intratympanic approaches where drugs are injected into the middle ear as liquids, gels or nanoparticles. Systemic delivery provides poor control over dosage and often leads to severe side effects and eventual cessation of therapy. Intratympanic delivery is typically much safer, but relies on transport across the RWM or other structures separating the middle ear from the cochlea. The pharmacokinetics of delivery across these structures is complex and very difficult to control and, therefore, empirical approaches are typically used. These limitations of systemic and intratympanic delivery, already significant with relatively simple drugs such as steroids, will be further exacerbated as more complex therapeutic approaches involving regeneration emerge. These systems will probably require timed-sequence delivery of multiple agents in a synchronized manner, necessitating the development of programmable devices with advanced functionality capable of extended delivery in a partially or fully implantable format. Continued advances in pharmacokinetic models for intracochlear drug delivery [33,68,84-88] will be required in order to design safe and efficacious systems for a range of target diseases.

Initial development of intracochlear delivery systems has centered on the use of osmotic pumps, constant infusion pumps and reciprocating delivery devices to enhance mixing and apical transport. These efforts have been focused on miniaturization of pumps, sensors and control systems to enable wearable and ultimately implantable devices. The emergence of micropumps with low power requirements, high precision and a size suitable for implantation is providing an opportunity for next-generation drug delivery systems [89-92]. Advances towards the development of *in vivo* biosensors [93,94] for real-time monitoring of disease biomarkers and the bioactivity of delivered compounds represent another important element of future closed-loop delivery systems. In addition to the development of devices for human clinical use, researchers will also benefit from the availability of wearable systems for animal studies of disease mechanisms and drug discovery. For the latter set of applications, untethered systems small enough to be worn by rodents, and with a drug payload sufficient for extended delivery, will be required. Several critical priorities must be addressed in order to bring these technologies into human clinical use. Foremost among these is safety; the device must be proven safe, preferably using compounds that are currently approved for therapeutic use, causing no harm to residual hearing or to other structures in the ear. In addition to hearing loss, other safety concerns with implants in the cochlea include risk of infection, a requirement for repeated surgical procedures and the potential for limitations regarding MRI. Drug storage and control over release must be implemented in a manner that allows acceptable control over dosage, preferably with the flexibility to alter delivery profiles in a patient-specific manner. Advances in controlled release systems and nanoparticle technology currently being explored using intratympanic delivery modes may be integrated with intracochlear delivery devices, thereby leading to a significant expansion in the versatility of these systems. Miniaturization of electronics and power sources represents another critical challenge that must be met in order to realize fully implantable intracochlear delivery systems, as the volume available for these devices is very limited [70]. Sensing capabilities, while perhaps not essential for first-generation systems, will ultimately add a degree of safety and better physician monitoring and control over delivery parameters. Regulatory hurdles for the coming generation of intracochlear delivery devices may be anticipated based on the precedents set by cochlear prostheses, which are implanted using a similar surgical procedure and represent a comparable level of technological complexity and integration of functionality. Along these lines, the most straightforward route to clinical use of these intracochlear delivery systems may be in concert with existing intracochlear devices such as cochlear implants. A drug delivery module associated with a cochlear implant, particularly one designed to preserve residual hearing structures, may provide patients with prosthetic hearing while simultaneously regenerating hair cells and neural cells to achieve superior levels of hearing and potential restoration of natural hearing function.

Declaration of interest

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