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Microsystems Technologies for Drug Delivery to the Inner Ear

Erin E. Leary Pararas¹, David A. Borkholder², and Jeffrey T. Borenstein^{1,*}

¹Charles Stark Draper Laboratory, 555 Technology Square, Cambridge, MA 02139, USA

²Rochester Institute of Technology, Department of Electrical and Microelectronic Engineering, 79 Lomb Memorial Drive, Rochester, NY 14623, USA

Abstract

The inner ear represents one of the most technologically challenging targets for local drug delivery, but its clinical significance is rapidly increasing. The prevalence of sensorineural hearing loss and other auditory diseases, along with balance disorders and tinnitus, has spurred broad efforts to develop therapeutic compounds and regenerative approaches to treat these conditions, necessitating advances in systems capable of targeted and sustained drug delivery. The delicate nature of hearing structures combined with the relative inaccessibility of the cochlea by means of conventional delivery routes together necessitate significant advancements in both the precision and miniaturization of delivery systems, and the nature of the molecular and cellular targets for these therapies suggests that multiple compounds may need to be delivered in a time-sequenced fashion over an extended duration. Here we address the various approaches being developed for inner ear drug delivery, including micropump-based devices, reciprocating systems, and cochlear prosthesis-mediated delivery, concluding with an analysis of emerging challenges and opportunities for the first generation of technologies suitable for human clinical use. These developments represent exciting advances that have the potential to repair and regenerate hearing structures in millions of patients for whom no currently available medical treatments exist, a situation that requires them to function with electronic hearing augmentation devices or to live with severely impaired auditory function. These advances also have the potential for broader clinical applications that share similar requirements and challenges with the inner ear, such as drug delivery to the central nervous system.

Keywords

Cochlea; Intracochlear; Intratympanic; Hearing; Local drug delivery; Device; Micropump; Implantable

1. Introduction

The inner ear represents one of the most challenging target organs for drug delivery, yet the potential clinical benefit to patients and the size of the patient population are immense [1]. Conventional routes such as oral delivery and injections are largely ineffective for several reasons, principally because of the blood-cochlear barrier that blocks most compounds from entering the inner ear from the bloodstream. Further, drugs that are introduced systemically

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*Corresponding author: jborenstein@draper.com, Telephone: + 1-617-258-1686, Fax: + 1-617-258-1131.

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are likely to reach unintended targets and may be toxic, and therefore progress towards development of compounds capable of treating inner ear diseases including hearing and balance disorders and tinnitus has been very limited. Most existing delivery approaches utilize direct injection of compounds into the middle ear space, with a reliance on transport through the round window membrane (RWM) into the cochlea, a process that is inefficient because of enormous variability in drug diffusion rates due to anatomic differences between patients and limits on the achievable intracochlear drug concentration. The small size and relative inaccessibility of the cochlea in humans present additional challenges regarding delivery mechanisms; it is surrounded by the hardest bone in the body, and the coiled tubes within it are roughly 2 mm in diameter at their entrance and narrow rapidly as they ascend toward the apex. Further, the hearing structures within the cochlea are extremely delicate; in particular the hair cells that line the basilar membrane within the organ of Corti (OC) are highly sensitive to shear stresses and mechanical or chemical damage from a variety of sources. In addition to its sensitivity to fluid shear, the cochlea comprises a fluid volume of only 80 μ l in humans and is therefore susceptible to very small changes in total fluid volume. It is these considerations regarding the relative inaccessibility, small size and sensitivity of the inner ear that render it an ideal target for microsystems-based implantable drug delivery systems [2]. Many of these requirements associated with miniaturization and precision are even more challenging considerations for the development of delivery platforms for pre-clinical studies in animals, where the total device volume and perilymphatic fluid volume may be more than an order of magnitude smaller for guinea pigs or mice relative to humans.

Recent advances in molecular biology related to regeneration of sensory and neural cells within the inner ear point the way towards eventual treatments for hearing loss and other diseases [3]. The complex nature of regeneration and repair processes and the range of molecular and cellular targets for regeneration highlight the need for precisely controlled systems capable of delivering a broad range of compounds over extended periods of time. These compounds may include apoptosis inhibitors, cytokines, neurotrophin ligands, antioxidants and gene therapy agents, and stem cell therapies, potentially introduced in a complex timed-sequenced manner, with precise control over delivery kinetics, transport mechanisms and binding reactions. These considerations heighten the requirements for next generation delivery systems well beyond currently available implants that typically comprise drug-loaded polymer matrices that introduce single compounds passively over limited periods of time [4]. Progress towards safe and efficacious inner ear delivery systems will benefit from microsystems-based approaches, where multiple therapeutic compounds can be introduced in a highly controlled and time-sequenced manner over periods of months to years, enabling precise control over the drug concentration, kinetics and molecular and cellular targeting of therapies for hearing restoration.

Microsystems-based drug delivery systems are emerging for a range of clinical applications, and these capabilities have been leveraged towards the inner ear [5–9]. As noted in these investigations, there are several aspects of inner ear delivery that present specific technological challenges. These include the small space available for the delivery system, the extended duration of treatment required for many diseases of the inner ear, and the precise and gentle manner in which drugs may be introduced into the delicate structures of the cochlea. These and other considerations limit the applicability of many existing microsystems-based devices for inner ear delivery, and have spurred the development of novel technologies and surgical approaches aimed at providing precisely controlled, extended and safe delivery of compounds to the cochlea.

Here we will begin with an overview of clinical targets for therapy for diseases of the inner ear, broadly classified as auditory and vestibular disorders and tinnitus, followed by a review

of inner ear physiology and relevant considerations for delivery systems. We will then review four basic approaches for microfluidic inner ear delivery, including micropump-based systems, reciprocating approaches, directed perfusion and finally cochlear prosthesis-mediated delivery. Finally we will address emerging challenges and opportunities as these technologies are advanced toward clinical practice.

2. Diseases of the Inner Ear

Diseases of the inner ear that represent targets of opportunity for drug delivery approaches include a host of auditory diseases, vestibular disorders, and tinnitus. Of these, by far the largest target patient population suffers from SensoriNeural Hearing Loss (SNHL), which occurs because of damage to, or death of hair cells resulting from aging, disease, noise exposure, or drug ototoxicity. Roughly 278 million individuals worldwide suffer from SNHL and over 1% of all children worldwide suffer from SNHL [3]. Hearing aids and cochlear prostheses represent the only currently available treatments for SNHL, but the total amplification possible with hearing aids is limited and there are several other barriers to their use. Cochlear implant technology has advanced rapidly over the past several years, and their use for profound hearing loss has expanded dramatically. However, there is growing interest and effort focused on the development of regenerative approaches for SNHL, with significant recent advances in the understanding of cellular and molecular targets for regeneration. These advances are spurring efforts to develop delivery systems capable of safely and efficaciously enabling a class of emerging therapeutic compounds to reach these targets in the inner ear.

Noise-induced hearing loss (NIHL) and ototoxicity associated with various systemic drug therapies represent two additional major causes of hearing loss. The prevalence of NIHL is increasing rapidly, caused by either acute or chronic exposure to loud sounds, and sounds at or above 85 dB is associated with hearing loss when patients are exposed to these levels over long periods of time [10]. Exposure to chronic loud noise leading to NIHL and tinnitus is one of the most prevalent injuries experienced by Armed Forces personnel [11]. Damage to both the hair cells and the auditory nerve occurs as a result of NIHL, largely associated with the formation of free radicals in the inner ear. Rescue therapies delivered systemically are being investigated as a means to treat NIHL, but direct delivery to the inner ear is also being pursued using nanoparticle-based techniques and related approaches [12]. Ototoxicity is frequently associated with chemotherapy and radiation therapy in cancer patients, and is a particularly severe concern with pediatric patients. Cisplatin-based chemotherapy results in destruction of auditory sensory cells in large numbers (20 – 40%) of patients and is generally irreversible [13, 14]. Platinum binders and antioxidants have been explored as systemic approaches to limit ototoxicity, but their use may result in a reduction in the efficacy of the cancer treatment. Therefore drug- and radiation-induced ototoxicity [15] represent important targets for local inner ear drug delivery that would protect hearing without adversely affect the efficacy of the primary treatment of the neoplasm.

Less common but very severe auditory diseases include conditions such as sudden sensorineural hearing loss (SSNHL) [16] and autoimmune inner ear disease (AIED) [17–19]. High-dose systemic steroid treatments are the principal route of therapy for both of these diseases, but are often associated with severe side effects that may cause the patient to terminate the medication and move to a cochlear implant. Currently, intratympanic delivery and catheter-based approaches to deliver drugs to the middle ear are used on some patients with limited success. Direct delivery of steroids or other compounds to the inner ear may represent a safer and more efficacious way to treat AIED and SSNHL.

Vestibular diseases represent a somewhat smaller patient population but comprise a set of potentially disabling conditions such as Meniere's disease, labyrinthitis and bilateral loss of labyrinthine function. Meniere's disease, or endolymphatic hydrops, represents a swelling of fluid and concomitant increase in fluid pressure within the cochlea that results in hearing loss, severe vertigo and pain, pressure and fullness of the affected ear [20–22]. Causes of this disease include trauma to the head, infections and allergy, and autoimmune disorders. Existing surgical and medical approaches may cause permanent loss of vestibular function [23], and therefore interest is rising in therapeutic approaches involving the inner ear.

Tinnitus, or ringing in the ears, affects 10% of the population and may be debilitating in severe cases. Tinnitus is the most common complaint reported by Armed Services personnel returning from duty, and often results from exposure to loud noise or trauma and may be accompanied by hearing loss. It is a particularly challenging target for therapy due to the complex nature of the condition and the difficulty in quantifying tinnitus and the efficacy of therapeutic approaches. Transtympanic injections with dexamethasone [24] and steroids have achieved some success in reducing tinnitus while preserving hearing, but a direct intracochlear approach might ultimately be more effective in treatment of severe cases of tinnitus using one of the emerging therapeutic compounds currently being investigated with pump-based delivery systems.

3. Inner Ear Physiology

The inner ear is comprised of the cochlea, the auditory end organ, and the vestibular system for balance. It is housed deep in the petrous bone, the hardest bone in the body, near the brainstem. Its small size coupled with its inaccessibility presents unique challenges for drug delivery. In addition, the sensitive and complex inner ear structures are important considerations for drug delivery systems development.

The cochlea is a bony spiral filled with three fluid spaces that continue longitudinally along the length of the spiral from apex to base. It measures 31–33 mm long in humans [25], varies in diameter along its length, and is bounded at the base by the round window and the oval window. The RWM is highly compliant and bulges into the middle ear space when pressure is applied or fluid volume increases. It separates the fluid-filled space of the cochlea from the middle ear. The oval window is connected to the stapes, a middle ear bone, and transmits acoustic vibrations to the inner ear. The cochlea is a closed fluid system in humans, as the cochlear aqueduct connecting the scala tympani (ST), one of the three coiled tubes in the cochlea, to cerebrospinal fluid (CSF) is generally not patent. However, in guinea pigs and in mice, two species often used in inner ear research, the cochlear aqueduct is open. This anatomic distinction between the species complicates analysis of drug delivery results and transfer of knowledge from animal testing to the clinical setting.

Stretching across the middle of the cochlea is the OC, a basilar membrane holding the hair cells which are the mechano-sensory cells of the inner ear. The hair cells are covered with stereocilia on their apical surface. The membrane moves in response to sound waves and is organized tonotopically so that high frequency sounds cause the greatest movement at the basal region where they are detected. Low frequency sounds, by contrast, cause greater movement at the apex [26]. Hair cells are arranged in rows that run the entire length of the cochlea. Three rows of outer hair cells amplify the motion of the basilar membrane to more effectively stimulate the inner hair cells. One row of inner hair cells releases a neurotransmitter in response to sound that excites afferent auditory neurons.

The three fluid spaces of the cochlea coil along with the OC from base to apex. Viewed in cross-section, the upper and lower compartments are the scala vestibuli (SV) and the ST. They are filled perilymph, a fluid that is quite similar to CSF, and are in communication

with each other at the apex through a structure known as the helicotrema. The round window is located at the base of the ST while the SV terminates at the oval window. The middle compartment, the scala media (SM), is filled with endolymph. The SM is bordered by the OC, with the apical surfaces of the cells lining the organ, including hair cells, projecting into the SM. The structures of the inner ear are illustrated in Figure 1.

Perilymph is the most abundant fluid in the cochlea, filling the ST and SV. It bathes most of the cochlear cells, including hair cells in the basal region and the neurons. The fluid is in diffusional continuity with CSF. Relative to CSF, its composition is high in sodium ions and low in potassium ions. However, protein concentration is significantly higher (3 to 20 times) in the perilymph than in CSF [27–31]. This elevated protein concentration may be responsible for drug binding interactions that attenuate drug penetration during the delivery process [32]. More than one third of the proteins in perilymph comprise protease inhibitors, with serpins predominant. Additionally, apolipoproteins and enzymes each constitute approximately 15% of the total protein content. The single most abundant protein is albumin at 14% [33]. In the human cochlea, the volume of perilymph is about 70 μl , with 40 μl of that volume in the ST [34].

Endolymph fills the SM with a volume of approximately 8 μl in human. The ionic composition of endolymph is similar to the intracellular environment, high in potassium and low in sodium. The cells that line the SM form tight junctions, and this forms a unique environment for the apical surface of the hair cells. The compartment provides an electrochemical environment with about 100 mV of positive electrical potential to support the hair cells' ability to transduce mechanical motion into electrical potentials. The potential is maintained by the stria vascularis, a structure running along the outside of the SM.

The coil of fluid compartments and OC wind around a central structure called the modiolus. The cell bodies of the auditory neurons, spiral ganglion neurons, are packed into the modiolus. The neurons send dendrites to the inner hair cells and axons to the brain.

In the auditory process, a sound wave passes through the external ear and displaces the tympanic membrane, causing motion of the ossicles, the three tiny middle ear bones. The stapes, the last bone in the series, transfers the motion to the fluid-filled space of the inner ear behind the oval window. The middle ear matches the acoustic impedance of the airborne sound to the fluid of the inner ear. Perilymph motion causes the basilar membrane to move which in turn produces motion of the stereocilia on the apical portion of the hair cells. Mechanically sensitive ion channels on the stereocilia open and close, causing the hair cells to depolarize and repolarize. The inner hair cells respond by releasing neurotransmitter from their base, which activates the auditory nerve fibers.

A number of electrophysiological parameters can be measured for cochlear function monitoring. Those used most often include distortion product otoacoustic emissions (DPOAEs) and auditory brainstem responses (ABRs); both are non-invasive and are often used clinically. The DPOAEs serve as a monitor of outer hair cells. The mechanical response of the outer hair cell results in an acoustic signal propagated back out through the auditory canal. These acoustic signals correspond to discrete frequencies and can be measured to non-invasively assess cochlear function. Using external electrodes, ABRs monitor the synchronous activity of a group of nerve fibers in response to a click or tone pip. By varying the frequency of the tone pips, specific regions along the length of the cochlea can be studied. Measurement of a related parameter, the compound action potential, (CAP) requires an electrode to be placed near the RWM.

4. Catheter and Micropump-based Delivery Systems

Various systems have been developed to facilitate local delivery to the inner ear. Early generations of devices were the Silverstein MicroWick™ and the Round Window Microcatheter™ (μCath) which have been used clinically to deliver agents to the intratympanic space, while the Alzet osmotic pump has been used in animal studies for both intratympanic and intracochlear delivery to study a number of applications. The intratympanic delivery systems rely on diffusion through the RWM. Variability in thickness and composition of the membrane, along with potential loss of drug through the Eustachian tube, limit dosing control of drug reaching the inner ear. Intracochlear delivery requires a more invasive surgical technique. Cannulation through the round window or bony wall of the cochlea is most often used to gain direct access to the inner ear. An advantage of this approach is a greater degree of control over dosing relative to intratympanic approaches.

The MicroWick consists of an absorbant polyvinyl acetate wick that is passed through a vent hole in the tympanic membrane and inserted to contact the round window. The wick absorbs medication that is administered in the external ear and transports it to the RWM for diffusion into the inner ear [35]. It can be placed under local anesthesia and allows patients to self-administer their treatment. The wick is removed at the conclusion of treatment.

Studies have shown the utility of the MicroWick in the treatment of Meniere's disease, immune-mediated hearing loss, and sudden hearing loss. Patients suffering from vertigo due to Meniere's were dosed with gentamicin for two weeks in a study by Suryanarayanan. Results showed good control of vertigo symptoms, but approximately a quarter of patients experienced some degree of hearing loss [36]. In another follow-up study, the authors concluded that long-term control of vertigo symptoms can be achieved by gentamicin application using the MicroWick, but they acknowledged that the optimum treatment paradigm has not yet been determined [37].

The MicroWick has been used for local delivery of steroids in the treatment of AIED and in sudden deafness. Dexamethasone drops were administered three times daily for two weeks, and about a third of patients with sudden deafness experienced improvement in hearing. Results were inconclusive for AIED patients due to the small sample size [38]. Another study of methylprednisolone administered through the MicroWick twice a day for three weeks also showed hearing improvement in patients suffering from sudden hearing loss [39]. Van Wijk reported on application of infliximab, a tumor necrosis factor α blocker, for the treatment of AIED. The pilot study resulted in improved hearing and reduced relapse [40].

The Round Window Microcatheter™ has been used clinically in a number of applications. The catheter has two lumens, one for infusion and one for withdrawal, and has a rounded tip intended to be compressed into the bony niche next to the RWM. During anesthesia, the catheter is guided through the tympanic membrane and secured in place. The other end of the catheter exits the outer ear and can be connected to various pumping systems for infusion of drug.

Several studies have reported on the use of the μCath for the treatment of Meniere's disease. One report on the infusion of low-dose gentamicin used a minipump from Disetronics attached to the catheter to deliver for 10 days. The catheter was removed at the end of treatment. Most patients experienced an elimination of vertigo and reduction in tinnitus associated with Meniere's, and hearing remained stable in all but one patient [41]. Similar improvement in vertigo symptoms were seen in a long-term follow-up study [42]. Two other studies reported significant improvement in vertigo but variable and unacceptable levels of

hearing loss. Authors discuss the need to better control the dosage of gentamicin and better understand the disease and therapeutic mechanisms [43, 44].

Plontke and colleagues have published research on the use of the μ Cath to locally deliver dexamethasone to patients suffering from SSNHL. In these studies, a Panomat pump continuously delivered the glucocorticoid for 2–4 weeks, and the catheter was removed at the conclusion. Typical infusion rates were on the order of 5 μ L/hr for periods of up to 4 weeks. Results were mixed with one showing statistically significant hearing improvement [45]. However, the other showed minimal improvement over placebo. The authors did express their belief that the results supported further investigation of the technique [46]. The location of the μ Cath implant in the round window niche, shown in Figure 2 of Ref. 46, necessitates reliance on additional transport mechanisms through tissue to reach intracochlear targets.

Pre-clinical osmotic pumps have been used extensively both for middle and inner ear delivery studies in animals. The small volume pump is subcutaneously implanted usually in rodents, and a cannula is routed to the round window niche or directly into the cochlea. Various models allow for reservoir volumes of 0.1 to 2 ml and flow rates from 0.1 to 10 μ L/hr, and the pumps provide continuous infusion for 1 day to 6 weeks. The quantity of drug delivered over this period can greatly exceed the amount of perilymph in the cochlea, but the slow infusion rate allows for clearance mechanisms to equilibrate total fluid volume. The pump operates by osmotic pressure in the outer section of the pump forcing drug in an inner, impermeable chamber out through the cannula. Delivery cannot be started or stopped nor can the flow rate be changed in situ. These devices are only approved for laboratory studies and have not been used in clinical studies.

Osmotic pumps have been used to test therapies for a number of inner ear disorders including NIHL, ototoxicity, vertigo, and others, and have been reviewed elsewhere [47]. Recent developments include a study of betamethasone to treat a vestibular disorder in a guinea pig model, resulting in a shorter recovery time than the control [48]. Another recent report of osmotic delivery involved substance P, a neuropeptide in the class of tachykinins that has been found in abundant amounts in the vestibular system. Substance P was investigated for its influence on the system and its usefulness in functional recovery in peripheral vestibular disorder. Results showed that substance P caused excitatory actions in the vestibular system and therefore may hold the potential to be used as a treatment for patients suffering from vestibular dysfunction [49].

Emerging therapies to understand and treat hearing loss are being testing in guinea pigs using osmotic pumps. Gene therapy is a promising approach for the treatment of hearing disorders, and a great deal of research is focused on non-viral methods of delivery. Linear polyethylenimine (PEI) has relatively low transfection efficiency, but sustained release from the osmotic pump improved efficiency and indicated the PEI presents an alternative for nonviral cochlear gene therapy [50].

The anti-apoptotic agent, z-VAD-FMK, is a caspase inhibitor. The therapeutic efficacy of this agent was tested in guinea pigs after noise-induced trauma by continuous infusion from an osmotic pump for 14 days. Threshold shifts were less in the treated ear compared to the untreated ear 2 days after exposure, and hair cell losses were significantly lower in the treated ear. Results suggest that the caspase pathway is involved in NIHL [51]. The versatility and ease of use of osmotic pumps in rodents will likely ensure their continued use in the study of novel therapies to treat inner ear disorders.

5. Reciprocating Microfluidic Delivery System

A team from Draper Laboratory and the Massachusetts Eye and Ear is developing a reciprocating delivery system for direct intracochlear delivery [52]. The core of the delivery device is a reciprocating flow system for perfusion of drugs into the cochlear perilymph through a single hole in the basal turn of the ST. The single cannula is directly implanted in the ST and acts as both inlet and outlet. Using the endogenous perilymph as the carrier fluid for highly concentrated drug, the system repeatedly injects a small volume (0.2 to a few μl) of fluid into the cochlea over a short (1–10 sec) time, and then withdraws the lower concentrated perilymph into the device over a period of several minutes. The critical elements of this device consist of an overall size consistent with surgical placement in a cavity formed within the mastoid space behind the ear, a pumping element capable of infusing the drug into the cochlea, a valve-controlled drug reservoir, and integration with sensors for control of flow rate [53]. Studies have been conducted using three-dimensional virtual reconstructions of human temporal bones to determine the appropriate overall size of the implant. A device measuring 8.5 cm^3 would accommodate 90% of patients [54].

The system operates by an actuator that applies cyclic pulses to a membrane covering the drug reservoir for delivery into the cochlea; relaxation of the actuator and the membrane permits return of the fluid to the system. The solenoid actuator impinges on the pumping chamber's membrane to decrease its chamber volume and dispenses fluid from the reservoir into the cochlea. Releasing the membrane refills the system with cochlear fluid. The infusion and withdrawal cycles are timed such that substantial mixing of drug and perilymph occurs in the cochlea. The refill step draws diluted fluid back into the reservoir [55]. A diagram of the system and an example of a wearable embodiment of the device for guinea pig studies are shown in Figure 2.

The reciprocating system is capable of safely accommodating the pulse volumes from the pump, restricting the flow into and out of the ear, and producing no net flow into the cochlea. Drug delivery occurs through diffusion and mixing of the high concentration fluid injected into the inner ear, while lower concentration fluid is returned to the device. Over time, no net volume change in the cochlea occurs while the drug concentration in the cochlea increases. The intent of this method is to create a net increase in drug concentration while protecting the sensitive hair cells from changes in perilymph volume and pressure.

The system has been constructed and tested with acute delivery of DNQX, a glutamate receptor blocker, in the guinea pig. Perfusion with the control artificial perilymph showed no effect, while delivery of DNQX showed a reversible, dose-dependent CAP threshold increase. The effect was also dependent on location along the length of the cochlea with larger shifts at higher frequencies near the infusion location and decreasing shifts at lower frequencies in more apical regions. DPOAEs, a measure of outer hair cell function, were not changed which served as an internal control [53]. More recent studies showed a threshold shift dependence on infusion flow rate with higher flow rates causing increased threshold rises [56], as shown in Figure 3.

Initial modeling efforts of reciprocating drug distribution in the cochlea have been conducted using the data from these studies. Analysis showed a strong dependence on diffusion, especially in regions apical to the delivery site. Near the delivery site, flow rate effects were seen. However, the study also showed what may be interpreted as a strong dependence on drug binding [56]. As discussed above in the Physiology section, many types of proteins that are known to bind drugs in plasma were identified in perilymph, including albumin and apolipoproteins [33]. Current efforts are underway to construct a numerical

model to incorporate diffusion, reaction, convection, and other mechanisms important in understanding drug distribution.

To enable long-term wearable testing, a self-contained, programmable system was built. It was designed to weigh less than 50 g and sized at approximately 80 cm³ to facilitate mounting on the skull of adult guinea pigs. The system runs in an uninterrupted fashion for two weeks and allows extended testing of the device functionality and drug distribution [57]. In order to meet the size and weight requirements, the delivery device was further miniaturized and fabricated from laminated layers of polyimide sheets that were machined using standard XY milling tables [58]. The laminated portions comprise a flexible membrane covering the displacement chamber, valves, and channels. The membrane is depressed using a commercially-available mini-actuator [55]. The electronic control system was custom-designed and built in-house and powered by lithium polymer batteries. It enables wireless programmability with a standard infrared remote control.

Future directions are focused on continued miniaturization and increased functionality. A reservoir capable of storing highly concentrated drug and controlling dosing is being fabricated using identical laminate fabrication techniques and tested. Additionally, designs for custom micro-actuators in order to actuate the reciprocating system are underway. Further plans include the implementation of an in-line flow sensor to monitor delivery profiles. Ongoing long-term animal testing will incorporate upgraded hardware as it becomes available.

6. Directed Cochlear Perfusion

Delivery of compounds to the inner ear is most commonly achieved by absorption or direct injection through the RWM, or infusion through a cochleostomy at the basal turn as described above. These methods provide direct access to cochlear structures, but with a strong basal-to-apical concentration gradient consistent with a diffusion-driven distribution [59, 60]. This gradient may impact treatment efficacy for pharmaceuticals with a narrow therapeutic window, or molecular therapies involving protection or regeneration in apical cochlear structures. Understanding and control of concentration gradients associated with different inner ear drug delivery protocols is critical for development of therapies which address auditory and vestibular dysfunction.

The issue of diffusion limited access to apical cochlear structures can be partially mitigated by directed perfusion through the cochlea. A basal turn ST infusion (cochleostomy) coupled with an exit hole in the posterior semicircular canal (canalostomy) creates a preferential perfusion flow pattern from base to apex in ST, through the helicotrema, and from apex to base in the SV [9]. This contrasts with infusion at the basal turn of the ST with no exit hole, where presumably all excess fluid is pushed through the cochlear aqueduct into the cranial subarachnoid space, with diffusion as the dominant mechanism for carrying therapeutic agents to the apical turns. The theoretical flow paths for both surgical approaches are represented in Figure 4.

Spatially dependent concentrations within the cochlea are indirectly quantified via frequency dependent DPOAE threshold shifts during fixed flow rate (16nl/min) delivery of ototoxic agents through a cochleostomy in the basal turn of the ST. Sodium salicylate, a reversible outer hair cell electromotility inhibitor [61], can be used to access relative concentrations, with DPOAE threshold recovery confirming no acute damage to hearing due to the surgery or infusion. Experiments in young adult CBA/CaJ mice with syringe pump controlled infusions examined DPOAE threshold shifts for both the cochleostomy-only (CO) and cochleostomy-plus-canalostomy (C+C) surgical approaches [9]. Average threshold shifts and statistical significance of peak response compared to baseline across frequencies for

each surgical approach are presented in Figure 5. Both surgical approaches allow direct, intracochlear delivery of compounds without acute impact to auditory function as demonstrated by stable thresholds during the initial artificial perilymph infusion and subsequent threshold recovery during the washout phase. Greater shifts at high frequencies are consistent with higher salicylate concentrations in the basal turn of the cochlea; near the point of infusion. The CO approach provided statistically significant threshold shifts from baseline for frequencies above 17.9 kHz, while the C+C approach provided statistically significant threshold shifts at all frequencies tested, suggesting enhanced access to apical cochlear structures. Examination of the time course of DPOAE threshold shifts for each measured frequency reveals statistically significant differences between methods, with the most significant differences occurring for more apical frequencies, consistent with higher achieved salicylate concentrations in apical regions with the directed perfusion cochleostomy-plus-canalostomy approach.

These findings support the hypothesis that a fluidic exit in the posterior semicircular canal enhances access to apical structures as compared to a basal turn cochleostomy-only infusion through facilitated longitudinal flow from cochlear base to apex. This enhanced access has important implications for research into new therapeutic approaches for hearing loss. Reduced cochlear concentration gradients are important for compounds with a narrow therapeutic dose range, and for therapies targeting low-frequency dysfunction. The magnitude of concentration gradients will scale with scalae length, suggesting concentration gradient control will become critically important for translation of therapies to humans, where cochlear size limits efficacy of diffusion-mediated distribution.

Correlation of concentration gradients to physiological response, as has been done in this study, is potentially complicated by non-uniform sensitivity throughout the cochlea. Future investigations may utilize more direct measures of drug concentration as has been done in the guinea pig with TMPA [62], but must accommodate the size limitations of the mouse cochlea. One such approach involves delivery of a contrast agent to the cochlea during microCT imaging to directly quantify the infused agent concentration throughout the cochlea with fine spatial and temporal resolution [63]. Such quantification could be used to enhance existing models of inner ear drug delivery through refined clearance parameters and a better understanding of modes of interscalar transport. Enhanced models ultimately will permit simulated exploration of infusion paradigms for reduction of concentration gradients; a critical step in the development of advanced deafness therapies involving intracochlear drug delivery.

7. Cochlear Prosthesis-mediated Delivery

Development of safe, robust and reliable surgical approaches for inner ear drug delivery represents a challenge equal to that of the technical tasks associated with development of the delivery device. This surgical challenge suggests that a logical route for early implementation of inner ear drug delivery systems may be provided by integrating a delivery device with a cochlear prosthesis, a device that directly stimulates the auditory nerve in patients with profound hearing loss. Cochlear prostheses, also known as cochlear implants, comprise a microphone, transmitter, speech processor and electrode array, and are generally implanted through the RWM or via a cochleostomy into the ST. This direct implantation approach provides a pathway for drug delivery using a device and drug reservoir that is attached to the implant. One such approach is described by Shepherd et al. [64]; total drug volumes of roughly 200 μL were delivered at very low infusion rates of 0.25 $\mu\text{L/hr}$.

One clinical approach for cochlear implant-mediated delivery is the infusion of neurotrophic factors aimed at preserving spiral ganglion cells to enhance hearing in implanted patients.

Multiple growth factors, either singly or in combination, have been explored as a means to preserve SG cells. The simplest inner ear delivery approach for systems with a cochlear implant involves coating the implant device with a drug-eluting polymer that provides simple release kinetics for short periods of time. This approach is limited by a lack of control over the release kinetics and a short duration of delivery. A more advanced approach integrates a catheter or an infusion pump with the implant. These systems take advantage of recent developments in cochlear implant technology such as the use of shortened electrodes and partial insertion of the electrode, both aimed at avoiding structural damage during insertion of the implant. Bioresorbable coatings applied to the surface of the cannula appear to reduce insertion forces, and the infusion of steroids at the time of implantation may minimize surgical trauma. A single-use catheter with syringe delivery represents the simplest implementation of this approach, but infusion pumps have also been explored for longer-term delivery. One interesting approach to achieve longer-term delivery is laser machining of the cannula to generate multiple delivery ports that will improve apical distribution of the drug. Hole diameters as small as 50 μm have been machined into the cannula to enhance drug distribution profiles, as shown in Figure 6 [65].

8. Emerging Challenges

Drug delivery to the inner ear without damaging hearing remains a significant challenge. Microsystems technologies continue to play a key role in addressing these challenges and will ultimately yield solutions that overcome the limitations of currently available prostheses. Delivery of agents to the cochlea in animal models presents significant size constraints which are spurring innovations that aid therapy development, and may enable new opportunities in human translational results.

Drug delivery to the inner ear in animal models presents specific challenges associated with size, fluid volumes, the cochlear interface, and chronic delivery. Generally a small capillary tube, either polyimide or polyimide coated fused silica, is used to connect the pump system to the cochlea. The diameter of the target scalae at the point of infusion determines maximal allowable insertion depth into the cochleostomy, which for the mouse can be smaller than 200 μm . This is generally controlled either by use of a micromanipulator and microscope visualization by the surgeon, or by creation of an insertion stop on the cannula. The latter requires precise placement of the insertion stop to control insertion depth; precision which is difficult to achieve using manual production methods. A micromachined mold approach which provides precise control of insertion depth with a silastic insertion stop has been demonstrated[66]. A silicon mold was created using standard micromachining fabrication processes, involving a combination of anisotropic KOH etching and a backside aligned circular deep reactive ion etch which allows the cannula tubing to be inserted through the mold. The molding process and resulting cannula with molded insertion stop are shown in Figure 7. The mold fabrication process and molding techniques permit insertion depth control within 5 μm with a controllable interface area to promote robust sealing to the tympanic bulla at the cochleostomy site.

The low fluid volumes (< 10 μl) and flow rates (<50 nl/min) associated with small rodent inner ear drug delivery dictate precise control of fluidic interfaces and entrapped air in the fluidic system. While entrapped air can be used to separate fluids for diffusion isolation within the capillary tubing [9] the volumes must remain small (a few nl) to avoid errors in infused volumes. Larger volumes (> 0.5 μl) of air result in compression during pumping and delayed flow to the cannula outlet. Leaks in the system at fluidic interfaces or defects in the cannula tubing can drastically impact actual flow rates. Thus, each experiment requires careful verification that intended flow rates are achieved, using microscope-based observation as well as measurement of interface movement distances over time.

Chronic infusions require departure from syringe pump systems if the complications of tethering are to be avoided. Backpack systems allow inclusion of power, the micropump, control electronics, and a reservoir of the drug to be delivered. As drug infusion systems shrink in size, implantation becomes another possible alternative for chronic infusions.

Inner ear drug delivery with implantable microsystems presents significant challenges and unique requirements, including accurate dosing at low flow rates, low voltage operation, a fluid flow path with controlled characteristics, and the ability to interface to infusion tubing. Emerging technologies are beginning to address these challenges in a platform targeted for implantation in the mouse, but with scalability to larger animals and potentially humans [67].

Accurate dosing requires control of flow rates, ideally with sensing feedback for confirmation of achieved flow. In the laminar, low flow rate regime, sensing is most easily accomplished through the use of a thermal anemometer. A resistive element generates heat that is transferred to the fluid, with the rate of heat transfer correlated to the fluid flow rate. The bridge structure within the resistor consists of a boron-doped polysilicon heater encapsulated by silicon oxide and silicon nitride, with the dimensions optimized to balance sensitivity, efficiency and mechanical robustness.

The fluid flow path within an implantable micropump must be non-reactive, non-water absorbing and biocompatible. A process for the creation of deformable diaphragms over pump chambers and channels with simultaneous coating of channel surfaces has been developed, enabling integration of a biocompatible fluid flow path. The process utilizes an oxide mask patterned with line/space pairs to define fluidic channels and pump chambers, which are then isotropically etched in the silicon substrate through the mask. Subsequent deposition of Parylene-C (chlorinated poly-para-xylylene), a biocompatible polymer with a long mean free path in the vapor phase, provides a coating for the interior surfaces of the fluidic channels. Continued deposition encapsulates the oxide hard mask, sealing the cavities and creating deformable membranes over the pump chambers.

Capillary tubing is generally used to connect the micropump system to the cochlea for inner ear drug delivery. Coupling to the microfluidic system can add unacceptable volume for implant applications if additional coupling structures or out-of-plane approaches are utilized. Adhesives, epoxies and elastomers for coupling can result in blocked capillaries and/or gap formation and dead volumes. Recent advances in in-plane interconnects for small diameter capillary tubing has significantly reduced overall fluidic interconnect volume while minimizing gap formation and eliminating blocked capillaries [68]. This robust interconnect technology requires only a single mask level, and leverages deposition of parylene-C onto room temperature surfaces to capture small diameter capillary tubing. Parylene-C provides the requisite controlled deposition of a biocompatible sealing material into the small spaces between the capillary and the microfluidic channel. The characteristics of Parylene-C deposition into channels were invoked in conjunction with equations describing molecular flow and diffusion to spatially model monomer concentration and to estimate the polymer deposition within tapered channels. Modeling of the deposition process permitted optimization of channel geometries for full gap filling without voids at the tubing/channel interface. Devices based on this process modeling have been fabricated and characterized for voids along the length of the interconnect, burst/leakage pressure, and pull strength. The interconnects occupied a total volume of 0.018 mm^3 (18 nl), had zero dead volume, held 120 psi pressure, and exhibited a pull strength of 2.9N with an insertion depth of only $500 \text{ }\mu\text{m}$. An image of a microcapillary exiting the side of the microfluidic chip is shown in Figure 8.

Pumps for implantable applications may require the development of low voltage actuation systems which can be integrated over deformable pump membranes as an alternative to high voltage piezoelectrics. Thermo-pneumatic actuation is one approach recently investigated for inner ear drug delivery systems. Using direct write dispensing technologies, multilayer structures were written over a four chamber peristaltic micropump consisting of pump chambers, channels and interconnects [69]. This hybrid MEMS approach allows utilization of aspects of both traditional MEMS and emerging direct write MEMS fabrication capabilities, and may potentially expand the pool of available actuation technologies that can be easily integrated with microsystems-based pump systems.

One of the principal challenges in intracochlear drug delivery is the avoidance of biofouling of implanted devices during extended delivery. This challenge necessitates the use of highly biocompatible materials for all components in contact with biological fluids such as perilymph, and robust encapsulation of device elements that may be prone to fouling or trigger inflammatory responses such as electronic components, power sources and flow sensors. Fouling mechanisms and general biocompatibility may be associated with chemical interactions with the material surfaces themselves, but may also involve mechanical factors such as the relative stiffness or compliance of tubing, wiring and device structures that may impart stresses to the surrounding tissue. Another critical aspect of biofouling is the danger of partial or total occlusion of the delivery cannula itself, due to crystallization of the drug, protein coating of the surface of the inner lumen, or other related phenomena. The slow infusion rates used in most systems may exacerbate this process because they do not provide sufficient pumping forces to clear blockages as they form in the delivery tubing.

9. Summary

The inner ear is a complex organ requiring special considerations for drug delivery. Challenges including small size, inaccessibility, and delicate pressure-sensitive structures necessitate capabilities beyond those of most common microsystems-based approaches for this application. These challenges present opportunities for novel microsystems uniquely designed for delivery to the inner ear. Researchers are developing methods including micropumps, reciprocating systems, directed cochlear perfusion, and cochlear prosthesis-based systems that hold great promise in treating the unmet needs of many patients suffering from inner ear diseases and for whom current treatments are limited.

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References

1. Swan EE, Mescher MJ, Sewell WF, Tao SL, Borenstein JT. Inner ear drug delivery for auditory applications. *Adv Drug Deliv Rev.* 2008; 60:1583–1599. [PubMed: 18848590]
2. McCall AA, Swan EE, Borenstein JT, Sewell WF, Kujawa SG, McKenna MJ. Drug delivery for treatment of inner ear disease: current state of knowledge. *Ear Hear.* 31:156–165. [PubMed: 19952751]
3. Holley MC. The auditory system, hearing loss and potential targets for drug development. *Drug Discovery Today.* 2005; 10:1269–1282. [PubMed: 16214671]
4. Saltzman, WM. *Drug Delivery: Engineering Principles for Drug Therapy.* Oxford University Press; New York: 2001.

5. Chen Z, Kujawa SG, McKenna MJ, Fiering JO, Mescher MJ, Borenstein JT, Swan EE, Sewell WF. Inner ear drug delivery via a reciprocating perfusion system in the guinea pig. *J Control Release*. 2005; 110:1–19. [PubMed: 16274830]
6. Fiering J, Mescher MJ, Leary Swan EE, Holmboe ME, Murphy BA, Chen Z, Peppi M, Sewell WF, McKenna MJ, Kujawa SG, Borenstein JT. Local drug delivery with a self-contained, programmable, microfluidic system. *Biomed Microdevices*. 2009; 11:571–578. [PubMed: 19089621]
7. Mescher MJ, Swan EE, Fiering J, Holmboe ME, Sewell WF, Kujawa SG, McKenna MJ, Borenstein JT. Fabrication Methods and Performance of Low-Permeability Microfluidic Components for a Miniaturized Wearable Drug Delivery System. *J Microelectromech Syst*. 2009; 18:501–510. [PubMed: 20852729]
8. Borkholder DA. State-of-the-art mechanisms of intracochlear drug delivery. *Curr Opin Otolaryngol Head Neck Surg*. 2008; 16:472–477. [PubMed: 18797291]
9. Borkholder DA, Zhu X, Hyatt BT, Archilla AS, Livingston WJ 3rd, Frisina RD. Murine intracochlear drug delivery: reducing concentration gradients within the cochlea. *Hear Res*. 2010; 268:2–11. [PubMed: 20451593]
10. Lynch ED, Kil J. Compounds for the prevention and treatment of noise-induced hearing loss. *Drug Discov Today*. 2005; 10:1291–1298. [PubMed: 16214673]
11. DePalma RG, Burris DG, Champion HR, Hodgson MJ. Blast injuries. *N Engl J Med*. 2005; 352:1335–1342. [PubMed: 15800229]
12. Sendowski I, Abamrane L, Raffin F, Cros A, Clarencon D. Therapeutic efficacy of intra-cochlear administration of methylprednisolone after acoustic trauma caused by gunshot noise in guinea pigs. *Hearing Research*. 2006; 221:119–127. [PubMed: 17008037]
13. Rybak L. Mechanisms of cisplatin ototoxicity and progress in ototprotection. *Curr Opin Otolaryngol Head Neck Surg*. 2007; 15:364–369. [PubMed: 17823555]
14. Rybak LP, Whitworth CA. Ototoxicity: therapeutic opportunities. *Drug Discov Today*. 2005; 10:1313–1321. [PubMed: 16214676]
15. Bhandare N, Antonelli PJ, Morris C, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. *Int J Radiat Oncol Biol Phys*. 2007; 67:469–479. [PubMed: 17236969]
16. Mosnier I, Bouccara D, Sterkers O. Management of idiopathic sudden sensorineural hearing loss. *Otorhinolaryngologia Nova*. 1999; 9:217–223.
17. Ryan AF, Harris JP, Keithley EM. Immune-mediated hearing loss: basic mechanisms and options for therapy. *Acta Oto-Laryngologica, Suppl*. 2002; 548:38–43.
18. Yang GS, Song HT, Keithley EM, Harris JP. Intratympanic immunosuppressives for prevention of immune-mediated sensorineural hearing loss. *Am J Otol*. 2000; 21:499–504. [PubMed: 10912694]
19. Matteson EL, Fabry DA, Strome SE, Driscoll CL, Beatty CW, McDonald TJ. Autoimmune inner ear disease: diagnostic and therapeutic approaches in a multidisciplinary setting. *J of the American Academy of Audiology*. 2003; 14:225–230.
20. Harner SG, Driscoll CL, Facer GW, Beatty CW, McDonald TJ. Long-term follow-up of transtympanic gentamicin for Meniere's syndrome. *Otol Neurotol*. 2001; 22:210–214. [PubMed: 11300271]
21. Harner SG, Kasperbauer JL, Facer GW, Beatty CW. Transtympanic gentamicin for Meniere's syndrome. *Laryngoscope*. 1998; 108:1446–1449. [PubMed: 9778281]
22. Chia SH, Gamst AC, Anderson JP, Harris JP. Intratympanic gentamicin therapy for Meniere's disease: a meta-analysis. *Otol Neurotol*. 2004; 25:544–552. [PubMed: 15241234]
23. Hoffer ME, Allen K, Kopke R, Weisskopf P, Gottshall KR, Wester D. Transtympanic versus sustained-release administration of gentamicin: kinetics; morphology; and function. *The Laryngoscope*. 2001; 111:1343–1357. [PubMed: 11568567]
24. Hoffer ME, Wester D, Kopke RD, Weisskopf P, Gottshall K. Transtympanic management of tinnitus. *Otolaryngol Clin N Am*. 2003; 36:353–358.
25. Schuknecht, H. *Pathology of the Ear*. Lea and Febiger; Malvern, PA: 1993.
26. Tsuji J, Liberman MC. Intracellular labeling of auditory nerve fibers in guinea pig: central and peripheral projections. *The J of Comparative Neurology*. 1997; 381:188–202.

27. Thalmann R, Comegys T, Thalmann I. Amino acid profiles in inner ear fluids and cerebrospinal fluid. *Laryngoscope*. 1982; 92:321–328. [PubMed: 7070173]
28. Thalmann I, Kohut R, Ryu J, Thalmann R. High resolution two-dimensional electrophoresis: technique and potential applicability to the study of inner ear disease. *Am J Otol*. 1995; 16:153–157. [PubMed: 8572113]
29. Thalmann I, Kohut R, Ryu J, Comegys T, Senarita M, Thalmann R. Protein profile of human perilymph: in search of markers for the diagnosis of perilymph fistula and other inner ear disease. *Otolaryngol Head Neck Surg*. 1994; 111:273–280. [PubMed: 8084635]
30. Scheibe F, Haupt H. Biochemical differences between perilymph, cerebrospinal fluid and blood plasma in the guinea pig. *Hear Res*. 1985; 17:61–66. [PubMed: 3997682]
31. Medina J, Drescher D. The amino-acid content of perilymph and cerebrospinal fluid from guinea-pigs and the effect of noise on the amino-acid composition of perilymph. *Neuroscience*. 1981; 6:505–509. [PubMed: 7219728]
32. Swan EE, Peppi M, Chen Z, Green KM, Evans JE, McKenna MJ, Mescher MJ, Kujawa SG, Sewell WF. Proteomics analysis of perilymph and cerebrospinal fluid in mouse. *Laryngoscope*. 2009; 119:953–958. [PubMed: 19358201]
33. Swan EEL, Peppi M, Chen Z, Green KM, Evans JE, McKenna MJ, Mescher MJ, Kujawa SG, Sewell WF. Proteomics analysis of perilymph and cerebrospinal fluid in mouse. *The Laryngoscope*. 2009; 119:953–958. [PubMed: 19358201]
34. Igarashi M, Ohashi K, Ishii M. Morphometric comparison of endolymphatic and perilymphatic spaces in human temporal bones. *Acta Otolaryngol*. 1986; 101:161–164. [PubMed: 3518332]
35. Silverstein H. Use of a new device, the MicroWick, to deliver medication to the inner ear. *Ear Nose Throat J*. 1999; 78:595–600. [PubMed: 10485154]
36. Suryanarayanan R, Srinivasan VR, O'Sullivan G. Transtympanic gentamicin treatment using Silverstein MicroWick in Meniere's disease patients: long term outcome. *J Laryngol Otol*. 2009; 123:45–49. [PubMed: 18533050]
37. Hill SL, Digges NB, Silverstein H. Long-term follow-up after gentamicin application via the Silverstein MicroWick in the treatment of Meniere's disease. *Ear Nose Throat J*. 2006; 85:494–498. [PubMed: 16999055]
38. Silverstein H, Jackson LE, Rosenberg SI. Silverstein MicroWick for treatment of inner ear disease. *Operative Techniques in Otolaryngology*. 2001; 12:144–147.
39. Wijk, Fv; Staecker, H.; Lefebvre, PP. Topical steroid therapy using the Silverstein MicroWick in sudden sensorineural hearing loss after failure of conventional treatment. *Acta Otolaryngol*. 2007; 127:1012–1017. [PubMed: 17851934]
40. Wijk, Fv; Staecker, H.; Keithley, E.; Lefebvre, PP. Local perfusion of the tumor necrosis factor alpha blocker infliximad to the inner ear improves autoimmune neurosensory hearing loss. *Audiol Neurotol*. 2006; 11:357–365. [PubMed: 16988499]
41. DeCicco MJ, Hoffer ME, Kopke RD, Wester D, Allen KA, Gottshall K, O'Leary MJ. Round window microcatheter-administered microdose gentamicin: results from treatment of tinnitus associated with Meniere's disease. *Int Tinnitus J*. 1998; 4:141–143. [PubMed: 10753403]
42. Suryanarayanan R. Long-term results of gentamicin inner ear perfusion in Meniere's disease. *The J of Laryngology & Otology*. 2004; 118:489–495.
43. Thomsen J, Charabi S, Tos M. Preliminary results of the new delivery system for gentamicin to the inner ear in patients with Meniere's disease. *Eur Arch Otorhinolaryngol*. 2000; 257:362–365. [PubMed: 11052245]
44. Weisskopf P, Hoffer ME, Kopke RD, Gottshall K, Allen K, Wester D. Microdose gentamicin delivered via the round window microcatheter: a therapeutic option in Meniere's disease. *Operative Techniques in Otolaryngology*. 2001; 12:154–156.
45. Plontke SK, Lowenheim H, Preyer S, Leins P, Dietz K, Koitschev A, Zimmermann R, Zenner HP. Outcomes research analysis of continuous intratympanic glucocorticoid delivery in patients with acute severe to profound hearing loss: basis for planning randomized controlled trials. *Acta Otolaryngol*. 2005; 125:830–839. [PubMed: 16158529]
46. Plontke SK, Lowenheim H, Mertens J, Engel C, Meisner C, Weidner A, Zimmermann R, Preyer S, Koitschev A, Zenner HP. Randomized, double blind, placebo controlled trial on the safety and

- efficacy of continuous intratympanic dexamethasone delivered via a round window catheter for severe to profound sudden idiopathic sensorineural hearing loss after failure of systemic therapy. *Laryngoscope*. 2009; 119:359–369. [PubMed: 19172627]
47. Swan EEL, Mescher MJ, Sewell WF, Tao SL, Borenstein JT. Inner ear drug delivery for auditory applications. *Adv Drug Del Rev*. 2008; 60:1583–1599.
 48. Shimogori H, Yamashita H. Efficacy of intracochlear administration of betamethasone on peripheral vestibular disorder in the guinea pig. *Neurosci Lett*. 2000; 294:21–24. [PubMed: 11044577]
 49. Orita H, Shimogori H, Yamashita H. unilateral intra-perilymphatic infusion of substance P enhances ipsilateral vestibulo-ocular reflex gains in the sinusoidal rotation test. *Neurosci Lett*. 2009; 449:207–210. [PubMed: 19022352]
 50. Tam BTG, Foong KH, Lee MMG, Ruan R. Polyethylenimine-mediated cochlear gene transfer in guinea pigs. *Arch Otolaryngol*. 2008; 134:884–891.
 51. Abaamrane L, Raffin F, Schmerber S, Sendowski I. Intracochlear perfusion of leupeptin and z-VAD-FMK: influence of antapoptotic agents on gunshot-induced hearing loss. *Eur Arch Otorhinolaryngol*. 2011; 268:987–993. [PubMed: 21246210]
 52. Sewell WF, Borenstein JT, Chen Z, Fiering J, Handzel O, Holmboe M, Kim ES, Kujawa SG, McKenna MJ, Mescher MM, Murphy B, Swan EE, Peppi M, Tao S. Development of a microfluidics-based intracochlear drug delivery device. *Audiol Neurotol*. 2009; 14:411–422. [PubMed: 19923811]
 53. Chen Z, Kujawa SG, McKenna MJ, Fiering JO, Mescher MJ, Borenstein JT, Swan EEL, Sewell WF. Inner Ear drug delivery via a reciprocating perfusion system in the guinea pig. *J Control Release*. 2005; 110:1–19. [PubMed: 16274830]
 54. Handzel O, Wang H, Fiering J, Borenstein JT, Mescher MJ, Swan EEL, Murphy BA, Chen Z, Peppi M, Sewell WF, Kujawa SG, McKenna MJ. Mastoid cavity dimensions and shape: method of measurement and virtual fitting of implantable devices. *Audiol Neurotol*. 2009; 14:308–314. [PubMed: 19372649]
 55. Sewell WF, Borenstein JT, Chen Z, Fiering J, Handzel O, Holmboe M, Kim E, Kujawa SG, McKenna MJ, Mescher MJ, Murphy BA, Swan EEL, Peppi M, Tao SL. Development of a microfluidics-based intracochlear drug delivery device. *Audiol Neurotol*. 2009; 14:411–422. [PubMed: 19923811]
 56. Pararas EEL, Chen Z, Fiering J, Mescher MJ, Kim ES, McKenna MJ, Kujawa SG, Borenstein JT, Sewell WF. Kinetics of reciprocating drug delivery to the inner ear. *J Control Release*. 2011; 152:270–277. [PubMed: 21385596]
 57. Fiering J, Mescher MJ, Swan EEL, Holmboe ME, Murphy BA, Chen Z, Peppi M, Sewell WF, McKenna MJ, Kujawa SG, Borenstein JT. Local drug delivery with a self-contained, programmable, microfluidic system. *Biomedical Microdevices*. 2009; 11:571–578. [PubMed: 19089621]
 58. Mescher MJ, Swan EEL, Fiering J, Holmboe M, Sewell WF, Kujawa SG, McKenna MJ, Borenstein JT. Fabrication Methods and Performance of Low-Permeability Microfluidic Components for a Miniaturized Wearable Drug Delivery System. *IEEE JMEMS*. 2009; 18:501–510.
 59. Plontke SK, Biegner T, Kammerer B, Delabar U, Salt AN. Dexamethasone concentration gradients along scala tympani after application to the round window membrane. *Otol Neurotol*. 2008; 29:401–406. [PubMed: 18277312]
 60. Chen Z, Mikulec AA, McKenna MJ, Sewell WF, Kujawa SG. A method for intracochlear drug delivery in the mouse. *J Neurosci Methods*. 2006; 150:67–73. [PubMed: 16043228]
 61. Oliver D, He D, Klocker N, Ludwig J, Schulte U, Waldegger S, Ruppertsberg J, Dallos P, Fakler B. Intracellular anions as the voltage sensor of prestin, the outer hair cell motor protein. *Science*. 2001; 292:2340–2343. [PubMed: 11423665]
 62. Salt AN, Ohyama K, Thalmann R. Radial communication between the perilymphatic scalae of the cochlea. II Estimation by bolus injection of tracer into the sealed cochlea. *Hear Res*. 1991; 56:37–43. [PubMed: 1769923]

63. Gladstone, M.; Zhu, X.; Luebke, A.; Frisina, R.; Borkholder, DA. Using micro-computed tomography to assess transport parameters through fluid spaces of the cochlea. Biomedical Engineering Society National Conference; Austin: University of Texas; 2010.
64. Shepherd R, Xu J. A multichannel scala tympani electrode array incorporating a drug delivery system for chronic intracochlear infusion. *Hearing Res.* 2002; 172:92–98.
65. Staecker H, Jolly C, Garnham C. Cochlear implantation: an opportunity for drug development. *Drug Discov Today.* 2010; 15:314–321. [PubMed: 20184966]
66. Johnson DG, Zhu XX, Frisina RD, Borkholder DA. Micro-molded cannulae for intracochlear infusions in small rodents. *Conf Proc IEEE Eng Med Biol Soc.* 2007; 2007:6617–6620. [PubMed: 18003542]
67. Johnson DG, Waldron MJ, Frisina RD, Borkholder DA. Implantable micropump technologies for murine intracochlear infusions. *Conf Proc IEEE Eng Med Biol Soc.* 2010; 1:6441–6444. [PubMed: 21096713]
68. Johnson D, Frisina R, Borkholder D. In-Plane Biocompatible Microfluidic Interconnects for Implantable Microsystems. *IEEE Trans Biomed Eng.* 2011; 58:943–948. [PubMed: 21147591]
69. Johnson, D.; Getpreecharsawas, J.; Balasubramanian, S.; Datar, A.; Cormier, D.; Borkholder, DA. Hybrid MEMS: extending micro manufacturing with direct write processes. Technical Digest of Transducers Research Foundation Technologies for Future Micro-Nano Manufacturing Workshop; 2011.

Figure 1.

a. A mid-modiolar section from a human temporal bone indicates the coiled structure of the cochlea as it winds around a central modioli. Each segment (b.) contains 3 fluid filled structures, the scala tympani (ST) scala media (SM) and scala vestibuli (SV). The organ of Corti (OC) is shown at the base of the SM. Used with permission from Elsevier [47].

Figure 2.

a. A schematic drawing of the reciprocating delivery system showing the flexible membrane and actuator. b. Photograph of wearable device for guinea pig studies. The device measures $5.5 \times 4.0 \times 3.8$ cm. Used with permission from Karger AG Basel and Springer [52, 57].

Figure 3.

CAP threshold shifts due to DNQX delivery at various frequencies. Three flow rate profiles are shown with higher flow rates causing increased threshold rises. Multiple experiments for each flow rate are shown. Used with permission from Elsevier [56].

Figure 4.

Theoretical flow path within the cochlea and vestibular system for a cochleostomy-only infusion (green), and a cochleostomy-plus-canalostomy perfusion (red). Pressure driven flow is depicted with solid lines while dotted lines represent diffusion mechanisms. Cochlear aqueduct (ca); scala tympani (st), scala vestibuli (sv). Used with permission from Elsevier [9].

Figure 5.

Frequency dependent DPOAE threshold shifts. Surgery and infusion of artificial perilymph had insignificant impact on thresholds, while frequency dependent threshold shifts were observed with 10mM salicylate. Statistical comparison of peak threshold shifts to baseline for each frequency and each surgical approach are shown on the figure (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Data are plotted as mean $\pm$ SEM ($n = 8$ animals for each approach). Used with permission from Elsevier [9].

Figure 6. Illustration of drug delivery enabled by laser-drilled holes of 50 micron diameter to enable enhanced drug distribution in the cochlea. Used with permission from Elsevier [64].

Figure 7. Micromolded cannula insertion stops. (Left) Polyimide micro-tubing is inserted through a micromachined silicon mold, with a precise volume of Silastic delivered and the tubing cut to length following Silastic cure. (Right) Scanning electron micrograph of the cannula with integrated insertion stop. Inset is tubing tip (magnification 320 $\times$). Insertion depth is A, the contact area for bonding is defined by dimensions B and C, and post-cut roundness is defined by D and E. Used with permission from IEEE [65].

Figure 8. SEM of the side of the microfluidic chip with small diameter (140- μm OD) tubing exiting in-plane. Used with permission from IEEE [67].