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Microsystems technologies for drug delivery to the inner ear ☆

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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.

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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 are likely to reach unintended targets and may be toxic, and therefore progress toward 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

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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 μl 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 toward 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 toward 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 toward 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 otoxocity, 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.