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Intracochlear drug delivery systems: a novel approach whose time has come

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1. Introduction

There is a growing prevalence of hearing loss across the globe, with over 360 million patients worldwide suffering from this condition. Factors such as an increasingly aging population, overexposure to noise in the youth and in the military, and exposure to ototoxic but lifesaving drugs such as aminoglycoside antibiotics and platinum-based chemotherapy, exacerbate the spreading of hearing loss disability. An overview of the various modes of hearing loss and current Standard of Care is shown in Figure 1. Over the past two decades, tremendous progress in understanding the underlying mechanisms of hearing loss at the cellular and molecular level has been made, and a number of promising approaches toward hearing restoration are focusing in establishing regeneration of the hair cells and cochlear nerve endings [1,2], including novel regeneration molecules, apoptosis inhibitors, gene therapies and small-interfering RNA therapies. Translation of these discoveries into clinical therapies has been gated by the fact that the inner ear is a privileged space protected by the blood-cochlear barrier (BCB), and the small size, delicate nature of hearing structures and remoteness of the cochlea from conventional routes of delivery represent significant obstacles toward clinical therapies for these diseases. Existing modes of administration such as oral or injectable routes, or local approaches such as infusion pumps, cochlear implants, and single intratympanic (IT) injections, are not particularly effective in reaching or precisely dosing drugs to the cochlea. For safe and efficacious inner ear administration, precisely controlled, programmable and chronic delivery systems may be required. Design and development of these systems, guided by computational models for drug transport in the cochlea [3], have leveraged rapid advances in microfabrication and microfluidics technologies toward platforms suitable for preclinical and clinical use.

2. Advances in drug development

Emerging therapeutic interventions for SensoriNeural Hearing Loss (SNHL) associated with exposure to loud noise, aging, infection, and ototoxicity, are being evaluated at multiple stages of development. Emerging therapeutic approaches for various types of hearing loss are listed in Table 1. Principal strategies for treating SNHL include hair cell and cochlear nerve afferents regeneration, reversal of cochlear oxidative stress damage, and apoptosis inhibition. Large numbers of industrial, government, and academic groups are conducting clinical trials at various phases [5], with many novel treatments on the horizon. One such example is the clinical trial with the JNK ligand AM-111 that show functional recovery in humans with severe SNHL [6]. On 28 November 2017, it was however announced that the HEALOS Phase 3 clinical trial of AM-111 in severe to profound sudden deafness did not meet its primary efficacy end point on the per protocol population. The mode of delivery of the drug to these patients stands as one hypothesis as a cause for this clinical failure.

Noise-induced hearing loss (NIHL) is often characterized by cumulative and irreversible loss of hair cells and auditory neurons in the cochlea, which leads to reductions in threshold sensitivity [7]. Recent drug development strategies focus on hair cell regeneration and regrowth of the cochlear nerve afferents below the hair cells. The gamma secretase inhibitor LY411575 (a selective γ-secretase inhibitor that blocks Notch activation), alone or in combination with the glycogen synthase kinase inhibitor CHIR-99,021 (a potent and highly selective inhibitor of glycogen synthase kinase 3 (GSK-3)), has shown efficacy in generation of new hair cells in noise injury models in mouse studies [8] as well as in vitro studies [9]. Another route for repair of noise injury, targeting of synaptic regions between hair cells and cochlear nerve terminals, has been demonstrated in mouse studies using the neurotrophic factor NT-3, which is responsible for neuronal differentiation and survival. Noise-exposed mice treated with NT-3 exhibited regeneration of synapses and unmethylated nerve terminals at the hair cell-cochlear nerve interface as measured by immunostaining and functional recovery [10]. For Sudden SensoriNeural Hearing Loss (SSNHL), guinea pigs treated with glucocorticoids have shown efficacy with a combination therapy following lipopolysaccharide (LPS)-induced injury, where coadministration of a bronchodilator results in hearing recovery in contrast with a lack of response when glucocorticoids are given alone [11].

3. Drug delivery technologies

The presence of the BCB limits access of many compounds to the inner ear, although oral, intravenous and intramuscular
routes remain as standard modes of administration for many diseases [12]. Inefficiencies in these routes necessitate high dosages, resulting in systemic side effects that can be severe or life-threatening, as in the case of corticosteroids for autoimmune inner ear disease. As an alternative to systemic administration, several local delivery methods (described in Table 2) have emerged, including IT delivery of solutions or controlled release matrices to the Round Window Membrane (RWM), osmotic pumps [13], magnetic nanoparticles, cochlear prosthesist-mediated delivery [14], microneedle-based penetration of the RWM [15], and constant infusion intracochlear delivery systems [16]. These technologies have been demonstrated in preclinical animal studies and in human clinical trials to evaluate safety and efficacy, and some patients have experienced partial restoration of hearing while maintaining a margin of safety for sudden sensorineural hearing loss [17] and NIHL [18]. However, limitations in precision and duration of delivery [19], and the presence of large basal-to-apical gradients in drug distribution [16] represent potential stumbling blocks in advancing novel therapeutics to human clinical use. For instance, IT delivery of drug-loaded gels to the round window niche is reliant upon permeation of compounds through the RWM, a process sensitive to numerous factors including the size, charge, and lipophilicity of the molecule [20,21]. In addition, permeation rates between individuals and between species vary widely, presenting challenges in terms of the number of studies and replicates required to gather reliable data, and for future regulatory approval based on the performance of the delivery technology.

A micropump-based intracochlear route has the potential to overcome many of the aforementioned access limitations of other methods, providing direct access to the inner ear and enabling precise targeting of drug concentrations within the therapeutic window for extended delivery. Technologies such as osmotic pumps and direct infusion pumps have been demonstrated as a means to access the cochlea directly, but their limited duration of delivery and potential for shear-induced damage represent technical challenges. Further, the multiple targets for hearing loss, including sensory cells and cochlear afferent neural fibers, may necessitate administration of multiple compounds in a time-sequenced fashion, a capability within reach for intracochlear micropumping systems. Limitations on the maximum rate at which fluid can be introduced into the perilymph volume of the inner ear [12] place stringent requirements on infusion-based pumping systems, in order to avoid safety issues associated with mechanical damage to hearing structures. Toward this end, a reciprocating intracochlear delivery system has been developed, in which a precision micromechanical pump is operated in a push-pull mode to mix drug into perilymph while maintaining a constant fluid volume in the inner ear [22,23]. A prototype of this system is shown in Figure 2. This type of system can ultimately be designed to deliver compounds at a steady or time-varying rate for periods of several weeks, either singly or in combination therapies, followed by removal of the device and closure of the surgical site.

Advantages of micropump-based intracochlear delivery must be balanced against the invasive nature of the surgical procedure and the potential impact on safety and suitability for various patient populations. The most commonly demonstrated surgical approach for ICDD is through a cochleostomy [22,24,25], similar to that used for cochlear implants, but opportunities exist to establish access through the RWM to reduce the invasive aspects of the procedure and avoid drilling through cochlear bone. For extended duration delivery for patients with profound hearing loss, ICDD via surgical access with a cannula through cochleostomy may be most suitable, while larger patient populations may be addressed by acute (<1 h) micropump delivery through a temporary penetration of the RWM in a less invasive procedure.

4. Expert opinion

Hearing loss represents one of the most prevalent unmet needs in all of medicine, and bringing new treatments to market will require concerted advances along multiple fronts, due to the major challenges presented by the nature of the inner ear as a target for therapy. Challenges in achieving safety and efficacy faced by clinicians treating inner ear diseases are similar to the difficulties encountered during preclinical drug development, and delivery remains the central barrier to
Table 1. Selected therapeutic compounds are organized by delivery method, class of action, disease target, and stage of development.

<table>
<thead>
<tr>
<th>Route</th>
<th>Company</th>
<th>Compound</th>
<th>Class of action</th>
<th>Disease Target</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-tympanic route</td>
<td>Auris</td>
<td>AM-111</td>
<td>JNK inhibitor</td>
<td>Sudden sensorineural hearing loss</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Auris</td>
<td>AM-101</td>
<td>NMDA receptor antagonist</td>
<td>Tinnitus</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Otonomy</td>
<td>Otividec</td>
<td>Dexamethasone</td>
<td>Ménière's disease &amp; cisplatin-induced hearing loss</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Symphora</td>
<td>Latanoprost</td>
<td>PGF2 alpha agonist</td>
<td>Ménière's disease</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Stekin</td>
<td>STR901</td>
<td>PPAR gamma agonist</td>
<td>Sudden sensorineural Hearing Loss</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Otonomy</td>
<td>OTO-311</td>
<td>NMDA receptor antagonist</td>
<td>Tinnitus</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>FX:322</td>
<td>Undisclosed small molecules</td>
<td>Chronic noise-induced</td>
<td>Phase I</td>
</tr>
<tr>
<td>Intra-cochlear route</td>
<td>Auris and Cochlear</td>
<td>AM-111</td>
<td>JNK inhibitor</td>
<td>Sudden sensorineural hearing loss</td>
<td>Phase II</td>
</tr>
<tr>
<td>Oral route</td>
<td>Sensorion</td>
<td>SENS-111</td>
<td>Histamine H4 receptor antagonist</td>
<td>Vestibulopathy</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Edison pharmaceuticals</td>
<td>EPI-743</td>
<td>Antioxidant</td>
<td>Noise-induced hearing loss</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Sound pharmaceuticals</td>
<td>SPI-1005 (Ebselen)</td>
<td>NFE2L2 activator</td>
<td>Noise-induced hearing loss, Ménère’s disease, chemo-induced</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Autifony</td>
<td>AUTO0063</td>
<td>KCNJ1 modulator</td>
<td>Age-related hearing loss, Tinnitus, noise-induced hearing loss, Adjunct to cochlear implants</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>GSK</td>
<td>Vestipitant</td>
<td>NK1 receptor antagonist</td>
<td>Tinnitus</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>OtoLogic Pharmaceuticals</td>
<td>NHPN-1010 (HPN-07 + NAC)</td>
<td>Antioxidant</td>
<td>Cisplatin-induced hearing loss, noise-induced hearing loss</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Sensorion</td>
<td>SENS-401</td>
<td>5-HT3 receptor antagonist</td>
<td>Sudden sensorineural hearing loss</td>
<td>Phase I</td>
</tr>
<tr>
<td>IV route</td>
<td>Fennec</td>
<td>STS</td>
<td>Sodium thiosulfate</td>
<td>Chemo induced (prevent)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Intra-nasal route</td>
<td>Auris</td>
<td>AM-125</td>
<td>Histamine H1-receptor agonist + a H3-receptor antagonist</td>
<td>Ménière’s disease</td>
<td>Phase I</td>
</tr>
<tr>
<td>Intra-labyrinth route</td>
<td>GenVec/Novartis</td>
<td>CGF166</td>
<td>Gene therapy</td>
<td>Hearing loss &amp; vestibular dysfunction</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

EXPERT OPINION ON DRUG DELIVERY
Table 2. The effects of drugs on the inner ear depend in large part on the pharmacokinetics of the drug within the fluids of the inner ear, specifically what drug concentrations reach different regions of the ear and how long the drug stays in each region before disappearing.

<table>
<thead>
<tr>
<th>Systemic administration</th>
<th>Transtympanic injection</th>
<th>Intracochlear injection</th>
<th>Intra-cochlear drug delivery device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficiency (reaching perilymph)</td>
<td>Severely limited by low cochlear blood flow and BCB [26]</td>
<td>Limited, produce variable outcomes.</td>
<td>High minimized systemic exposure. Excellent dose and time control. Moderate if introduced by cochleostomy, but development of surgical approach for the device through the RWM is possible.</td>
</tr>
<tr>
<td>Safety</td>
<td>Moderate. Drugs can induce systemic toxicity.</td>
<td>High, minimally invasive procedure that can be performed in a physician's office.</td>
<td>Moderate if introduced by cochleostomy, but development of surgical approach for the device through the RWM is possible.</td>
</tr>
<tr>
<td>Drug diffusion in the perilymph</td>
<td>Entry shows saturation kinetics, but concentrations never exceed plasma levels; drug not actively accumulated [26] Electrical charge affects drug entry into the scala media.</td>
<td>RWM an anatomic barrier to absorption; patient variability in RWM thickness and permeability. Large molecules (MW 70,000) cannot diffuse across easily. Drug may enter via oval window into scala vestibuli and vestibule [27].</td>
<td>Bypass middle ear, minimize side effects. Reduce variability and distribute uniformly along scala tympani [27]. Drug retention dependent on size of RWM perforation. Fluid leakage controlled by encasing drug in gel or use of adhesive. Reciprocating flow enables zero-net-volume delivery and enhances drug mixing and apical transport. The base-to-apex concentration gradient reduced. Fouling reduced.</td>
</tr>
<tr>
<td>Drug bioavailability</td>
<td>Very limited. Kinetics of drug entry from BCB depends on local properties.</td>
<td>Limited. Loss of drug in the middle ear through the Eustachian tube, highly variable. Difficult to reach the apex. Drug leakage to CSF via the cochlear aqueduct close to the RW [28].</td>
<td>Substantially increase drug bioavailability in the inner ear, but may establish a base-to-apex gradient. Drug leakage to CSF via the cochlear aqueduct close to the RW [28]. Continuous drug application, enables access to cells of interest, increases target specificity. Multiple drugs could be injected.</td>
</tr>
<tr>
<td>Other</td>
<td>Can be conjugated with stimulating electrode. Possibility to make measurements of drug concentrations in real time [1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable for this type of drugs</td>
<td>Adapted for nanocarriers, hydrogels but not liquid formulations.</td>
<td>Can be used for liquid formulations and for large molecules (proteins, gene vectors, other macromolecules).</td>
<td>Can be used for liquid formulations and for large molecules (proteins, gene vectors, other macromolecules).</td>
</tr>
</tbody>
</table>
progress. Current preclinical models require very large numbers of animals due to significant variability and relatively small responses in hearing function, and this is largely related to difficulties in delivery rather than limitations of the compounds themselves. Without reliable delivery systems capable of maintaining control over drug concentrations within the therapeutic window for extended periods, it is difficult to assess efficacy, and functional assays for drug-treated groups often fall short of expected results for this reason.

To overcome the aforementioned barriers will require a convergence of disciplines and expertise working together to establish robust models for preclinical and ultimately clinical studies. The three critical components necessary for this concerted effort include the drug developers with expertise in the molecular biology and pharmacology of the auditory system, engineers and scientists capable of providing precise and reliable delivery technology, and experts in preclinical surgery and functional assays in animal models that are regulatory compliant. Together, those with knowledge and experience across these domains can establish robust and cost-effective approaches that will accelerate the pace at which new therapies will reach patients, by providing the tools necessary for biopharmaceutical companies to test their candidate therapies rapidly and accurately. Wide availability of such standard tools will principally benefit the drug development process initially, but as these advances become more established as a shared resource for the field, ultimately clinical implementation of new drugs paired with delivery systems will generate combination therapies available for patients suffering from hearing loss.

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Declaration of interest
Aurore Marie and Celia Belline are employees/founders of CILcare, a company focused on the development and implementation of pre-clinical models for the development of therapeutics for diseases of the inner ear. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References
   ** This review covers many of the principles involved in probing cellular and molecular targets involved in hearing loss.
   ** Major contribution to the field in defining the computational principles underpinning drug distribution in the inner ear.
   ** Important contribution covering many of the most recent emerging advances in therapeutic approaches for hearing loss.
   ** One of the more prominent reports on a clinical trial for SNHL.
   ** Major paper by one of the leading groups addressing advances in Noise-Induced Hearing Loss: Challenges and Opportunities.
   ** Key paper covering a newly discovered pathway for in vivo recovery of noise-damaged cochlea in small animal model.
   ** Major advance in understanding noise damage and the role of cochlear synapses, and therapeutic modality to recover hearing by treating synaptopathy.

- Comprehensive review of the field of inner ear drug delivery and the various modes of delivery and their advantages and disadvantages.


- Interesting approach to mitigating gradients in delivered drug concentration by reducing downstream fluidic resistance in the cochlea.


- Major report on variations and ranges of round window membrane permeability as a function of species.


- Detailed report on new microfluidic drug delivery technology for intracochlear administration in a guinea pig model.


- Round window membrane delivery of compounds demonstrating advantageous pharmacokinetics versus standard modes of delivery.