**Abstract**

**Objective**: To provide an overview of biotechnology and pharmaceutical companies active in the field of inner ear and central hearing disorders and their therapeutic programmes.

**Methods**: Scoping search of scientific and grey literature using broad search terms enabling data extraction on base of company and its therapeutic programme, its lead indications, products, targets, mechanisms of action and current phases of clinical development.

**Results**: A total of 43 biotechnology and pharmaceutical companies have been identified that are developing therapies for inner ear and central hearing disorders. Their programmes include drug-, cell- and gene-based approaches to prevent hearing loss or its progression, restoring hearing and regenerating the inner ear. Their therapeutic targets and specific mechanisms of action are wide-ranging, reflecting the complexity of the hearing pathways and the diversity of mechanisms underlying inner ear disorders. Whilst none of the novel products under investigation have yet made it to the clinical market, and a large proportion are still at preclinical phase, many therapies have already entered clinical testing with more expected to do so in the next few years.

**Conclusion**: A wide range of novel therapies targeting different hearing, balance and tinnitus pathways and patient populations are approaching the clinical domain. It is important that clinicians involved in the care of patients with hearing loss prepare for what may become a radically different approach to the management of hearing disorders, and develop a true understanding of the new therapies' mechanisms of action, applications and indications.

**Key Words**: Inner Ear, Regeneration, Clinical Trials, Small molecules OR Drug Therapy OR Pharmacological Therapy, Gene Therapy, Cell Therapy

## Introduction

Almost 500 million people worldwide currently suffer from hearing loss, of which over 90% are adults [1]. It is estimated that 10-14% of the world population will develop hearing loss during their life-times [2]. The most common form of hearing loss is sensorineural hearing loss (SNHL), which accounts for 90% of all hearing loss diagnoses [3–5]. Adult SNHL may present after noise exposure, use of ototoxic medication, as idiopathic (sudden onset hearing loss) and most commonly as age related hearing loss [6,7]. Many people with SNHL will also experience tinnitus, which may in fact be their most prominent symptom [8]. Other diseases of the inner ear such as Menière's disease or vestibular neuropathy may present with vertigo and/or tinnitus as the leading symptom, with or without an affected sense of hearing [9–11]

A wide range of genetic pathways and molecular mechanisms underlie these hearing disorders [12–15]. This is an area where major discoveries have been made over the past decade, which has allowed the development of novel drug, gene, and cell therapies to protect, restore and regenerate the hearing system [16]. This development is strongly driven by a growing number of biotech companies focusing on hearing therapies, some of which are spin-offs from universities or collaborations with large pharmaceutical companies. Their hearing disorders programs are supported by increasing investments from public and private funds.

Since these emerging therapies have the potential to radically change the management of hearing disorders, it is vital that clinicians prepare for this change and familiarise themselves with the new approaches. We have thus attempted to comprehensively review the field of emerging inner ear therapeutics to provide a map of the companies involved, their therapeutic programs, products, and stage of clinical development.

**Methods**

A search (June 2018) of both scientific and grey literature to identify companies working in the field of therapies for inner ear and central hearing disorders was performed.

Our scientific literature search strategy utilised Cochrane, Pubmed and EMBASE databases, with no restriction placed on publication date. Search terms used included combinations of: ‘novel’ or ‘innovative’ or ‘new’ AND ‘hearing’ or ‘tinnitus’ or ‘Ménière's’ or ‘ototoxic’ AND ‘gene’ or ‘stem cell’ or ‘molecule’ AND ‘therapy’ or ‘treat’ or ‘cure’ AND ‘company’ or ‘investment’.

Our grey literature searches utilised Google and other grey literature search engines as well as biotechnology and pharmaceutical company websites using combinations of the same terms as above. This enabled us to include potentially relevant government reports, policy statements and issues papers, conference proceedings, article pre- and post-prints, corporate statements, theses and dissertations, as well as company and biotechnology investment websites within our scope.

In our mapping, all scientific publications and data sources that featured information on a novel hearing therapy at any stage of development, as well as the biotechnology or pharmaceutical company driving this development were included. Publications that focused only on currently available therapies, that is hearing aids and cochlear implants without a gene, cell or drug strategy to improve device outcomes, were excluded.

We also approached professional networks to identify further relevant companies. Individuals contacted were from different stakeholders, including biotech, pharma, ENT, audiology and discovery hearing science. They were contacted directly

via email and asked for their knowledge of companies developing novel hearing therapies and grey literature. Individuals were contacted until content saturation was reached.

The following information from all data sources which met the inclusion criteria was extracted: company name and location, research programme, lead indications, products, therapeutic targets, mechanisms of action, methods of delivery and current phase(s) of clinical development.

**Results**

Table 1 (Supplementary Digital Content 1) presents the information collated from our search for companies working in the field of therapies for inner ear and central hearing disorders.

We identified 43 companies who to date have conducted pre-clinical or clinical studies in this field; 24 based in the USA, 4 in France, 4 in Germany, 3 in Switzerland, 2 in the UK, 1 in Japan, 1 in Israel, 1 in Sweden, 1 in Denmark, 1 in Belgium and 1 in The Netherlands .

Of these, 33 companies have research programs focusing on drug-based therapies, of which 16 have more than one hearing disorders program. Their programs cover 5 main areas; 1) Otoprotection - encompassing the lead indications of drug- or noise-induced or sudden onset SNHL and cochlear implant users (23 companies; 15 with products at preclinical phase, 2 at Phase I, 5 at Phase II and 3 at Phase III. 1 was discontinued at Phase II); 2) Regeneration - covering the lead indications of acute, chronic, or age-related SNHL and cochlear implant users (13 companies; 11 with products at preclinical phase and 2 at Phase I); 3) Tinnitus (13 companies; 8 with products at preclinical phase, 1 at Phase I and 1 at Phase II. 2 companies also had products that did not meet the endpoints at Phase II and 1 had products discontinued at Phase III); 4) Balance - including the lead indication of Meniere's disease (4 companies; 1 with products at preclinical phase, 1 at Phase I, 1 at Phase II and 1 at Phase III); and 5) Central Auditory Processing (1 company with products at preclinical phase).

Eight companies run programs involving gene-based therapies, of which 4 focus on AAV delivery (3 at preclinical phase for inherited SNHL lead indication and 1 at Phase II for SNHL regeneration), 1 focusing on CRISPR/Cas9 (at preclinical phase for

inherited SNHL) and 3 on RNAi (at preclinical phase across the lead indications of regeneration of SNHL, balance and tinnitus).

Two company's programs focused specifically on therapeutic delivery for inner ear therapies across two indications (SNHL and balance). The 62 products included in Table 1 (Supplementary Digital Content 1) cover a very wide range of mechanisms of action, with very few focusing on similar therapeutic targets. While some products have reached Phase III clinical trials, none of these novel therapies are yet available for clinical application.

## Discussion

With 43 companies working to develop novel therapeutics for inner ear and central hearing disorders, a number of new products are approaching our clinical domain. Since 2013, these companies have amassed $299.3 million in venture funding and $469.7 million in public funding, a leap from the $86.4 million in VC funding and $57 million in public funding raised in 2007-12 (see “Cranking the Volume”) [17]. The wide range of programs, targets and mechanisms of action covered by these companies reflects the diversity of the mechanisms that lead to inner ear and central hearing disorders and the complexity of research in the field. There will be no single cure for hearing, tinnitus or balance impairments and so clinicians will play a key role in advising patients which therapy to choose. We therefore strongly feel that clinicians involved in the care of these patients need to prepare for what may lead to significant changes to hearing care and services. Developing knowledge of these therapies and their mechanisms of action is vital and will require dedicated education and training for both the current and next generations of clinicians.

While major clinical research progress has recently been made, significant challenges specific to the various stages of the innovation pathway will still need to be overcome [18]. Clinical trials will need access to well-phenotyped, and ideally genotyped, patient populations. Registries of patients (for example, receiving cisplatin treatment, presenting with sudden sensorineural hearing loss, hereditary hearing loss) should be created, to allow industry, scientists and clinicians to successfully plan and run their clinical trials. While clinical data on some patient populations are already being collected locally; connecting such databases to national and international cohorts requires consensus and thus work to agree on funding, ownership, governance and content [19]. Biobanking of specimens will enable the application of newly emerging

diagnostics to vast numbers of patients [20]. Fast and (cost) effective screening for underlying causes of inner ear disease is not yet available but would accelerate the development of more targeted approaches and would provide valuable information to clinicians.

Capability for conducting clinical trials must also be improved within the hearing field. Professional and clinical trials networks specialized in inner ear and central hearing disorder research, with trained local trial support staff in place, will play vital roles in ensuring these trials (in particular later phase with larger numbers) can be delivered to time and target. At the same time, preclinical and clinical Contract Research Organisations (CROs) must develop specialised skills in order to provide appropriate operational support.

It is essential that the field starts thinking now about the implementation of novel therapies into clinical hearing services and how these therapies can be of most value to patients. Lessons should be learned from previous experiences of integrating novel ophthalmology therapies into health services; for example, insufficient preparation for anti-VEGF injections for patients suffering from macular degeneration has led to reports of sub-clinical outcomes and economic inefficiency [21,22].

Avoiding these difficulties will require research of novel hearing therapies beyond clinical trials and necessitates engagement with different stakeholder groups along the innovation pathway, including qualitative researchers, health economists, commissioners and, most importantly, patients and their families. The development of health economic models of novel hearing therapies could provide companies with a vital tool to help judge the viability of developing such therapies.

Given the nascent nature of the inner ear therapy field and the rapidly expanding rate of research, this data (Table 1, Supplementary Digital Content 1) will require

updating on a continual basis, which we intend to make freely available through the website of the UK based charity Action on Hearing Loss.

Greater opportunities for interdisciplinary discussion and cooperation are necessary in order to channel current progress in inner ear therapies toward effective treatments for hearing loss. To this end, the newly proposed International Society of Inner Ear Therapies intends to provide a forum for potential collaborators to share information and experiences. Under its wing, a network crossing the boundaries of countries, disciplines and diseases could be established.

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