Research Strategy: Jean-Claude Muller

The challenge of treating hearing loss as people age

Hearing loss, a health issue affecting around one billion people, has been ranked as the third highest cause of disability worldwide and the main modifiable risk factor for cognitive decline and dementia. Its prevalence is greater than that for cancer or diabetes. According to the World Health Organization (WHO) publication *World Report on Hearing*, issued in 2022, the incidence of hearing loss is surging and by 2050 nearly 2.5 billion individuals will experience varying degrees of deficiency during their lives, of whom 700 million will require care.

The primary drivers of this health crisis are an ageing population, noise-induced damage to the ears, the intake of ototoxic medications, and an increase of chronic diseases. To those affected, deafness can lead to social isolation, a deterioration in the quality of life, reduced work productivity, and higher rates of depression. Then there is the ongoing problem of being able to communicate in private and professional settings.

Hearing loss is not just a decrease in the perception of sound. It is also a loss of the ability to distinguish different types of speech. This involves a complex mix of health problems, including almost unbearable fatigue. The WHO estimates that the economic and social burden of hearing loss for entire communities represents a global cost of more than $980 billion annually.

Scientists have identified multiple hearing impairments that may require treatment. Some of these deficiencies are described below:

Otology, the branch of medicine which studies the anatomy and physiology of the ear, covers four types of impairments. Auditory processing disorders occur when the brain does not properly process information contained in a sound. Conductive hearing loss affects the ear's ability to conduct sound through the outer ear to the cochlea. Sensorineural hearing loss occurs when the cochlea or the auditory nerves are damaged. Mixed hearing loss describes the appearance of several of these disorders. Hearing loss can be bilateral or single-sided.

Otitis media is a suppurative or nonsuppurative ear condition characterised by inflammation of the inner ear. It results in a disruption of sound vibrations through the middle ear. Chronic suppurative otitis media commonly follows acute otitis media and may be associated with life-threatening complications. It is a major cause of conductive hearing loss, with soft sound being impaired and loud sound muffled.

Tinnitus, a condition which affects about 15 to 20% of the population, is the perception of ringing in one or both ears when no external sound is present. Although the pathophysiology of tinnitus is not clearly understood, both cochlear and central ear causes are described.

Hyperacusis is a hearing disorder that makes it hard to deal with everyday sounds. This hypersensitivity to sound is caused by changes in the way the brain processes sound and is usually centered on certain frequencies.

Vertigo is a condition with several causes. The most frequent is benign paroxysmal positional vertigo (BPPV) which occurs within the vestibule of the ear and causes tiny auditory crystals to move out of place and send false signals to the brain.

Ménière's disease, which mostly affects one ear and usually starts between youth and middle-age, appears to be linked to an abnormal amount of fluid in the inner ear.

Inner ear infections can also lead to moderate to severe vertigo and hearing loss side effects due to delayed treatment.

Cisplatin-induced hearing loss (CIHL) has a high prevalence, ranging from 20% to 80% of children treated with chemotherapy. The degree of cisplatin ototoxicity and hair cell loss is linked to high doses and multiple treatments of the chemotherapy. This can lead to the accumulation of platinum in the cochlea which was described in a study by Andrew Breglio and colleagues, published in *Nature Communications* in 2017. More than 200 marketed drugs are understood to elicit ototoxic side effects.

Cochlear synaptopathy, first described in 2009 by Kujawa and Liberman[1], is a clinical condition where patients have difficulty understanding speech in a noisy environment. This is despite the fact that they have normal hearing thresholds. The underlying cause is a deafferentation of auditory fibres to inner hair cells, altering the transmission of signals to the brain. Cochlear synaptopathy is involved in several pathologies of hearing impairment and is now considered to be an early sign of age-related diseases. The prevalence is even higher in patients with chronic diseases. As with other neurological disorders, cochlear synaptopathy is the result of a combination of neurocognitive and inflammatory disorders.

Tumours. Finally, in some rare cases, benign or malignant tumours can also induce significant hearing loss.

The most prevalent causes of hearing loss are excessive noise and ageing. Nevertheless, according to the WHO, 11 hearing loss syndromes have been identified with a monogenetic cause. These include Usher syndrome, Alport syndrome and Pendred syndrome. Currently more than 250 genes have been associated with syndromic and non-syndromic types of hearing loss. Analogic or digital hearing aids provide real benefit when the task is to amplify and deliver sound. But they are ineffective for many of the other hearing impairments. Similarly, cochlear implantation can address profound hearing loss, but it requires highly invasive surgery.

Recent progress in hearing biology

There is now a host of literature linking age-related hearing loss, also called presbycusis, to cognitive decline in the elderly. Until recently, hearing loss was not a priority of the biopharmaceutical industry, leaving companies that

Table 1

Name of Company	Country	Approach	Route of Administration
Acousia Therapeutics GmbH	Germany	Small molecules	TT
Akouos/Eli Lilly and Co	USA	Gene therapy	IC
Aposense Ltd	Israel	si-RNA	IC
Audiocure Pharma GmbH	Germany	Small molecules	TT
Audion Inc	USA	Small molecules	TT
Autigen Inc	USA	si-RNA	IC
Cilcare SAS	France	Small molecules	TT
Decibel Therapeutics/Regeneron Inc	USA	Gene therapy	IC
Dendrogenix SA	Belgium	Small molecules	NS
Heyu Pharma Ltd	USA and China	NS	NS
iN Therapeutics	Korea	Small molecules	TT
Oricula Therapeutics LLC	USA	Small molecules	Oral
Rinri Therapeutics Ltd	UK	Cell therapy	Graft
Sensorion SAS	France	Small molecules	Oral
Sensorion SAS	France	Gene therapy	IC
Spiral Therapeutics Inc	USA	Small molecules	TT
Sound Pharmaceuticals Inc	USA	Small molecules	Oral
Ting Therapeutics LLC	USA	Small molecules	NS

TT = Transtympanic, IC = Intracochlear, NS = not specified

provide prosthetic hearing aids to dominate the field. To date, the only novel drug to treat hearing loss is Pedmark (sodium thiosulfate), a prescription medicine from Fennec Pharmaceuticals Inc which was approved by the US Food and Drug Administration in 2022 to decrease the risk of hearing loss in children from one month and over who are receiving cisplatin to treat cancer.

However recent progress in understanding the root causes of the disorder and the discovery that a biological intervention might be effective in treating impairments linked to neurodegenerative conditions of the inner ear, have dramatically changed the landscape. This is illustrated by recent merger and acquisition activity in the industry. This activity includes Eli Lilly and Co's acquisition of Akouos Inc in 2022 for an upfront payment of $487 million. Akouos is developing gene therapies for inner ear conditions, including sensorineural hearing loss. This was followed by Regeneron Pharmaceuticals Inc's takeover of Decibel Therapeutics for an upfront payment of $109 million in August 2023. Decibel is also developing a gene therapy – in this case for a rare form of congenital hearing loss caused by mutations in the OTOF gene.

In late 2023, Jazz Pharmaceuticals Plc entered into a licensing agreement with Autifony Therapeutics Ltd to discover and develop drug candidates aimed at two different ion channel targets associated with neurological disorders. Autifony has a pre-clinical programme in schizophrenia and hearing loss. The value of the deal, including upfront and milestone payments, is $770.5 million. Besides Lilly, Regeneron and Jazz Pharmaceuticals, Astellas Pharma Inc and Boehringer Ingelheim GmbH have also become players in the hearing sector.

A recent report in the journal *Biomedicines*[2] listed as many as 40 ongoing gene therapy clinical trials in hearing loss. Besides Akouos and Decibel, these companies include Myrtelle Inc and Rescue Hearing Inc, which are developing gene therapies for hearing loss and Sensorion SA which is developing both small molecules and gene therapies. Among the exceptional clinical events was the disclosure by Lilly and Akouos in January of positive results from a Phase 1/2 trial of a gene therapy in an 11-year old patient who had been suffering from a profound hearing loss since birth. The therapy restored hearing in the patient within 30 days of administration. The treatment enabled the transfer of a functional copy of the OTOF gene and the expression of otoferlin protein to the inner hair cells of the cochlea. In addition to gene transfer therapies, gene editing programmes are also underway, but at an earlier stage.

In addition to Sensorion, there are at least 40 companies or academic institutions developing small molecule drugs for hearing loss, however these drugs are more difficult to deliver. Systemically administered drugs are often poorly taken up by the cochlea, which lies behind the blood-labyrinth barrier which protects the inner ear from toxic substances. Innovative delivery technologies are in development. Companies with clinical-stage products in this field are listed in Table 1.

Hearing loss and chronic diseases

Recent research suggests that peripheral and central auditory system dysfunction occur in the prodromal stage of Alzheimer's disease and may be an early valuable and underestimated indicator of the disease[3]. Hearing loss is also an important complication of diabetes. Patients with prediabetes have a 30% higher rate of hearing loss than normal subjects.

Although the causal relationship between diabetes and hearing loss is not fully understood, there seems to be increasing evidence that hearing loss is a comorbidity factor of diabetes mellitus, especially type 2 diabetes with insulin resistance. Recent studies are pinpointing systemic inflammation, cochlear microangiopathy and peripheral neuropathy as triggers of damage to the inner ear. They represent known biological targets. Cilcare SAS, a clinical-stage biotechnology company based in Montpellier, France, and Boston, US, has put forward the hypothesis that progressive hearing loss in type 2 diabetes may start with auditory peripheral neuropathy affecting 'speech-in-noise' intelligibility. The company notes that inadequate glycaemic control is likely to trigger early presbycusis.

Digital auditory signatures

In November 2023, the journal *Scientific Reports-Nature* published an article by Stéphane Maison et al[4] citing evidence that cochlear neural degeneration (CND) is linked to the appearance of tinnitus in human subjects. In their conclusion, the authors say that "developing diagnostic assays in CND is therefore key to identifying candidates for future therapeutics."

An increasing number of digital markers have become available in several diseases, and are already useful tools for early adopters in clinical settings. However, these new tools are not yet recognised by many health and regulatory authorities as markers for the identification of surrogate clinical endpoints.

Collaborations between academic and private institutions will be needed to further confirm the value of digital auditory markers. Non-invasive auditory signatures are expected to play a pivotal role in otology clinical settings and serve as functional biomarkers, just as the electrocardiogram (ECG) does for cardiovascular investigations.

People with cochlear synaptopathy do not have their hearing thresholds (41 to 68 dB) affected. Their symptoms, due to a neural-evoked output of the auditory nerve, cannot be evidenced by standard audiometry across the 0.125 to 8Hz frequency range and therefore remain a 'hidden' hearing deficit. Auditory profiling will become a necessary tool for detecting and assessing the intensity of cochlear synaptopathy in a given subject.

Damages to synapses between hair cells and auditory nerve fibres are a possible cause of poor auditory responses. Digital auditory profiling will progressively include measures like optoacoustic emissions (OAEs), a sound that is generated within the inner ear, auditory brainstem responses (ABRs), an electrophysiologic response to rapid auditory stimuli, and speech evoked responses. This is in addition to the standard 0.25-8Hz audiogram that could be extended in the high frequency range.

Hearing and vision loss

Traditionally, both sight and hearing disabilities have been treated with external physical devices. In the case of sight, these devices are optical rectifying glasses; in the case of hearing, they are amplifier hearing aids. In recent years however biological interventions have successfully tackled and treated ophthalmologic diseases. Beta blockers and prostaglandins have been used to treat glaucoma, and anti-angiogenic agents to treat both age-related macular degeneration and diabetic retinopathy. Based on the results in ophthalmology, biological interventions might be applied for the targeted treatment of hearing loss from neurological origins. In both cases local administration of the treatment would be feasible, allowing for a high concentration of the drug at the point of injection.

As with other neurodegenerative induced diseases, combining auditory profiling with imaging techniques like functional magnetic resonance imaging (MRI) or positron emission tomography (PET) will substantially increase knowledge of the dysfunction of the auditory system. Artificial intelligence algorithms are already being conceived to recognise subtle patterns associated with cochlear synaptopathy and will contribute to the emergency of novel, non-invasive useful auditory signatures for the diagnosis and prognosis of hearing loss.

Celia Belline, chief executive of Cilcare, told the recent JP Morgan healthcare conference in San Francisco, US, that "we are identifying highly specific auditory signatures (DAS) of auditory-related diseases selecting new targeted therapies to pave the way for new clinical developments. Combining DAS and innovative approaches in rehabilitation of functional circuits will restore high quality hearing comprehension in patients who long waited for a therapeutic solution."

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This article was prepared by Jean-Claude Muller, special advisor to several international institutions and previously senior vice president of research and development at Sanofi SA. He is a member of the *MedNous* Editorial Board.