The search for pharmacological treatments for hearing loss and tinnitus

BY NICOLA ROBAS

Where are we in our search for a hearing restoration grail? **Nicola Robas** leads us through the map pieces discovered in creating a pharmaceutical answer to hearing loss and tinnitus.

Together, hearing loss and tinnitus affect over one in six of the population, but current treatment options are limited to hearing aids and cochlear implants for hearing loss, and management strategies for tinnitus. Despite this unmet and growing need [1] there are no approved pharmacological treatments (small molecule or biologic pharmaceuticals) to prevent or reverse the root causes of these conditions. However, this is set to change, as recent advances in our understanding of the biological mechanisms underlying hearing loss and tinnitus, have led to an increase in efforts to identify and rationally design pharmacological interventions to prevent hearing loss, restore hearing and silence tinnitus.

Prevention / otoprotection

The search for pharmacological interventions to protect inner ear hair cells and spiral ganglion neurones (SGNs) and thus prevent acquired hearing loss – age-related (ARHL) , noise-induced, and drug-induced ototoxicity - has mainly focussed on promoting antioxidant pathways to combat the action of reactive oxygen species (damaging, highly reactive oxygen-based free radicals generated in response to trauma), or inhibiting the downstream signalling cascades that lead to cellular damage and death [2]. Two such programmes are currently in clinical development:

- Ebselen is an orally available small molecule that mimics and induces glutathione peroxidase, one of the dominant antioxidant enzymes in the cochlea and whose activity is diminished after cochlear trauma. Sound Pharmaceuticals are currently testing ebselen-containing investigational drugs in multiple Phase 2 trials for the treatment and prevention of acute noise-induced hearing loss, and cisplatin and aminoglycoside antibiotic ototoxicity.
- Auris Medical's AM-111 is a peptide inhibitor of c-Jun N-Terminal Kinase (JNK) and inhibits JNK-mediated apoptosis and inflammation. AM-111 is being clinically tested for the treatment of sudden sensorineural hearing loss and the protection of residual natural hearing following cochlear implantation.

Preclinical studies to identify additional pharmacological targets in the apoptotic and inflammatory pathways induced by cochlear trauma, are also being investigated by several research groups.

To date, the application of otoprotective strategies have mainly focussed on the prevention of noise, cisplatin-and aminoglycoside-induced hearing loss. Similar oxidative stress-mediated mechanisms are thought to play a role in the development of ARHL, but this becomes more challenging to translate clinically as there is an expectation that clinical trials to demonstrate efficacy of a pharmacological intervention to prevent ARHL, would need to be of several years duration and in large patient cohorts.

"Despite this unmet and growing need, there are no approved pharmacological treatments to prevent or reverse the root causes of these conditions."

Restoration of hearing

In postnatal mammals (unlike birds and amphibians), the sensory cells of the cochlea do not spontaneously regenerate, meaning that cellular damage leads to permanent hearing impairment.
As approximately 90% of hearing loss is sensorineural i.e. caused by damage to the hair cells or auditory nerve, significant effort is currently being devoted to the identification of pharmacological approaches to trigger regeneration of these cell types from precursor cells already present in the cochlea, as a route to restore natural hearing. Key areas for target identification are the pathways that modulate the transcription factor ATOH1; the master 'switch' controlling hair cell differentiation during development. In rodent models of hearing loss, induction of ATOH1 expression in certain cell types of the inner ear has been sufficient to induce differentiation into hair cells and, in some cases, partial recovery of auditory function.

The most advanced of these approaches is CGF-166, a gene therapy which delivers copies of the ATOH1 gene to the cochlea to generate new hair cells from existing supporting cells. Intra-labyrinthine delivery of CGF-166 is currently being tested in a Phase 1/2 clinical trial in profoundly deaf patients. Small molecule drug approaches targeting this pathway are also being investigated. The international REGAIN (REgeneration of inner ear hair cells with GAmma-secretase INhibitors) consortium is developing a locally delivered small-molecule gamma-secretase inhibitor, which aims to increase ATOH1 levels and stimulate hair cell differentiation via inhibition of Notch signalling. REGAIN have been awarded EU Horizon 2020 funding to progress towards clinical proof of concept. The recent increase in efforts to characterise cellular pathways involved in hair cell development, including ATOH1 –dependant hair cell generation, and proliferation and transdifferentiation of

"Advances in understanding the biological mechanisms of hearing loss and tinnitus have dramatically increased opportunities for the development of targeted pharmacological treatments."

cochlear progenitor cells, should enable identification of additional targets for pharmacological intervention [3].

An alternative pharmacological approach in development is Autifony Therapeutics' AUT00063, a Kv3 potassium channel modulator, currently being tested in a Phase 2 trial to improve the hearing of adult cochlear implant users, particularly in challenging environments such as with background noise. AUT00063 aims to improve central auditory processing, so improving speech perception and understanding. This experimental drug has also recently been tested in a Phase 2 trial for age-related hearing loss, but did not demonstrate a beneficial effect when compared to placebo treatment.

Silencing tinnitus

To date, the search for pharmacological treatments for subjective tinnitus has been directed at peripheral approaches, mainly for the treatment of acute (short-term) tinnitus. The most advanced along the development pathway is Auris Medical's Keyzilen (AM-101), a non-competitive N-methyl, D-aspartate (NMDA) receptor antagonist, which is currently in Phase 3 trials for the treatment of acute tinnitus, and has recently been granted fast track designation by the FDA. Following trauma to the inner ear, the auditory nerve may become susceptible to aberrant excitation mediated by the activity of the neurotransmitter glutamate at NMDA receptors. Inhibiting these potentially early tinnitus-causing signalling events, aims to prevent tinnitus from becoming centralised in higher auditory structures. Kyorin Pharmaceuticals and Otonomy also have NMDA receptor antagonists in clinical development for tinnitus.

Identification of pharmacological treatments designed to treat chronic, long-term tinnitus is proving to be more challenging. Recent research has focussed on identifying and modulating tinnitus-related neural hyperactivity in auditory centres, including the dorsal cochlear nucleus, inferior colliculus and auditory cortex, and increasing understanding of the neural interaction between central auditory pathways and non-auditory systems (including emotional centres) in the perception of tinnitus. Of particular interest is recent evidence that chronic tinnitus and chronic pain may exhibit many of the same CNS compensatory changes in response to loss of peripheral input [4]. This could provide new opportunities for both de novo target discovery and drug repurposing.

Outlook

While good progress is being made, there are still challenges to the development of pharmacological treatments. The path through clinical trials to market has not been tried and tested, increasing the perceived risk of investment in this field. Outcome measures that are appropriate to use in clinical trials for assessing efficacy of pharmacological treatments are limited. New audiological measures of efficacy that are more representative of real world hearing than pure tone audiometry are needed, as are objective measures of tinnitus, and strategies for stratifying and selecting patients for clinical trials, to name a few. Action on Hearing Loss is actively working through its Translational Research Initiative for Hearing (TRIH) [5] to tackle these and other challenges by facilitating multidisciplinary partnerships between industry, academia, clinicians and research audiologists, providing information about the hearing loss and tinnitus markets, and help in recruiting people with hearing loss and tinnitus into clinical trials.

Advances in understanding the biological mechanisms of hearing loss and tinnitus have dramatically increased opportunities for the development of targeted pharmacological treatments, and with several programmes already in late-stage clinical trials, we await the results with anticipation.

References

1. Hearing Matters (2015) www.actiononhearingloss.org.uk/hearingmatters
2. Dinh CT, Goncalves S, Bas E, et al. Molecular regulation of auditory hair cell death and approaches to protect sensory receptor cells and/or stimulate repair following acoustic trauma. *Front Cell Neurosci*. 2015;**31(9)**:96.
3. Fujioka M, Okano H, Edge A. Manipulating cell fate in the cochlea: a feasible therapy for hearing loss. *Trends Neurosci* 2015;3**8(3)**:139–44.
4. Rauschecker JP, May ES, Maudoux A, et al. Frontostriatal Gating of Tinnitus and Chronic Pain. *Trends Cogn* Sci 2015;**19(10)**:567-70
5. Translational Research Initiative for Hearing (TRIH) www.actiononhearingloss.org/trih

Nicola Robas,

Translational Research Manager,
Action on Hearing Loss,
19-23 Featherstone Street,
London EC1Y 8SL, UK.

E: Nicola.robas@hearingloss.org.uk
www.actiononhearingloss.org/trih

Declaration of Competing Interests: None declared.

ABOUT THE AUTHOR

Nicola is the Translational Research Manager at Action on Hearing Loss (formerly RNID), the UK's largest charity representing people with hearing loss and tinnitus. Nicola leads the Translational Research Initiative for Hearing (TRIH) which aims to accelerate the discovery and development of new medical treatments to prevent and treat hearing loss and tinnitus. Before joining the charity, Nicola worked in drug discovery and early clinical development in the pharmaceutical industry.