The Role of Collaboration in Accelerating Patient Focused Hearing Therapeutic Development

Workshop Report

Workshop A: 25 May 2021, organised by the Hearing Medicines Discovery Syndicate. Event run and owned by Hanson Wade innerear-disorders-therapeutics.com
Overview

In this workshop we explored the evolving landscape of hearing therapeutics and the role of collaboration in advancing the field. Participants and panellists reviewed the global hearing therapeutic pipeline for hearing disorders and shared their perspectives on ongoing initiatives and future opportunities for collaboration to overcome challenges. We considered examples of collaborative innovation in drug discovery beyond hearing and key success factors and priorities for hearing therapeutics.

This report summarises and highlights actions resulting from the workshop which was organised by the Hearing Medicines Discovery Syndicate and attended by participants across industry, academia and charitable organisations as part of the 1st Inner Ear Disorders Therapeutic Summit run and owned by Hanson Wade in May 2021.

Key Outcomes and Recommendations

We identified opportunities for focused research efforts to overcome challenges in the development of hearing therapeutics and further prioritised those which will be best delivered through collaborative efforts. These were:

1. Clinical trial outcome measures
2. Open and accessible patient registries
3. Mapping and gap analysis of preclinical models
4. Accessible temporal bone banks towards human cell atlas of the ear
5. Novel biomarkers
6. Supporting and nurturing the future pipeline of hearing therapeutics

The Hearing Medicines Discovery Syndicate will seek to work with the community to define how best to support the advancement of these recommendations. We welcome your ongoing insight and input. If you are already developing solutions for these recommendations and/or would like to further these efforts, please get in touch.
Hearing Loss (HL) is an condition that affects over 1.5 billion people globally, with 2.5 billion people projected to be affected by 2050. Hearing Loss is the 4th leading cause of disability globally with 430 million people currently requiring some form of care. Approximately 10% of adults in the US experience Tinnitus. Whilst hearing devices and rehabilitation help, many people still struggle to hear when there is background noise, they don’t restore natural hearing and they don’t delay the progression of further hearing loss. There are no approved therapeutics to treat hearing loss or tinnitus and unaddressed hearing loss remains a significant issue.

Unaddressed HL impedes communication, leads to social isolation and related to this people with HL are more likely to experience emotional distress, depression and loneliness. Mild hearing loss doubles the risk of developing dementia. Hearing loss is also associated with increased risk of cardiovascular disease, stroke, diabetes and obesity. The economic cost is also significant. People who are severely deaf are four times more likely to be unemployed and costs to the UK economy are up to £30 billion each year (Ear Foundation, 2014).

The global therapeutic pipeline for inner ear disorders comprises 23 in clinical trials with at least 56 in the preclinical pipeline (Figure 1). A significant number of assets have entered the pipeline in the last 3 years and preclinically there are programs targeting novel mechanisms and using a wider diversity of modalities including gene and cell therapy than is seen in the clinical pipeline.
This innovative pipeline is being driven by at least 50 institutions globally, the majority small and medium enterprises. Given the lack of approved therapeutics, the roadmap for this promising pipeline is not yet validated and there are challenges to overcome. 5 key challenge areas to hearing therapeutic discovery were identified from a survey conducted by the Hearing Medicines Discovery Syndicate in 2020 of 20 organisations engaged in hearing medicines discovery:

- Identify optimum outcome measures for clinical trials
- Better understand and define target patient populations
- Realise translational PK/PD models for the ear
- Deliver robust preclinical disease modelling
- Fuel the pipeline

These areas were discussed in detail during the following section of the workshop to enable leaders in the field to identify opportunities for collaborative working to overcome these challenges and ultimately drive desired outcomes for patients.

Precompetitive collaboration in hearing research – ongoing initiatives and future opportunities

An expert panel, moderated by Ralph Holme shared their perspectives and ideas on the role of collaboration in overcoming the challenges identified in hearing medicines discovery with workshop participants also contributing their thoughts.

**Challenge 1 | Identify optimum outcome measures for clinical trials**

**Current Status:** Selection of clinical trial outcome measures that accurately measure the effectiveness and safety of treatments is non-trivial in HL and tinnitus. In HL, pure tone audiometry and sometimes word recognition (WR), words-in-noise (WIN) are used but the methods used are not consistently applied and the measures themselves may not be optimal as evidenced by the high placebo effects observed in recently completed trials. In tinnitus, outcome measures tend to rely solely on subjective self-reported questionnaires.

Opportunities for pre-competitive collaboration:

- **Further development of patient reported outcomes** to understand real impact of new therapies are essential. Based on know-how from the device industry and through engagement with patients, HTA and payers to ensure outcomes important to patients are evaluated for relevant indications
More sophisticated objective measures beyond audiogram are needed. Invest in, develop and adopt minimally invasive biomarkers e.g. imaging and ultimately aspire to developments seen in the wider neuroscience field that have started to adopt peripheral blood biomarkers.

Develop guidance and consensus on trial design based on successes and failures in the field e.g. use of a lead-in period with multiple baselines to avoid a practice effect where there are also parallels with migraine and depression. Further analysis and review of specific speech-in-noise tests used would also be of value.

**Challenge 2 | Better understand and define target patient populations**

**Current Status:** Selection of patient populations for clinical trials is largely based on the primary etiology and the severity of HL. This empirical classification often does not adequately describe a condition and is one of the reasons organisations are often forced to conduct multiple Phase 1a/b trials in an effort to identify appropriate patient populations for later phase trials. There is a key need to be understand the pathogenesis of HL.

Opportunities for pre-competitive collaboration:

- **Develop open and accessible patient registries** building and integrating across already ongoing efforts to ensure data available across multiple geographies. Patients are key stakeholders with advocacy groups likely to be key to operation. Incorporate baseline data to begin to understand natural history of disease alongside molecular genetics. Clinicians also key stakeholders as ideal datasets often not routinely captured as part of routine clinics.

- **Strengthen and exploit temporal bone banks using newly available techniques.** Geographical differences exist regarding access to cadaveric tissue e.g. in the US, NIDCD maintain a temporal bone bank whereas in the UK, clinicians have access to temporal bone for surgical training but there is no openly accessible bone bank for research purposes. Potential to exploit new omics technologies with single cell resolution to better understand both disease pathophysiology.

- **Develop novel diagnostics** that can be used to define relevant patient populations. Significant progress is being made with molecular diagnostics but structural diagnostics is more challenging, a key need is cellular level imaging in a live ear but also relevant would be markers in peripheral blood.

**Challenge 3 | Realise effective drug delivery to the inner ear**

**Current Status:** Delivery of the active drug or gene vector to the appropriate inner ear structure or cell type at the right time and at the right quantity remains a critical pillar. A biological target for HL is most likely to reside in the inner ear or central nervous system (CNS) for which molecules need to cross the blood labyrinthine barrier (BLB) or blood-brain barrier (BBB) respectively. This biology, safety considerations and feasibility of local delivery by intratympanic/surgical administration has led to a strong focus on local delivery and novel formulations are enabling this. Specialised protocols in rodents are in place to enable measurement of drug levels in the inner ear through sampling the perilymph. Measurement of drug levels clinically is very limited (i.e. during cochlear implant surgery).

Opportunities for pre-competitive collaboration:
● Development and application of imaging technology to enable understanding of drug target engagement and duration of action intravitally. A multidisciplinary engineering challenge? A solution analogous to OCT for the eye or PET imaging in the CNS was envisaged.

● Significant interest in development of novel formulations and novel gene delivery vehicles but these areas were not viewed as pre-competitive.

**Challenge 4 | Deliver robust preclinical disease modelling**

**Current Status:** The challenge of adequately modelling the human pathophysiology of HL and tinnitus was highlighted. In general, there is a lack of human tissue, however, developments in the stem cell field begin to offer platforms for utility in identifying and testing novel therapies. There are a number of knockout rodent strains in use to test gene therapy strategies but not all relevant genetics have been successfully modelled in this way and development of preclinical models of multifactorial hearing loss remains challenging. Preclinical models of Tinnitus were also highlighted as a gap. Given the relative immaturity of the field, drug discovery organisations without internal lab capability reported difficulties in accessing the models needed and similarly more mature companies reported they had taken decisions to build internal lab capability. It was recognised that this landscape will continue to evolve with CROs already operating in this space.

Opportunities for pre-competitive collaboration:

● **Disease model gap analysis** in terms of development of new models (e.g. tinnitus was highlighted as an area of need along with modeling of multifactorial hearing loss) and in access via outsourcing.

● A longer term aspiration was identified towards defining best practice and gold standard models but it was recognised that this would be largely driven by clinical success.

**Challenge 5 | Fuel the pipeline**

**Current Status:** Further insights are required to align biological targets with patient groups, to reveal novel pathways and targets that can overcome the irreversibility of hearing loss and enable successful regenerative treatments. Advances have been made in identifying intrinsic genetic associations but further studies and larger datasets are required to increase confidence and provide a range of druggable molecular targets.

Opportunities for pre-competitive collaboration:

● **Mechanisms to support innovators in defining key experiments** required to secure follow-on investment.

● Ensure drug discovery organisations without lab capability have access to high quality virtual R&D to enable advancement of their programs.

● **Integrated datasets**, linked to patient registries above that can facilitate mining for new targets and pathways.
Perspectives on what makes drug discovery consortia successful

Having identified a number of collaborative opportunities to overcome key challenges in hearing medicines discovery, the final session in the workshop, led by Beverley Isherwood focused on collaborative R&D, and drew on case studies and participant experiences to share key considerations for success.

Research consortia, neutral environments that use collective expertise and distributed management to accelerate individual research efforts by building broadly needed resources, have been catalysed by such initiatives as the IMI and their number continues to grow. Such collaborative R&D efforts have been used to great effect across the sector and when executed well have been shown to deliver a number of benefits to the field and the parties involved;

1. More efficient use of resources – decreased costs, decreased time to clinic
2. Creative and innovative approaches and technologies
3. Fit for purpose approaches
4. Access to new products through in-licensing and creating opportunity

Research consortia range in scale from disease-specific collaborations catalysed by a single charity to groups comprised of multiple cross-sector partners. Collaborations broadly fall into those seeking to advance.

1. Fundamental knowledge (e.g. Project Hercules, Duchenne UK)
2. Biomarkers (e.g. Critical Path Institute Consortia)
3. Tools (e.g. CF Syndicate in AMR)
4. Products (e.g. Alderley Park Oncology Development Programme)

Multiple models for collaboration have been deployed successfully but some common success criteria were identified:

- **Right Mission and Goals:** a clearly defined mission and milestone-driven workstreams ensure drug discovery organisations without lab capability have access to high quality virtual R&D to enable advancement of their programs
- **Right Structure:** Dedicated staff (often neutral) to manage the collaboration, shared planning and clear governance
Priorities and Recommendations

Participants were invited to share their views on the most important collaborative opportunities identified during the workshop to advance hearing therapeutics along with any factors to ensure success and proposed next steps. Recommendations shared were:

**Recommendation 1 | Clinical Trial Outcome Measures**
Development of fit-for-purpose patient reported outcomes for hearing therapeutics through involving patients, payers and health technology assessment centres. Incorporate learnings on the use of outcome measures from the device industry.

**Recommendation 2 | Develop Open and Accessible Patient Registries**
Building and integrating across already ongoing efforts to make key data needed for drug discovery available across multiple geographies. Patients are key stakeholders with advocacy groups likely to be key to operation.

**Recommendation 3 | Mapping and gap analysis of preclinical models**
To build a virtual R&D map and inform focus of future development efforts.

**Recommendation 4 | Human Cell Atlas of the Ear**
Making temporal bone banks accessible and combine it with spatial omics technology towards a cellular level understanding of the ear and drug site of action.

**Recommendation 5 | Novel Biomarkers and objective outcome measures**
Investment in the development of novel biomarkers including a focus on intravital imaging in the ear at cellular resolution.

**Recommendation 6 | Supporting and nurturing the future pipeline of inner ear therapeutics**
Development of a supporting ecosystem to accelerate commercialisation of novel hearing therapeutic approaches.

The Hearing Medicines Discovery Syndicate will seek to work with the community to define how best to support the advancement of these recommendations. **We welcome your insights and input.**

If you are already developing solutions for these recommendations and/or would like to further these efforts please get in touch.
Acknowledgements

The core team at the Hearing Medicines Discovery Syndicate responsible for the development of the workshop and the landscape analysis was: Cláudia Gonçalves, Ralph Holme and Bev Isherwood.

We would like to thank our panel members (Alan Foster, CSO, Otonomy; Elaine Hamm, CEO, Otologic Pharmaceuticals; Chieri Hayashi, Medical Director, Astellas; Marcelo Rivolta, CSO, Rinri Therapeutics and University of Sheffield and Jonathon Whitton, VP Clinical Development, Decibel Therapeutics) and all the participants of the workshop for their helpful insights before, during and since the workshop.
## Appendix I | Workshop Agenda

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>10:00 - 10:05</td>
<td><strong>Welcome from the Hearing Medicines Discovery Syndicate and workshop overview</strong></td>
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<td><em>Ralph Holme and Bev Isherwood, Workshop Leaders</em></td>
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<td>An introduction to the Hearing Medicines Discovery Syndicate and the aims of the workshop.</td>
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<td>10:05 - 10:25</td>
<td><strong>The unmet patient need and therapeutic landscape for inner ear disorders of hearing</strong></td>
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<td></td>
<td><em>Ralph Holme, Executive Director, RNID</em></td>
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<td></td>
<td>This presentation will highlight the unmet patient need for hearing therapeutics and review the global hearing therapeutic pipeline for inner ear disorders highlighting challenges to overcome.</td>
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<td>10:25 - 11:20</td>
<td><strong>Precompetitive collaboration in hearing research – ongoing initiatives and future opportunities</strong></td>
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<td><em>Panel Discussion moderated by Ralph Holme</em></td>
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<td>Perspectives will be shared on the main barriers to hearing therapeutic discovery and development with a focus on the role of ongoing and future opportunities for collaboration to overcome them.</td>
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<td>Panel: Alan Foster; CSO, Otonomy</td>
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<td>Topics to be discussed will include the potential for collaboration to;</td>
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<td>• Identify optimum outcome measures for clinical trials</td>
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<td>• Fuel the pipeline</td>
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<td>11:20-11:25</td>
<td><strong>Break</strong></td>
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<td>11:25 - 11:50</td>
<td><strong>Perspectives on what makes drug discovery consortia successful</strong></td>
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<td><em>Open discussion, moderated by Bev Isherwood, Syndicates Programme Manager, MDC</em></td>
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<td>This session will open with a presentation on collaborative innovation in drug discovery and through discussion of case studies from a number of therapy areas share key considerations for success.</td>
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<td>Participants are invited to share perspectives on their experience and impact of collaboration across academia, biotech, biopharmaceutical, advocacy, regulatory and other organisations and to identify key priority areas for hearing.</td>
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<td>11:50 - 12:00</td>
<td><strong>Next Steps: Discussion and Wrap-up</strong></td>
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<td><em>Ralph Holme and Bev Isherwood, Workshop Leaders</em></td>
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Appendix II | The Hearing Medicines Discovery Syndicate

About Us
RNID and the Medicines Discovery Catapult (MDC) launched the Hearing Medicines Discovery Syndicate (HMDS) in 2020 as a strategic partnership with the Cell and Gene Therapy Catapult and the National Institute of Health Research (NIHR), through its 3 Biomedical Research Centres with specialist hearing themes (Uunivesit College London Hospital, Nottingham and Manchester).

Our Mission
To accelerate research in hearing therapeutics to bring new treatments to people with hearing disorders faster.

Our Strategic Goals
- Facilitate access to a unique cross-sector network.
- Identify and support promising hearing therapeutics through access to required capability and expertise underpinned by funding.
- Engage the research community to catalyze R&D focused on challenges with hearing therapeutics.
- Ensure a patient-focused approach to hearing research.

How to contact us
Please contact us (beverley.isherwood@md.catapult.org.uk) if you would like to explore how we may be able to support your work or how we may be able to work together.

Beverley Isherwood
Syndicates Programme Manager
MDC

Ralph Holme
Director of Research and Insight
RNID