## Commentary: Simon Chandler

# A cell therapy approach for hearing loss

More than 430 million people globally suffer from disabling hearing loss – by a significant margin the most common human sensory disability. Sensorineural hearing loss is caused by damage to, or loss of, auditory hair cells or neurons and accounts for 90% of all hearing loss cases.

Mammals cannot repair or regenerate auditory sensory cells, leading to an irreversible loss of hearing if they are damaged. But work underway in the field of regenerative medicine has shown that when stem cell-derived auditory neuron progenitor cells are delivered to the cochlea they can mature and re-establish neural connections to auditory hair cells and the wider auditory neural architecture. This commentary explores Rinri Therapeutics' approach to treating hearing loss in the context of significant progress in regenerative medicine.

Nearly 30 years ago scientists discovered methods to derive embryonic stem cells, which have the potential to make any cell in the body, from early mouse embryos. This technology created an entirely new way of studying genetic disease and also offered the tantalising prospect of creating truly regenerative therapies if this research could be translated for humans. In the late 1990s, this possibility was brought a step closer when researchers derived stem cells from human embryos. But these early human embryonic stem cell lines were not derived or manufactured in a way that was compatible with clinical applications.

Since then, huge progress has been made on all fronts to bring the prospect of regenerative therapies closer to reality. Multiple clinical-grade parental human embryonic stem cell lines are now available. In the mid-2000s scientists identified specific conditions that would allow adult cells to be reprogrammed to revert to a stem cell like state. This new type of stem cell, known as induced pluripotent stem cells (iPSCs), bypassed the residual concerns with human embryonic stem cells and formed the basis of universal donor material, or the patient-specific therapies of the future. All of this has taken place against improvements in manufacturing as contract manufacturers have gained experience in working with live cell therapies. Now differentiation protocols and manufacturing processes are better understood and controlled. This has led to safe and reproducible manufacturing, a prerequisite for the transition to clinical use.

Alongside technical advances, governments and global regulators have recognised the potential of regenerative therapies and taken steps to work in partnership with developers to accelerate development and regulatory pathways. In the UK, this acceleration has taken place through the Cell and Gene Therapy Catapult, and by a strategic decision by the Medicines and Healthcare products Regulatory Agency (MHRA) to engage extremely early with advanced therapy developers to help accelerate progress. Rinri has recently been accepted onto the MHRA's innovative licensing programme. To qualify for the award, developers have to demonstrate that their target is a seriously debilitating condition and has the potential for delivering transformative benefit to patients. In this scheme, the agency and other UK stakeholders partner with selected companies to develop a plan for accelerating access for patients in the UK healthcare system.

The convergence of scientific advances and industrial know-how means that there are now multiple cellular and gene therapy products on the market and clinical programmes are increasing exponentially. Some standout clinical breakthroughs include Phase 1 trials for Type 1 diabetes using stem cell-derived therapy and the successful first-in-human trials of a stem cell therapy to restore vision in patients with wet age-related macular degeneration. Other notable examples include an iPSC-based chimeric antigen receptor (CAR) T cell therapy for lymphoblastic leukaemias and stem cell-based therapies for Parkinson's disease.

Rinri Therapeutics is therefore well placed to take advantage of the current landscape for advanced therapies to try and realise the potential of cell therapy for the biological treatment of hearing loss.

Despite the large hearing loss population, the development of hearing loss therapies has been overlooked by big pharma in preference for classic indications like oncology. There are no approved therapies for hearing loss and whilst the current standards of care – hearing aids and cochlear implants – have undergone significant improvement since their origin, they remain unable to restore natural hearing.

Rinri's lead therapy Rincell-1, which is in preclinical development, is a regenerative cell therapy designed to treat auditory neuropathy, a type of sensorineural hearing loss with no treatment options, not even devices. Rinri's regenerative medicine approach seeks to restore natural hearing by returning the inner ear to a healthy, undamaged state. Here, stem cells are grown into progenitor cells and delivered into the cochlear where they complete their transformation into mature auditory neurons, replace damaged cells and restore function.

The company's technology is based on the pioneering work of Marcelo Rivolta, professor of sensory stem cell biology at the School of Biosciences, University of Sheffield, UK. His research showed in models of auditory neuropathy hearing loss, improvements in hearing thresholds that could be achieved that would be significant if replicated in humans. Therefore, it might be possible to use stem cell-derived progenitors to recover the damaged sensory cytoarchitecture of the inner ear in patients with sensorineural hearing loss.

Taking advantage of the supportive UK cell therapy landscape, Rinri has made rapid preclinical progress and is now looking confidently at the path ahead to clinical trials.

This commentary was written by Simon Chandler, chief executive of Rinri Therapeutics Ltd in the UK.