STEM CELL AND REGENERATIVE THERAPIES FOR HEARING LOSS

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The year 2018 marks a notable milestone in the history of stem cells and regenerative medicine. It was twenty years ago, in 1998, that James Thompson and John Gearhart published methods for the creation of the first human embryonic stem cell (hESC) lines. In the intervening 20 years, the field of stem cell research has made many critical discoveries that advance our understanding of exogenously modified and expanded cells and their therapeutic potential in human medicine. New technologies such as induced pluripotent stem cell lines (iPSCs) and CRISPR/Cas9 editing are expanding the possibilities offered by pluripotent cell therapeutics.

At the same time as these cell technologies were being investigated, a parallel interest in activating and utilizing endogenous regenerative capabilities in patient populations has benefitted from advancements in molecular assays and information processing. Data-intensive “-omics” and informatics offer the promise of achieving the same regenerative and reparative goals as customized cell implants, with the additional safety benefits of recruiting each patient’s own biological mechanisms to create the therapeutic effect.

These two parallel but related fields have begun to deliver on the promise envisioned 20 years ago. Multiple clinical trials are underway for a variety of indications, including diabetes, retinal disorders, and postoperative tissue repair and regeneration. One area that may finally benefit from these new technologies is the field of hearing and ototoxic disorders. These have lagged behind other fields of therapy for several reasons, including the difficulty of accessing the relevant anatomy for therapeutic treatments, a lack of suitable preclinical models, and a limited commercial interest in these indications. As of the publication of this article, the FDA still recognizes no efficacious therapy for the preservation or restoration of hearing, an astounding admission in light of the numerous advances seen in other, related areas. Fortunately, recent advances in our understanding of auditory pathways and the discrete mechanisms underlying auditory function lead us to believe that real, viable therapies will become a reality in the near future.

15% (1 billion)
global adult population suffering from hearing disorders

360 million
People worldwide have disabling hearing loss

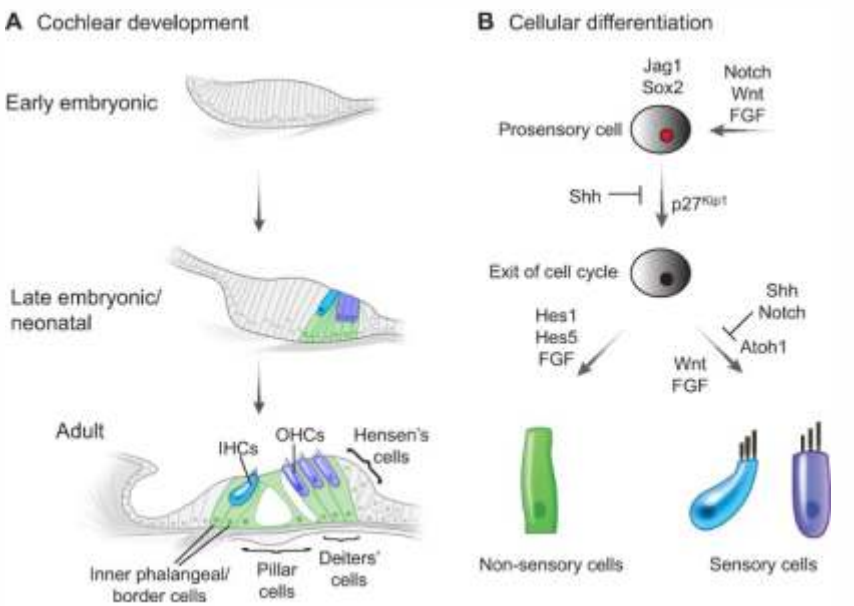
600 million
People affected by tinnitus

2.2 million
Annual episode of acute media otitis in the US

Mechanism of disease for hearing disorders

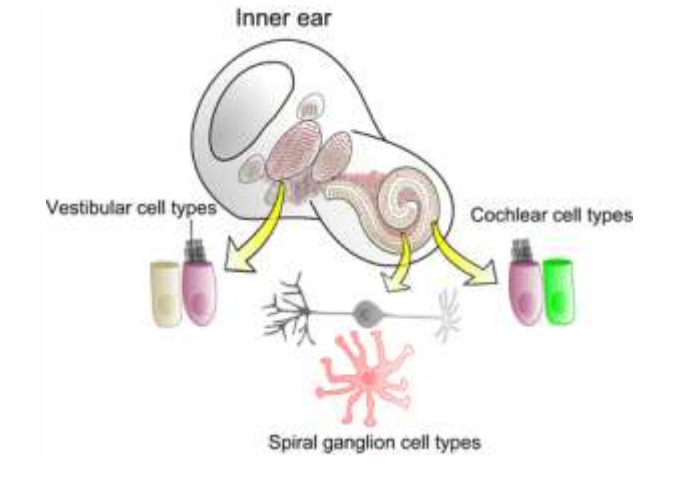
Addressing hearing disorders via drug- and cell-based therapies remains a very challenging task due to the functional and anatomical limitations associated with the cochlea: a fully encompassed, closed, and integrated auditory system encased in a dense layer of bone. These delivery barriers are compounded by the complexity of the development, maturation, and functionality of each individual cell type in the cochlea, which together orchestrate an optimally functional hearing mechanism (see Figure 1).

Figure 1: Development of the inner ear (Atkinson *et al.,* 2015)



Deafness or hearing dysfunction can result from genetics or induced deregulation of one of several cell types in the cochlea. Most research has focused on therapies targeting two cell types of primary functional importance in the cochlea: the hair cells (HC), and the spiral ganglia neurons (SGN). Both cell types are fully differentiated post-mitotic cells, and any HC and/or SGN loss will adversely impact hearing function and acuity.

Figure 2: Cells with stem-cell-like properties in the inner ear (McLean *et al.,* 2016)



Therapeutic approaches

Several possibilities are advancing through preclinical trials and demonstrate great potential to reach the clinic as efficacious therapies. One approach uses a traditional cell-based method of directly replacing the missing cells *in situ*. This could be achieved through direct injection of differentiated stem cells into the cochlea; these cells could become either HCs or SGNs according to their injection site. Although straightforward, and consistent with previous successful stem-cell-targeting therapies, there are several scientific and regulatory shortcomings associated with this approach (see Table 1).

Building on an increased understanding of molecular and cell-based pathways to induce the activation of endogenous precursor cells in the area of treatment, a second approach seeks to replace the same cellular machinery through the regeneration of damaged or missing cells. In this regenerative-medicine approach, the goal is the activation of endogenous "stem-like cells" through small molecules or biologics in order to repopulate the missing cells. It has been shown that stem-like cells (usually referred to as endogenous precursors) exist in several compartments of the cochlea. These cells are the Lgr5+ cells for the sensory epithelium and the PLP1+ cells for the SGN (see Figure 2).

Recent research supports the possibility that such cells could be activated/ reprogrammed through the injection/passive diffusion of small molecules into the cochlea in order to repopulate any damaged sensory epithelium and/or

Table 1: Comparison of stem-cell-based and regenerative-medicine-based therapeutic approaches

Stem cells	Regenerative medicine
Administered locally to site of cell replacement	Can be administered systemically, or locally by a less invasive/traumatic route
Introduction of exogenous cells into the inner ear to substitute injured hearing Administered neurons	Activate and mobilize endogenous stem cells into new hair cells
May require an immunosuppressed system	Doesn't require an immunosuppressed system
Require additional safety testing for cell migration and tumorigenicity	Less risks of miss-differentiation, migration or tumor
Could be effective on hereditary deafness, sensorineural hearing loss	Could be effective on age related and noise induced hearing loss
Potential difficulty to reach the targeted location from the site of transplantation	Targeted-site accessibility depends on the route of administration

Table 2: Regenerative therapies in the pipeline

Company	Compound	Target pathway	Stage
Affichem	AF243	Neuron survival and neuronal differentiation	Preclinical
Akouos	Gene therapy		Preclinical
Acousia therapeutic	Otopotin	Dedifferentiation supporting cells into progenitor-like cells	Preclinical
Frequency Therapeutics	FX-322	Progenitor cell activation (PCA)	Preclinical
Sound Pharmaceuticals	SPI-5557 (siRNA)	Downregulation of p27Kip1	Preclinical
Quark Pharma	QP-HL3 (siRNA)		Preclinical
Audion therapeutic & Eli Lilly	LY3056480	Gamma-secretase inhibitor	Clinical phase I
Novartis & GenVec	CGF166 gene therapy	Atoh1	Clinical phase II

Stem cells	Regenerative medicine
Boehringer Ingelheim & China Southeast University Institute of Life Sciences	Regenerate hair cells from inner ear stem cells. Explore key signaling pathways and proteins involved in regeneration of hair cells, with an emphasis on finding small-molecule drugs that could stimulate the process.
Inception sciences & Roche	Create novel drug therapies that target inner ear hair cell protection and regeneration in the cochlea.
Decibel Therapeutics & Regeneron	Build the world's first comprehensive, integrated drug discovery, translational research, and drug development platform for hearing loss and tinnitus.
Consortium OTOSTEM	Develop 2 strategies for curing hearing loss: 1- stem cell-derived cellular agents for cell-based therapy. 2- stem cell-derived assays as a screening tool to identify novel drugs.
Consortium Hearing Restoration Project	Focus on investigating hair cell regeneration as a cure for hearing loss and tinnitus.

SGN. Advances in microfluidics and miniaturization are being applied in research models where a prolonged administration of trophic stimulus may be required for consistent and efficacious cell activation and integration. This allows revolutionary extended therapeutic access to one of the most inaccessible areas for therapeutic intervention.

As with other stem cell and regenerative medicine-based therapies, those targeting auditory dysfunction face specific regulatory and technical challenges related to the manufacture and deployment of each treatment. Fortunately, as hearing loss is a lagging indication, the auditory field can benefit from years of safety testing refinement by the FDA and its team at CBER (The Center of Biologics Evaluation and Research). This includes well-established guidelines for testing and evaluating both stem-cell-based and regenerative-medicine approaches. Some of the key considerations are summarized in Table 1.

It remains to be seen which approach, or combination of approaches, will reach the historic designation of being the first FDA-approved therapy for the treatment of hearing loss. What is certain is that advances in our understanding of the regenerative and restorative approaches pioneered in other areas of interest have finally reached the field of ototoxicity and auditory damage. A number of therapies are in the pipeline now (see Table 2). These and others hold the promise of transformative impacts on patient populations in the near future.

ABOUT THE COMPANIES

CBSET, Inc. – 500 Shire Way, Lexington, MA, USA – is a not-for-profit translational research institute specializing in the evaluation of drugs, biotherapeutics, combination products, and medical devices. We provide preclinical services, including in-life testing, histopathology, and regulatory consulting. Our GLP-compliant facilities host a multidisciplinary team of medical, scientific and regulatory experts who actively collaborate in getting novel technologies to market.

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IMPROVING LIVES

CILcare Inc. is the world-leading services company for drug development in hearing and otic disorders. CILcare has developed unique know-how to assess the safety and the efficacy of drug candidates and medical devices in drug-induced hearing loss, noise-induced hearing loss, age-related hearing loss, salicylate-induced tinnitus, noise-induced tinnitus and otitis.

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