

Stem cell-based strategies for hearing restoration: Current advances and future perspectives

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Abstract

Hearing loss is a growing global health concern. Sensorineural hearing loss is the most prevalent and intractable type. Current treatment options offer limited benefits and fail to restore hearing at its root cause, highlighting an urgent need to address the irreversible loss of hair cells and develop strategies for hearing restoration. Recent advances in stem cell-based strategies have opened promising avenues for inner ear regeneration. Progress in stem cell-derived cochlear organoids, which highly mimic native inner ear cells, not only facilitates the study of disease mechanisms and drug toxicity testing but also serves as a critical cell source for future stem cell therapies. This review summarizes the latest progress in stem cell research for hearing loss and discusses the regulation of auditory cell fate, optimization of stem cell sources and delivery routes, modulation of the immune microenvironment, and the application of organoid platforms. With deeper interdisciplinary integration, stem cell-based therapies are expected to fundamentally transform the treatment landscape for hearing impairment.

Key Words: Hearing loss; Stem cell; Cochlear organoids; Hair cell regeneration; Extracellular vesicles

Core Tip: Sensorineural hearing loss remains difficult to reverse as current treatments mainly compensate for dysfunction rather than restore damaged cochlear cells. This review highlights recent progress in stem cell-based hearing restoration, focusing on stem cell sources, auditory cell fate regulation, delivery optimization, immune microenvironment modulation, and cochlear organoids. It further emphasizes the emerging value of organoid platforms and cell-free strategies in advancing translational and regenerative therapies for hearing loss.

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INTRODUCTION

Hearing loss is a growing global health burden that affects an estimated 1.57 billion people worldwide. More than 400 million had hearing loss of at least moderate severity after adjustment for hearing aid use[1,2]. The burden of hearing loss remains high in children and adolescents and continues to rise in aging populations, emphasizing that hearing impairment is not only a clinical problem but also a major public health challenge[3,4].

Sensorineural hearing loss (SNHL) is the most prevalent and clinically intractable subtype because it is primarily caused by irreversible damage to cochlear hair cells, spiral ganglion neurons (SGNs), and their synaptic connections, whereas the mammalian inner ear has only minimal spontaneous regenerative capacity[5-7]. Although hearing aids and cochlear implants have substantially improved auditory rehabilitation, these interventions mainly compensate for functional deficits rather than restore the native cytoarchitecture and biological function of the injured cochlea[8-10]. Consequently, there remains a critical unmet need for regenerative strategies capable of repairing or replacing the cellular substrates of hearing loss at their source.

In recent years, stem cell-based approaches have emerged as a promising direction for hearing restoration. Current applications can be broadly divided into several interconnected areas. First, pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) and induced PSCs (iPSCs), can in principle be directed toward otic progenitors, hair-cell-like cells, supporting cells, and SGN-like neurons, providing a renewable cell source for replacement therapy[6,7,11,12]. Second, endogenous progenitor-like populations and supporting cells in the inner ear may be induced toward regenerative programs through developmental pathway manipulation and cell-fate reprogramming, offering the possibility of *in situ* repair[6,13]. Third, stem cell-derived paracrine products, including exosomes or small extracellular vesicles (EVs), have shown protective effects on auditory hair cells and SGNs in preclinical models, supporting their therapeutic value as cell-free regenerative tools[13-15]. Notably, recent studies have established stem cell-derived human inner cochlear organoids which will be widely used in modeling human inner ear development and disease, testing ototoxicity, and evaluating regenerative therapies[16,17].

In this review, we summarize recent progress in stem cell-based strategies for hearing loss, focusing on auditory cell fate determination, stem cell sources, delivery optimization to the inner ear, microenvironment regulation, and the emerging role of cochlear organoids in translational research. By integrating advances in stem cell biology, organoid technology, bioengineering, and microenvironmental regulation, this review provides a conceptual and translational framework from simple transplantation to a more comprehensive regenerative framework.

BIOLOGICAL BASIS OF STEM CELL-MEDIATED HEARING RESTORATION

Effective hearing restoration should be viewed as reconstruction of a multicellular cochlear functional unit, rather than simple replacement of lost hair cells. In addition to sensory hair cells, this unit includes supporting cells that provide structural and regenerative competence, SGNs and their afferent ribbon synapses that relay auditory information, as well as the lateral wall/stria vascularis niche that maintains ionic homeostasis, vascular integrity, and metabolic support for cochlear function[18]. Recent human stem-cell-derived cochlear and otic organoid studies, together with single-cell comparisons to native inner ear tissues, have reinforced the idea that durable hearing recovery depends on coordinated restoration of sensory, neural, and niche components of the injured cochlea[16,17,19]. In parallel, the immune niche also directly contributes to recovery, as resident cochlear macrophages are required for ribbon-synapse repair and functional restoration after synaptopathic noise damage[20].

Moreover, auditory neuron regeneration is becoming increasingly feasible, with both transcription factor-mediated reprogramming of fibroblasts and human PSC (hPSC)-derived otic neuronal spheroids generating SGN-like cells with molecular and functional features of auditory neurons[21,22]. Moreover, recent studies of the lateral wall and stria vascularis indicate that vascular, fibrocyte-associated, and metabolic dysfunction can secondarily drive sensory-cell degeneration, underscoring that successful stem cell-based hearing restoration will require reconstruction of a permissive cochlear niche[23-25].

Current stem cell-based repair strategies can be broadly grouped into three therapeutic paradigms. First, exogenous cell replacement aims to generate transplantable otic cell types from PSCs, including hair-cell-like, supporting-cell-like,

and SGN-like populations, to replenish cells that are irreversibly lost[16]. Second, endogenous progenitor activation and supporting-cell reprogramming aim to convert resident non-sensory or supporting cells into hair-cell-like cells through transcription factor-based, pharmacologic, or signaling-directed approaches[26]. Third, cell-free trophic and immunomodulatory repair leverages the paracrine activity of stem cells, particularly mesenchymal stem/stromal cell (MSC)-derived EVs, to reduce oxidative stress and inflammation, support survival of cochlear cells, and reshape the local immune milieu[27]. Taken together, the biological rationale for stem cell-mediated hearing restoration lies in rebuilding the sensory, neural, and microenvironmental architecture required for long-term functional recovery (Figure 1).

STEM CELL SOURCES FOR INNER EAR REGENERATION

PSCs as a source of auditory cells

PSCs, including ESCs and iPSCs, remain the most versatile exogenous source because they can generate multiple components of the cochlear functional unit rather than a single terminal cell type. Recent progress has shifted the field from asking whether hair-cell-like cells can be induced to whether high-fidelity cochlear organoids can be generated and rigorously benchmarked against the native human inner ear. In this context, hPSC-derived organoid systems have enabled the generation of cochlear-like sensory epithelia containing hair-cell-like cells, supporting-cell-like cells, and otic neuronal populations that transcriptionally resemble native human inner ear cell states[19,28]. These systems have also become powerful platforms for mechanistic and patient-specific studies: CHD7-dependent chromatin remodeling was shown to govern human otic lineage specification and hair-cell differentiation in cochlear organoids[29]. Human iPSC-derived CX26 gap-junction-forming cells have provided a disease-relevant model for GJB2-associated deafness[30], and patient-derived organoids have recently been used for rapid validation of variants linked to cochlear malformations[31].

Recent studies show that iPSC-based systems can extend from cell production to mechanistic analysis of disease vulnerability, genotype-to-phenotype investigation, and even therapeutic rescue, as demonstrated by genetic correction of deafness-associated iPSC lines[19,29,30]. By contrast, ESCs remain particularly valuable for standardized differentiation and auditory neuron reconstruction, owing to their robust pluripotency and reproducibility; notably, hESC-derived otic neurons have been shown to express SGN markers and form functional synaptic connections with cochlear nucleus neurons in coculture[32]. Together, these findings indicate that ESCs and iPSCs are complementary rather than competing pluripotent sources: ESCs provide greater standardization, whereas iPSCs offer unmatched patient specificity. At the same time, both still face major translational barriers, including incomplete maturation, tumorigenic risk, limited host accommodation, and quality-control challenges, while recent work on hypoinmunogenic iPSC-derived otic progenitors further suggests that immune compatibility may become as important as differentiation fidelity in future clinical translation.

MSCs in cochlear repair

In contrast to PSCs, MSCs are currently more compelling as trophic and immunomodulatory therapeutics than as bona fide replacement cells for the sensory epithelium. Recent studies consistently show that MSC-based benefit in the inner ear is dominated by paracrine signaling, anti-oxidative protection, and inflammatory remodeling rather than stable structural engraftment. Intravenous skin-derived MSCs ameliorated cisplatin-induced hearing loss and preserved outer hair cells in mice[33], while round-window delivery of bone marrow-derived MSCs protected cochlear structures after cisplatin ototoxicity and showed migration toward injured regions[34]. This paracrine logic is even clearer in EV-based studies: MSC-derived exosomes protected auditory hair cells from neomycin-induced damage[35], reduced oxidative stress and improved cell survival in cisplatin-exposed inner ear sensorineural cells[27], and have already reached early clinical translation, as illustrated by first-in-human intracochlear application of human stromal cell-derived EVs during cochlear implantation[36]. More recently, the MSC research is shifting from “cell transplantation” to “cell-free therapy” and “regulation of the immune microenvironment”, where Apelin-associated MSC-derived EV signaling promoted M2 macrophage polarization, reduced inflammation, and improved auditory function in aged mice[37]. Taken together, available evidence suggests that MSCs should be conceptualized primarily as biological drug factories that stabilize the injured cochlear niche, rather than as a realistic source for direct replacement of hair cells or SGNs.

Endogenous auditory stem/progenitor cells and supporting cells

A second major strategy seeks to harness endogenous regenerative competence within the cochlea, especially in supporting cells and progenitor-like populations marked by *Lgr5* or *Sox2*. This approach has gained substantial momentum because supporting cells are anatomically positioned, developmentally related to hair cells, and remain the most accessible endogenous substrate for reprogramming. Recent *in vivo* studies show that forced expression of *ATOH1*, *GFI1*, and *POU4F3* can reprogram mature non-sensory cells or supporting cells into hair-cell-like cells in the postnatal and adult cochlea[26,38], while additional factor combinations such as *Gfi1/Atoh1/Pou4f3/Six1* further enhance regenerative responses even in severe flat-epithelium models[39]. Small-molecule and signaling-based reprogramming strategies have likewise broadened the therapeutic landscape: A drug-like reprogramming cocktail induced cochlear hair-cell-like regeneration in adult wild-type mice[40], MEK/ERK inhibition promoted supporting-cell trans-differentiation through Notch modulation *in vitro*, in organoids, and to a limited extent *in vivo*[41], and Jagged1/Notch remodeling has recently been shown to exert a dual role by both constraining and preserving the progenitor-like state of supporting cells during regeneration[42]. Nonetheless, the adult mammalian cochlea remains markedly refractory. Reprogramming efficiency declines rapidly with maturation owing to reduced chromatin accessibility at hair-cell loci and to persistent

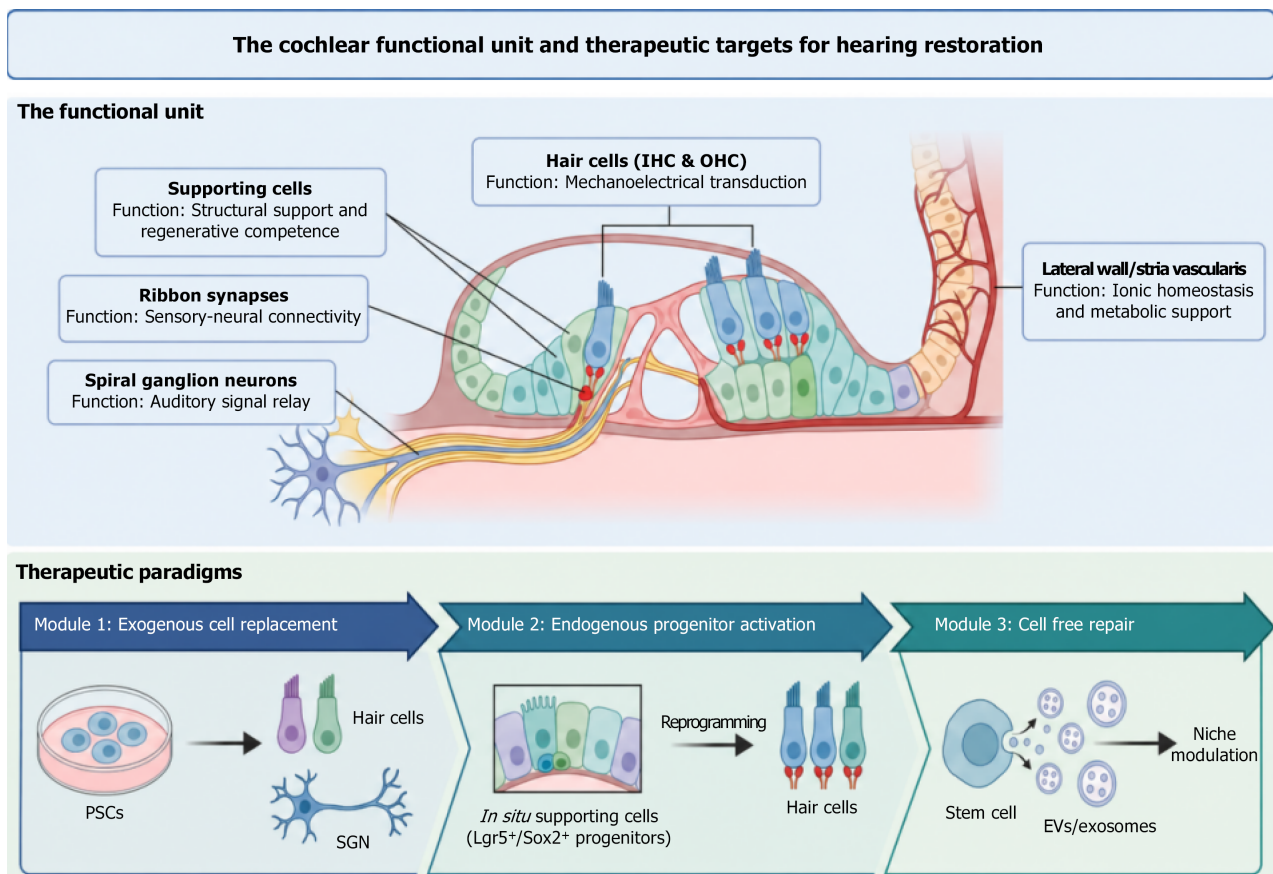


Figure 1 Cochlear functional unit and therapeutic targets for hearing restoration. The upper panel illustrates the cross-sectional anatomy of the organ of Corti, highlighting that hearing restoration requires the integrated reconstruction of a multicellular unit rather than a single cell type. Key targets include hair cells (mechano-electrical transduction), supporting cells (structural support and regenerative competence), spiral ganglion neurons (auditory signal relay), ribbon synapses (sensory-neural connectivity), and the stria vascularis/Lateral wall (ionic homeostasis and metabolic support). The lower panel summarizes three major stem cell-based therapeutic paradigms: Exogenous cell replacement utilizing pluripotent stem cells (module 1); endogenous progenitor activation and supporting-cell reprogramming (module 2); and cell-free repair mediated by stem cell-derived extracellular vesicles for niche modulation (module 3). IHC: Inner hair cell; OHC: Outer hair cell; PSCs: Pluripotent stem cells; SGN: Spiral ganglion neuron; EV: Extracellular vesicle.

inhibitory signaling from the mature epithelial environment[43]. Even so, the long-term survival of LGR5-positive supporting cells after severe ototoxic trauma suggests that the adult cochlea retains a residual regenerative substrate that may be therapeutically mobilized under the right molecular conditions[44,45].

Regenerative targets in hearing restoration

A key conceptual shift in the field is that the optimal regenerative strategy depends on the primary lesion target. Hair-cell replacement or supporting-cell reprogramming may be effective for sensory epithelial damage only when the downstream neural circuitry remains intact. By contrast, in cases of neural degeneration, regeneration must also address SGNs and synaptic connectivity. Recent advances in hPSC-derived otic organoids, otic neuronal spheroids, and direct lineage reprogramming have expanded the repertoire of candidate cell sources for SGN repair[19,21,22,28,46]. At the same time, studies showing functional synapse formation between regenerated hair cells and SGNs, synapse regeneration *via* cAMP/PKA signaling, and macrophage-dependent ribbon-synapse repair underscore that effective hearing restoration requires not only cell replacement, but also circuit reconstruction[18,20,47]. Together, these findings indicate that hearing restoration is a hierarchical regenerative goal - from hair-cell rescue to SGN repair and ultimately auditory circuit rebuilding - and that stem cell strategies must be tailored to the dominant lesion pattern rather than centered on hair-cell regeneration alone (Figure 2).

AUDITORY CELL FATE DETERMINATION

Auditory cell fate depends on cellular competence

Recent studies suggest that auditory fate depends less on single-factor induction than on whether target cells retain sufficient developmental competence. Accordingly, ATOH1, GFI1, and POU4F3 reprogramming is highly context-dependent and more effective in combination[26,43]. Single-cell analyses of human cochlear organoids show that transitions from pro-sensory cells to hair cells and supporting cells follow coordinated lineage trajectories rather than

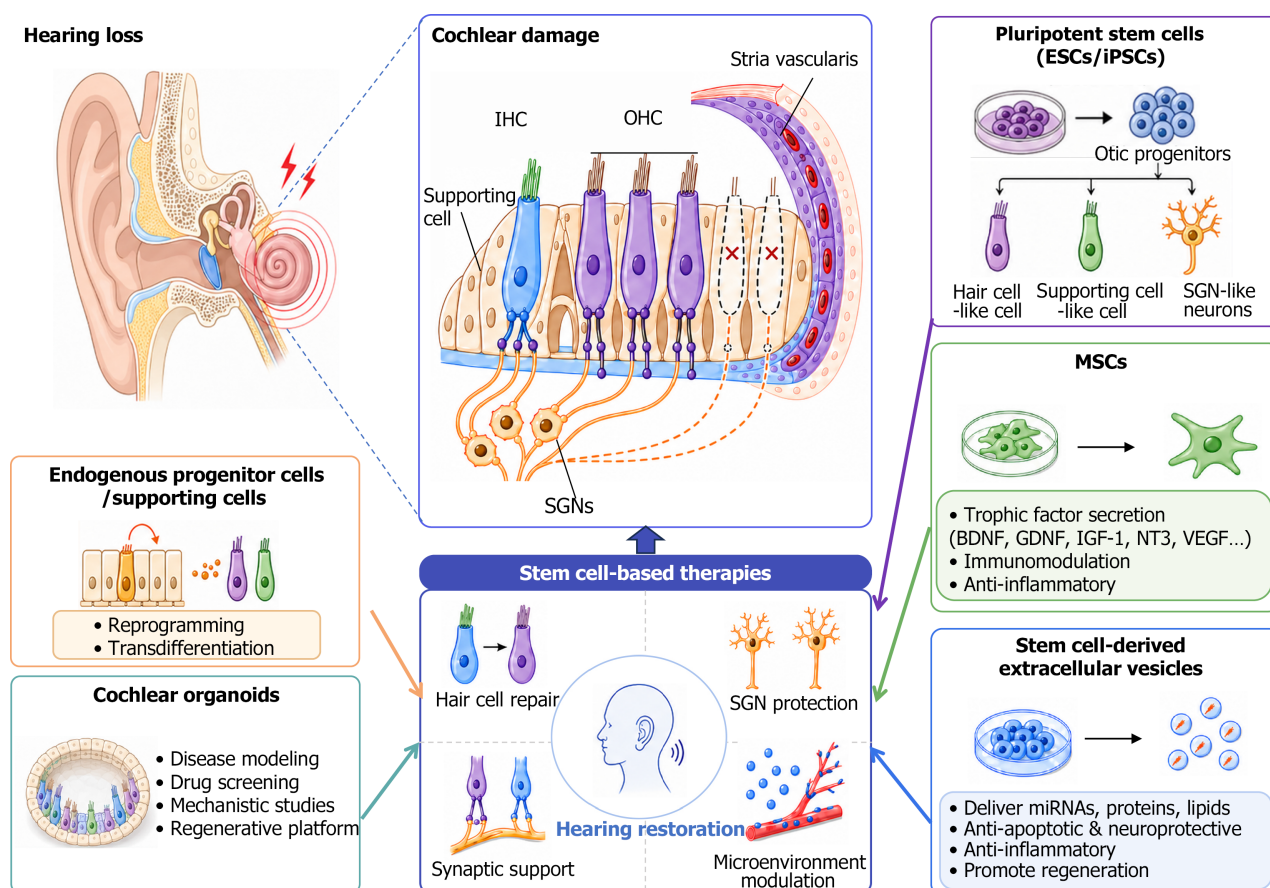


Figure 2 Stem cell-based strategies for cochlear repair and hearing restoration. This schematic summarizes major regenerative approaches for sensorineural hearing loss. Cochlear injury involves hair-cell loss, spiral ganglion neuron damage, synaptic disruption, and microenvironmental dysfunction. Pluripotent stem cells, mesenchymal stem/stromal cells, stem cell-derived extracellular vesicles, endogenous progenitor/supporting cells, and cochlear organoids provide complementary strategies for cell replacement, trophic support, cell-free protection, *in situ* reprogramming, and preclinical modeling. These approaches converge on hair-cell repair, spiral ganglion neuron protection, synaptic support, microenvironmental modulation, and ultimately hearing restoration. IHC: Inner hair cell; OHC: Outer hair cell; SGN: Spiral ganglion neuron; ESCs: Embryonic stem cells; iPSCs: Induced pluripotent stem cells; MSCs: Mesenchymal stem/stromal cells; BDNF: Brain-derived neurotrophic factor; GDNF: Glial cell line-derived neurotrophic factor; IGF-1: Insulin-like growth factor 1; VEGF: Vascular endothelial growth factor; miRNA: MicroRNA.

abrupt fate switching[48]. Consistently, MEK/ERK-Notch crosstalk, Jagged1/Notch signaling, and progenitor-associated programs such as LIN28B/Follistatin and TRIM71 all influence whether supporting cells remain quiescent, re-enter a progenitor-like state, or convert into hair cells[40-42,49,50]. Pharmacologic and vector-based interventions, including small-molecule reprogramming, AAV-Net1, and UCHL1 suppression coupled with mammalian target of rapamycin activation, further suggest that this competence can be modulated therapeutically[51-53]. However, adult regeneration remains limited because enhancer decommissioning, DNA methylation, and loss of long-range Atoh1 enhancer activity close the chromatin landscape and stabilize the mature non-regenerative state[54-56]. In essence, controlling auditory fate now means restoring competence, not merely inducing hair-cell genes.

Supporting cells define the regenerative capacity of the cochlea

A central question in mammalian cochlear regeneration is whether supporting cells still retain enough plasticity to generate new hair cells. Recent work suggests that they do, but only within a restricted and age-dependent window. *In vivo* studies show that supporting-cell reprogramming is enhanced after hair-cell loss, indicating a transient injury-induced regenerative window[26]. In parallel, organoid and neonatal cochlear studies also indicate that supporting cells display limited mitotic regenerative potential when progenitor-like programs are reactivated[42,49,50]. However, the dominant constraint remains the age-related loss of plasticity, driven by transcriptional stabilization and epigenetic restriction[55,56]. LGR5-positive supporting cells survive severe ototoxic injury in the adult mouse cochlea and remain detectable long after trauma, while human temporal-bone studies show that supporting cells often persist despite marked hair-cell loss[45,57]. This concept has already gained translational relevance, as shown by the phase I/IIa trial of intratympanic gamma-secretase inhibition[58]. Thus, supporting cells are not passive bystanders but the principal endogenous substrate that defines whether cochlear regeneration is biologically possible.

Cochlear immunity shapes whether regeneration succeeds

Another major shift in the field is the recognition that regeneration unfolds within an immune microenvironment, rather

than in a purely cell-intrinsic setting. Cochlear macrophages exhibit diverse functional states, including inflammatory, phagocytic, pro-resolving, and repair-associated responses, which change dynamically during injury and repair[59]. Their regenerative impact depends on activation state, timing, injury context, and interactions with sensory cells, SGNs, fibroblasts, and implanted or transplanted materials[60-64]. Resident cochlear macrophages can promote repair, as they are required for ribbon-synapse recovery after noise-induced cochlear synaptopathy, and this process is further enhanced by soluble CX3CL1/fractalkine[20,60]. This suggests that a temporally controlled, pro-resolving, repair-associated macrophage response may support debris clearance, synaptogenesis, and neural survival. However, macrophage activity is not uniformly beneficial: Activated tissue-resident macrophages can exacerbate acoustic injury, whereas macrophage depletion can attenuate cisplatin-induced ototoxicity, underscoring the context-dependent effects of cochlear immune cells[61,65]. This issue becomes even more relevant in translational settings, because cochlear implantation itself induces macrophage- and fibroblast-associated inflammation, tissue remodeling, and altered neural survival[62,64]. These findings clarify why correct lineage specification alone is insufficient: Even appropriately differentiated donor or regenerated cells may fail in a niche that is inflammatory, fibrotic, or immunologically non-permissive. Cochlear immunity should therefore be regarded as part of the regenerative mechanism, not as a secondary background variable, and future strategies should aim to modulate macrophage dynamics rather than simply suppress inflammation.

Niche engineering is required for survival and integration

Once cell fate and immune context are considered together, niche engineering emerges as a core regenerative strategy, because effective therapy requires not only the appropriate auditory cell type, but also a host environment that supports survival, maturation, and integration. This concept is reflected by the early intracochlear use of human stromal cell-derived EVs[36], improved graft survival with hypoinnogenic iPSC-derived otic progenitors[66], biomaterial-based strategies that reduce inflammation and foreign-body responses[67-69], and innervated cochlear organoids that better model maturation and early auditory circuit assembly[70]. Taken together, these studies show that durable hearing restoration requires both correct cell fate and a permissive niche for long-term survival and functional integration.

DELIVERY ROUTES AND BIOENGINEERING OPTIMIZATION FOR INNER EAR THERAPY

Barriers to inner ear delivery

Inner ear delivery remains a major challenge for stem cell-based therapy as the cochlea is protected by the blood-labyrinth barrier and constrained by a small, mechanically delicate anatomy[71,72]. As a result, delivery must achieve precise cochlear access while minimizing surgical trauma and preserving a niche permissive for cell retention, survival, and integration.

Local delivery routes

For stem cell-based therapy, the goal is not merely local access, but precise cell delivery with minimal cochlear injury. Although cochleostomy/intracochlear injection provides direct access, its use is limited by insertion trauma and the need to preserve residual hearing[73]. Alternative perilymphatic routes may offer safer access: Posterior semicircular canal injection can target the perilymphatic space while preserving auditory and vestibular function[74,75] and both the mastoid approach and a minimally invasive route to the human cochlear nerve may expand delivery options for regenerative therapies, particularly those aimed at auditory neurons or SGNs[76,77]. Overall, local delivery strategies are shifting toward routes that maximize access while minimizing structural damage.

Biomaterials and delivery systems

Recent progress in biomaterials has shifted inner ear delivery from free-drug administration toward engineered retention and controlled release, mainly through hydrogels and nanoparticles. Nanoparticle-based systems, including thermo-sensitive, magnetic, and mucoadhesive formulations, have been developed to improve cochlear retention, localization, and sustained delivery[78-80]. Implantable controlled-release platforms, including EVA mini-implants and PLGA-based intracochlear systems, further support sustained local delivery[26,81]. Conductive hydrogel coatings loaded with neural stem cells further suggest that biomaterials can function as bioactive interfaces linking cells, drugs, and electrodes[82]. Accordingly, biomaterials are becoming the engineering layer that determines whether inner ear delivery is sustained, localized, and biologically relevant.

Combining cell delivery with implants and devices

A key emerging innovation is the transformation of cochlear implants from passive stimulators into active regenerative platforms. This includes drug-eluting implants that reduce inflammation and preserve residual hearing[69,83], bioactive electrode coatings that interface regenerative cells with implant hardware[82], and the cochlear-bioelectrode concept, which combines electrical stimulation with stem cell delivery to enhance cell localization and auditory responses[84]. Together, these advances suggest that future cochlear implants may serve as biohybrid devices for both neuromodulation and regeneration.

Cell tracking, retention, safety, and functional integration

For stem cell-based therapy, successful delivery must be judged not only by cochlear access, but by whether transplanted cells can be retained, survive safely, and functionally integrate into the auditory pathway. Recent studies suggest that

immune compatibility is a major determinant of cell persistence, while early evidence of synaptic and functional integration is beginning to emerge[66,85]. Thus, the main translational challenge is not delivery alone, but durable retention, safety, and functional incorporation.

COCHLEAR ORGANOIDS AND STEM CELL-BASED PRECLINICAL MODELING PLATFORMS

Sources and rationale of cochlear organoids

Cochlear organoids are mainly generated from hPSCs, including ESCs and iPSCs, using staged 3D differentiation protocols that recapitulate key steps of otic induction and sensory specification[16,17]. Recent advances have shifted the field from producing generic inner ear vesicles to building higher-fidelity cochlear organoids, with increasing emphasis on benchmarking organoid cell states against fetal and adult human inner ear atlases[86,87]. These models are particularly valuable as native human inner ear tissue is scarce and experimentally inaccessible, whereas organoids provide a scalable human system for studying development, disease, and regenerative responses.

Organoid models

Based on recent studies, cochlear organoids are currently most informative in four areas: Human inner ear development, genetic hearing loss, ototoxicity, and patient-specific disease phenotypes. Human organoid systems have been used to reconstruct prosensory and otic developmental trajectories[88,89], to model pathogenic mechanisms such as CHD7-dependent defects in otic lineage specification and hair-cell differentiation[29], to reproduce cisplatin- and gentamicin-induced hair-cell and neuronal injury[90-92], and to functionally assess patient-specific variants linked to cochlear malformations[31]. At present, these are the clearest and most reproducible disease-modeling applications supported by recent primary literature.

Organoid applications

Functionally, cochlear organoids are now most useful for drug screening, personalized disease interpretation, and preclinical testing of regenerative strategies. Optimized organoid systems have been used to improve hair-cell yield and to model differential responses to ototoxic injury, supporting their use in compound testing and comparative toxicity studies[90-92]. Patient-derived organoids also provide a practical platform for rapid interpretation of disease-associated variants[93]. In addition, high-fidelity and innervated cochlear organoids offer a human preclinical system in which auditory-cell specification, early maturation, and sensory-neural interactions can be evaluated before *in vivo* translation [70]. Thus, current evidence supports organoids less as replacements for animal models than as a human preclinical layer for screening, phenotyping, and early regenerative assessment.

Limitations and future directions

Despite rapid progress, current cochlear organoids remain incomplete models of the mature human cochlea. Although they can generate inner ear sensory cell-like populations, they do not yet reproduce several defining features of the native cochlea, including tonotopic organization, scala compartmentalization, endolymph-perilymph separation, cochlear fluid mechanics, endocochlear potential, vascularization, mature organ of Corti architecture, and full sensory-neural connectivity[91,94]. These limitations restrict their ability to model adult cochlear physiology or predict functional hearing restoration.

At the cellular level, organoid-derived sensory cells often remain immature, and many systems still show vestibular-like identity or incomplete cochlear cell-type representation[95]. At the tissue level, current organoids lack the ordered cellular geometry, basilar membrane mechanics, stria vascularis-like ion regulation, and scala-specific fluid environment required for true auditory transduction[96-98]. Even high-fidelity or innervated models mainly capture early developmental and sensory-neural interactions rather than the full architecture and electrophysiological environment of the adult organ of Corti[70].

Future efforts should therefore move beyond increasing hair-cell yield alone. Key priorities include improving cochlear-specific patterning, establishing tonotopic and organ of Corti-like organization, incorporating vascular or stria vascularis-like components, reconstructing endolymph-like ionic conditions and endocochlear potential, and enhancing SGN innervation and ribbon synapse formation. These advances will be essential for improving the predictive value of organoids in disease modeling, drug screening, and regenerative assessment. At present, cochlear organoids are best regarded as platforms for developmental studies, disease modeling, drug screening, and cell-source optimization, rather than as complete equivalents of the native cochlea or directly transplantable cochlear tissues.

STEM CELL-DERIVED EVS/EXOSOMES AS CELL-FREE THERAPEUTICS

Rationale and advantages of EVs/exosomes

Stem cell-derived EVs/exosomes, most commonly from MSCs, are attractive for inner-ear therapy because they may recapitulate part of the paracrine signals of parent cells while reducing some risks associated with live-cell transplantation. In principle, EV-based products may offer advantages over cell grafts in storage, engineering, and cell-free administration. However, their clinical translation is still limited due to EV heterogeneity, batch-to-batch variability,

incomplete cargo definition, lack of standardized potency assays, and unresolved GMP manufacturing and quality-control requirements[35,99-101]. Thus, the main appeal of stem cell-derived EVs lies in their potential to provide a cell-free therapeutic format, but this potential remains constrained by incomplete control over composition, dosing, biodistribution, and long-term safety[102].

Mechanisms relevant to hearing restoration

Current evidence suggests that stem cell-derived EVs act mainly through cytoprotective and microenvironment-modulating mechanisms rather than true cell replacement. In inner-ear injury models, they reduce apoptosis, oxidative stress, and inflammatory dysregulation, thereby protecting hair cells and SGNs, while also reshaping the injured cochlear niche through immune modulation[35,37,103-107]. Overall, their therapeutic value appears to lie primarily in suppressing injury pathways and stabilizing the cochlear microenvironment, rather than regenerating lost cochlear architecture or restoring mature auditory circuits.

Preclinical progress and translational signals

Preclinical evidence is most consistent in ototoxic injury and implantation-associated inflammation, where stem cell-derived EVs have shown protective effects on cochlear structures and auditory function[35,104,105,107,108]. The first-in-human intracochlear application of MSC-derived EVs during cochlear implantation provides an early feasibility and safety signal, but it should not yet be interpreted as evidence of clinical efficacy or hearing restoration[109]. At present, EV-based therapy appears closest to translation as a protective and supportive strategy, rather than a standalone approach for structural cochlear reconstruction.

Engineered EVs and targeted delivery

Engineered EVs are an emerging direction, including cargo loading and donor-cell preconditioning to enhance therapeutic potency[104,110,111]. However, current studies still focus more on improving EV efficacy than on achieving precise cell-type-specific cochlear targeting. Thus, engineered stem cell-derived EVs represent an important emerging direction, but targeted inner-ear delivery remains an unresolved challenge.

Translational limitations of EV/exosome therapy

Despite these advances, EV/exosome-based therapies for hearing restoration are still in their early-stage. Beyond general challenges in heterogeneity, cargo definition, dosing, potency testing, and GMP manufacturing, inner-ear translation requires clearer evidence on cochlear biodistribution, retention, cell-type-specific uptake, repeat dosing, and long-term safety. Given the cochlea's narrow therapeutic window, EVs should currently be regarded as adjunctive cytoprotective and microenvironment-modulating agents, rather than established regenerative treatments for hearing restoration.

TOWARD CLINICAL TRANSLATION: MAJOR CHALLENGES AND FUTURE PERSPECTIVES

Why hearing regeneration still fails?

Over the past three decades, diverse stem cell-based strategies for hearing loss have achieved substantial progress (Figure 3). Nevertheless, clinically hearing regeneration has remained unsuccessful largely because multiple sequential steps - from cell-fate induction and maturation to synaptogenesis and functional circuit reconstruction - remain unresolved.

First, although current stem cell differentiation and organoid systems can generate hair cell-like cells, these cells are often developmentally immature and do not reliably acquire the features of adult cochlear hair cells[16,17]. More importantly, the mature mammalian cochlea has strong epigenetic barriers. Supporting cells progressively lose regenerative competence after birth through mechanisms such as enhancer decommissioning, H3K4me1 loss, and DNA methylation, making it difficult for limited transcription factor induction to overcome epigenetic locking[54,56]. Although ATOH1, GF11, and POU4F3 have achieved significant progress, reprogramming efficiency, lineage stability, and cellular maturation remain limited[38,43].

Second, generating hair cell-like cells does not necessarily restore hearing function. Functional recovery requires proper spatial organization, mechanotransduction, and ribbon synapse formation with SGNs[112,113]. At present, reliable synaptogenesis, SGN reinnervation, and long-term neural circuit integration remain insufficient. This helps explain why cellular or structural improvements often fail to translate into stable and clinically meaningful hearing recovery.

Third, the cochlear microenvironment is a highly restrictive niche. After noise exposure, ototoxic injury, aging, or surgical trauma, inflammation, macrophage activation, and tissue remodeling can impair graft survival, maturation, and integration[61,114]. In addition, allogeneic or xenogeneic cell transplantation faces immune rejection and poor long-term engraftment. The improved survival of hypoinmunogenic otic progenitors also suggests that graft accommodation is still a major limitation for inner-ear cell therapy[66].

Finally, inner-ear delivery itself is a major cause of translational failure. The cochlea is small, delicate, and fluid-restricted, and therapeutic access is limited by the blood-labyrinth barrier, round window permeability, and a narrow local dose window. Although local delivery can increase cochlear exposure, it may cause uneven distribution, poor dose control, mechanical trauma, and residual hearing loss[115,116]. Moreover, current gene- or drug-based studies still reveal a substantial translational gap between pathway activation and true functional hearing recovery[58].

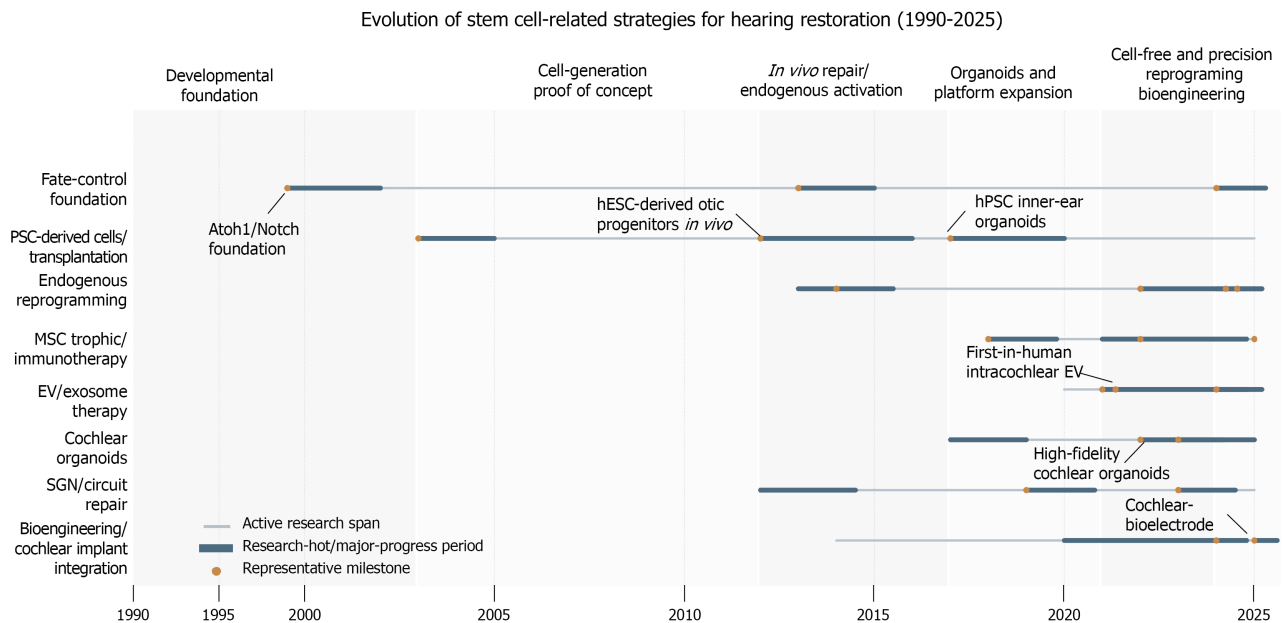


Figure 3 Evolution of stem cell-related strategies for hearing restoration from 1990 to 2025. The timeline summarizes the emergence and major progress of key strategies, including pluripotent stem cell-derived auditory cells, endogenous reprogramming, mesenchymal stem/stromal cell/extracellular vesicle-based therapies, cochlear organoids, spiral ganglion neuron/circuit repair, and bioengineering-assisted cochlear implant integration. PSC: Pluripotent stem cell; MSC: Mesenchymal stem/stromal cell; EV: Extracellular vesicle; SGN: Spiral ganglion neuron; hESC: Human embryonic stem cell; hPSC: Human pluripotent stem cell.

Therefore, success should not be defined solely by the generation of hair cell-like cells, but by strict functional criteria, including maturation, tonotopic organization, mechanotransduction, synaptogenesis, SGN reinnervation, long-term survival, safety, and ABR/DPOAE outcomes.

Future directions and clinical outlook

Future translation will likely depend on combinatorial and indication-specific strategies rather than any single modality. In this context, gene correction, biomaterial- or device-assisted delivery, and organoid- or omics-guided optimization should be viewed as enabling platforms that may improve the precision, safety, and predictability of stem cell-based interventions[16,17]. More importantly, SNHL should not be treated as a single regenerative target, because different etiological subtypes involve distinct pathological structures and therefore require different therapeutic strategies (Table 1).

From a translational perspective, stem cell-related strategies for SNHL are at different developmental stages. In the near term, EV-based therapy, immune modulation, and biomaterial- or implant-assisted delivery may be more clinically feasible. EVs carry lower safety risks than direct cell transplantation and can exert therapeutic effects in native or engineered forms. However, source heterogeneity, unclear active components, lack of standardized dose and potency assays, and quality-control challenges are major barriers[105,117,118]. The inner-ear immune microenvironment, particularly macrophage-mediated inflammation, is also an important regulator of SNHL injury, supporting immune modulation as another near-term strategy[114]. Moreover, EV- and immune-based approaches may be combined with biomaterials or cochlear implant-associated platforms to improve local retention, targeted delivery, and sustained release [119,120].

As a next-stage regenerative strategy, activating endogenous regeneration or reprogramming mature cochlear non-sensory cells with multiple transcription factors holds substantial potential but remains immature. The phase I/IIa trial of the Notch inhibitor has entered clinical exploration[58]. Transcription factor-based hair cell reprogramming also shows promise; however, reprogramming efficiency, cellular maturation, lineage stability, precise delivery, and functional integration remain key bottlenecks in the mature mammalian cochlea[26,38].

In the long term, iPSC/ESC-derived cell and organoid transplantation may achieve true cell replacement and cochlear reconstruction. However, clinical translation still faces major challenges, including differentiation purity, cellular maturation, spatial positioning, synaptic connectivity, long-term safety, ethical concerns, and tumorigenic risk[10-12]. High-fidelity human cochlear organoids currently appear more suitable for disease modeling and drug screening[16,121]. Integrating cell therapy with implantable devices, and bioengineering platforms may represent a long-term direction for regenerative hearing therapy[84].

CONCLUSION

Stem cell-based strategies are shifting hearing restoration from functional compensation toward biological repair of the inner ear. Effective recovery will likely require integrated reconstruction of sensory cells, neural elements, and the

Table 1 Regenerative strategies for major sensorineural hearing loss subtypes

SNHL subtype	Major pathological targets	Potential regenerative strategy	Supporting rationale
Noise-induced cochlear synaptopathy/hidden hearing loss	IHC ribbon synapses, auditory nerve fiber terminals, SGNs	Synapse repair, SGN protection, SGN reinnervation, NT-3 delivery, and CX3CL1/fractalkine-mediated immune modulation, instead of primary hair-cell replacement	Noise exposure can cause loss of IHC-auditory nerve synapses while hair cells may remain present. NT-3 delivery has been shown to regenerate cochlear synapses after acoustic trauma, and resident macrophages as well as CX3CL1/fractalkine signaling can promote ribbon-synapse repair[20,60,122-124]
Genetic hair-cell loss/genetic SNHL with sensory-cell involvement	Depending on the causal gene: Hair cells, supporting cells, synapses, ion channels, motor proteins, or auditory neurons	Gene replacement, gene editing, patient-derived iPSC/organoid modeling, drug screening, and long-term cell replacement when irreversible sensory-cell loss is present	Genetic hearing loss is highly heterogeneous and should be stratified by causal gene and residual cochlear structure. <i>OTOF</i> gene therapy supports gene replacement for selected monogenic synaptopathies, while CRISPR-corrected patient-derived iPSCs with <i>MYO7A</i> or <i>MYO15A</i> mutations support iPSC-based modeling and cell-source development[125-128]
Age-related hearing loss/presbycusis	Hair cells, SGNs, stria vascularis, IHC synapses, mitochondria	Multi-target protection and repair, including antioxidant/anti-inflammatory strategies, EV-based cytoprotection, SGN protection, synapse repair, stria/metabolic support, and selected regenerative approaches	Presbycusis is multifactorial and may involve sensory, neural, stria/metabolic, synaptic, mitochondrial, and inflammatory mechanisms. NT-3 overexpression can prevent age-related IHC synaptopathy and slow hearing decline, supporting synapse-targeted approaches as part of a broader multi-target strategy[129-131]
Auditory neuropathy/neural SNHL	IHC ribbon synapses, presynaptic vesicle release machinery, SGNs, and auditory nerve	Gene therapy for selected synaptopathies such as <i>OTOF</i> -related hearing loss, synapse repair, SGN protection/regeneration, neurotrophic support, auditory neuron replacement, tissue engineering, and cochlear implant-combined strategies	Auditory neuropathy spectrum disorders often involve impaired synaptic transmission or auditory nerve dysfunction rather than primary OHC loss. <i>OTOF</i> -related hearing loss is a prototypical auditory synaptopathy, and SGN protection/regeneration is considered a key therapeutic direction for neural SNHL[126,132,133]
Stria vascularis degeneration/metabolic SNHL	Stria vascularis, cochlear lateral wall, endocochlear potential, K ⁺ recycling, blood-labyrinth barrier	Strial repair, restoration of ion homeostasis, vascular/metabolic support, blood-labyrinth barrier protection, anti-inflammatory/EV-based strategies, and combination approaches rather than sensory-cell replacement alone	The stria vascularis is essential for cochlear fluid homeostasis, K ⁺ recycling, blood-labyrinth barrier function, and generation of the endocochlear potential. Strial dysfunction can independently contribute to SNHL and metabolic presbycusis, so sensory-cell replacement alone may be insufficient [134-137]

SNHL: Sensorineural hearing loss; IHC: Inner hair cell; SGNs: Spiral ganglion neurons; iPSC: Induced pluripotent stem cell; EV: Extracellular vesicle; OHC: Outer hair cell.

cochlear microenvironment rather than replacement of a single cell type alone. PSCs, endogenous reprogramming, organoid platforms, and stem cell-derived EVs together form a complementary framework for modeling disease and developing therapy. Although major challenges remain in maturation, delivery, safety, and long-term integration, these approaches are steadily bringing the field closer to clinically meaningful hearing restoration.

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