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· 专家论坛 ·

# 内耳精准给药赋能先天性耳聋基因治疗的策略、挑战与展望

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**专家简介** 舒易来, 教授、主任医师、博士生导师, 复旦大学附属眼耳鼻喉科医院副院长、遗传性耳聋诊治中心主任、上海市罕见病基因编辑与细胞治疗重点实验室主任。国家自然科学基金创新研究群体学术带头人, 国家杰出青年、优秀青年基金获得者, 并获第48届国际ARO“临床科学创新奖”、上海市青年科技杰出贡献奖、上海市级医院临床创新奖等。掌握耳鼻咽喉头颈外科疾病诊治和手术技巧, 尤其擅长耳显微、耳内镜、耳神经外科及人工耳蜗植入手术、耳聋三级防控。聚焦耳聋基因治疗及临床转化研究等, 研发 *OTOF* 耳聋基因治疗药物并开展国际首个先天性耳聋基因治疗临床试验, 使得聋哑患者恢复听力和言语。发表有影响力的SCI论文多篇, 包括

The Lancet、BMJ、Nature Medicine、JAMA Neurology、Nature Biomedical Engineering、Nature Human Behavior、Nature Review Genetics 等。担任中华医学会耳鼻咽喉头颈外科分会委员、上海市医学会耳鼻咽喉头颈外科分会委员等。

**摘要:**随着多项针对先天性耳聋的临床试验结果公布, 基因治疗有望成为根治耳聋的新型治疗策略。然而, 治疗体系能否高效、精准地递送至内耳, 仍是决定疗效的关键之一。本文基于内耳独特解剖与生理特征, 系统梳理了内耳精准给药策略从基础研究向临床转化的发展过程, 重点分析不同内耳递送路径对治疗安全性和有效性的影响。同时, 结合多项针对 *OTOF* 相关耳聋的基因治疗临床试验, 展示了内耳精准给药策略在临床转化研究中的实用价值, 并提出新形势下内耳外科的崛起。本综述为内耳精准给药提供了系统的认识和了解, 使相关从业人员具有清晰的可参考依据, 有助于促进先天性耳聋基因治疗的发展和推广。内耳外科概念的提出必将引领耳科学新的范式变革。

**关键词:**先天性耳聋; 基因治疗; 内耳局部递送; 腺相关病毒; 内耳外科

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## Targeted inner ear drug delivery empowering gene therapy for congenital hearing loss: strategies, challenges and prospects

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**Abstract:** Recent clinical trials targeting congenital hearing loss have demonstrated the promise of gene therapy as a curative approach. However, whether the treatment system can deliver agents to the inner ear efficiently and precisely remains one of the key determinants of therapeutic efficacy. Based on the unique anatomical and physiological features of

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the inner ear, this article systematically reviews the development process of targeted inner ear drug delivery strategies from basic research to clinical translation, with a focus on analyzing the impacts of different inner ear delivery pathways on treatment safety and effectiveness. Meanwhile, drawing on multiple gene therapy clinical trials for *OTOF*-related deafness, it highlights the practical value of targeted inner ear delivery strategies in clinical translation and the emergence of inner ear surgery in the current landscape. This review provides a systematic perspective on targeted inner ear delivery strategies, offering a clear reference framework for relevant practitioners and facilitating the development and translation of gene therapy for congenital hearing loss. Furthermore, the introduction of the inner ear surgery concept is poised to herald a new paradigm in otology.

**Keywords:** Congenital hearing loss; Gene therapy; Local delivery to the inner ear; Adeno-associated virus; Inner ear surgery

世界卫生组织(2025)最新数据显示,全球已有超4.3亿人患有残疾性听力损失,预计到2050年将超过7亿人,其中多数为感音神经性听力损失(sensorineural hearing loss, SNHL),是全球最常见的感官缺陷之一<sup>[1-2]</sup>。SNHL是由耳蜗、听神经或中枢听觉通路受损所致,病因复杂,根据发病时间可分为先天性与后天性两类<sup>[2-3]</sup>。其中,先天性SNHL约60%为遗传因素所致,在发达国家该比例更高,遗传性耳聋(hereditary hearing loss, HHL)已成为影响儿童言语与认知发育的重要公共卫生问题<sup>[4]</sup>。

目前,临床针对HHL的主要干预手段为助听器和人工耳蜗。助听器通过放大外界声学信号改善听觉感知,而人工耳蜗则绕过功能缺失的耳蜗毛细胞,直接电刺激螺旋神经节以恢复听觉信息传递<sup>[5-6]</sup>。然而,这两种方法仅能部分补偿听觉,无法从分子层面纠正致聋基因引发的功能异常、恢复自然听觉。随着对HHL分子机制的深入研究和基因诊断技术的快速发展,目前已鉴定出150余个非综合征型耳聋相关基因,为精准靶向内耳基因治疗提供了客观依据,使通过替换、修复或调控致病基因实现根治耳聋成为可能<sup>[7-8]</sup>。

以腺相关病毒(adeno-associated virus, AAV)为主要载体的基因治疗体系已在动物模型中证实可挽救多种基因(例如 *Vglut3*、*Tmc1*、*Otof*、*Whrn*、*Pcdh15*、*Klhl18*、*Myo6*、*Kcnq4* 及 *Mpzl2* 等)突变导致的耳聋,达到改善小鼠听觉的目的<sup>[9-18]</sup>。基础研究的成功推动了HHL基因治疗的临床转化,本团队在全球范围内率先开展了常染色体隐性遗传性耳聋9型(autosomal recessive deafness 9, DFNB9)患者的基因治疗临床试验<sup>[19-20]</sup>,随后,国内外多家单位也相继证实了内耳基因治疗的安全性和有效性,不仅为HHL的治疗提供了范式转变,也是内耳疾病治疗里程碑式的标志<sup>[21-27]</sup>。

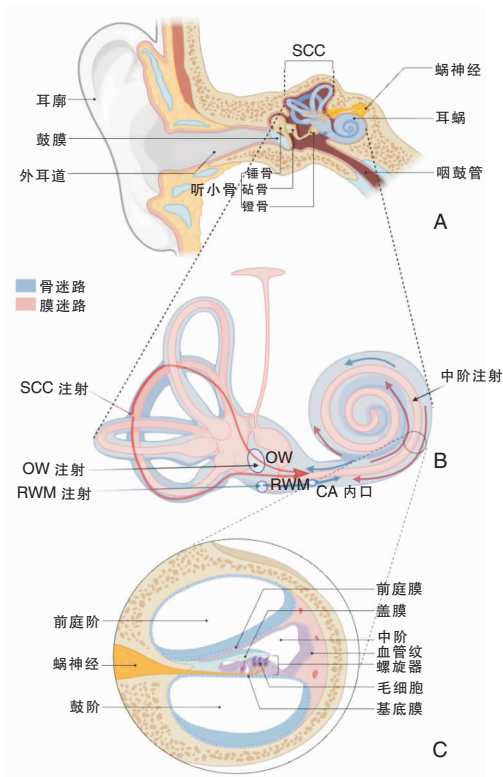
目前越来越多的患者接受治疗,但他们的听力

恢复水平表现出一定的个体差异<sup>[19-27]</sup>。内耳基因治疗的疗效受多种因素影响,首先,载体及启动子类型决定了基因治疗体系能否高效、特异地转导至内耳靶细胞并成功发挥作用<sup>[28-30]</sup>;其次,治疗时间窗尤为重要,需在内耳毛细胞或神经元发生不可逆损伤之前进行干预,以实现最佳疗效<sup>[31]</sup>;此外,给药剂量也需在安全性与有效性之间审慎权衡<sup>[32-34]</sup>。在满足上述因素的基础上,将基因治疗体系精准、安全递送至内耳成为决定疗效的核心基石之一。本文基于内耳的解剖与生理特性,系统梳理了内耳药物递送策略的研究进展和临床转化现状,剖析关键技术挑战与临床转化瓶颈,为优化内耳精准药物递送提供方向,赋能基因治疗发展。同时,对“内耳外科”概念提出了诠释和见解,以进一步补充和推动内耳外科治疗技术的范式变革。

## 1 解剖和生理特性对内耳给药的影响

内耳深藏于颞骨岩部,结构相对封闭,由充满外淋巴的骨迷路和充满内淋巴的膜迷路组成(图1)<sup>[35]</sup>。内、外淋巴液无直接沟通,且通过血迷路屏障(blood-labyrinth barrier, BLB)与血循环相隔。该屏障主要位于耳蜗中阶外侧壁的血管纹和螺旋韧带,由连续的毛细血管内皮细胞、基膜、周细胞、血管周围巨噬细胞样黑色素细胞以及这些细胞间的连接结构构成,在功能上类似于血脑屏障<sup>[36]</sup>。这些解剖和生理特性导致传统内耳给药方式的有效性明显受限。

既往内耳疾病药物治疗通常采用静脉或鼓室内注射。静脉注射全身给药虽侵入性小,但受BLB限制,导致到达内耳的药物有效剂量低,且全身暴露伴有潜在的系统毒副作用;此外,以AAV为载体的治疗体系易受中和抗体影响<sup>[37-41]</sup>。鼓室内注射作为常用的局部注射方法,可使药物经圆窗膜(round



**图1** 人耳解剖结构与内耳局部注射给药途径 A: 显示外耳、中耳及内耳的主要结构; B: 展示内耳骨迷路与膜迷路的分布, 并标注了4种常用的内耳局部注射给药途径: SCC注射、OW注射、RWM注射及中阶注射; C: 为耳蜗横断面, 清晰显示前庭阶、中阶与鼓阶的相对位置, 以及血管纹、螺旋器和毛细胞等关键结构 注: SCC(半规管); OW(卵圆窗); RWM(圆窗膜); CA(耳蜗导水管)。下同。

window membrane, RWM) 和卵圆窗 (oval window, OW) 渗透入内耳。RWM 作为主要的药物递送通道, 其通透性与分子大小密切相关。小分子药物相对易穿透 RWM 进入内耳, 而大分子药物——如 AAV 载体或脂质体颗粒——则因体积较大而通透率显著降低。这种基于分子尺寸的通透性限制, 使得以 AAV 为主要载体的基因治疗体系难以在内耳达到足够的有效浓度, 成为临床转化中的技术瓶颈之一<sup>[42-43]</sup>。OW 被镮骨足板与环韧带封闭, 辣根过氧化物酶示踪实验提示其为药物渗透入内耳的次要通道<sup>[44]</sup>, 但钆造影剂与壳聚糖纳米颗粒均主要通过 OW 进入前庭细胞, 提示靶向前庭时可考虑经 OW 渗透<sup>[45-46]</sup>。此外, 鼓室内药物易经咽鼓管排出, 无法保证药液与 RWM 和 OW 具有稳定且充分的接触面积与时间, 有研究证实, 个体间中耳黏膜状态差异可使外淋巴液药物浓度相差百倍<sup>[47-48]</sup>。

传统给药方式面临的困境促使研究者们探索新的内耳给药方法, 即将药物直接注射至内耳, 借助其

独特的解剖和生理使药物局限在目标区域内, 不仅可以提高内耳药物浓度, 也降低了全身给药带来的潜在风险<sup>[49-50]</sup>。但内耳局部注射给药也面临一系列问题, 首先, 内耳解剖位置深, 且为骨性相对封闭结构, 仅在 RWM 与 OW 处与中耳呈膜性分隔, 虽然它们可作为直接注射窗口, 但经此两者穿刺可能存在一些问题和风险: RWM 可因解剖变异 (如骨性嵴遮挡、圆窗龛狭窄) 导致暴露困难从而影响操作, 而 RWM 穿刺损伤本身即可引起潜在听力波动<sup>[51-53]</sup>; OW 穿刺时可能出现镮骨足板损伤诱发外淋巴瘘、刺激前庭引发眩晕等<sup>[54-55]</sup>。其次, 内、外淋巴液在离子组成上存在显著差异, 外淋巴液呈高  $\text{Na}^+$  ( $\sim 140 \text{ mM}$ )、低  $\text{K}^+$  ( $\sim 5 \text{ mM}$ ), 与脑脊液或细胞外液相似; 而内淋巴液则呈现独特的“细胞内液”样高  $\text{K}^+$  ( $\sim 150 \text{ mM}$ )、低  $\text{Na}^+$  ( $\sim 1 \text{ mM}$ ) 环境, 有研究表明, 内淋巴的高  $\text{K}^+$  环境可能影响某些 AAV 血清型的衣壳构象和基因组释放效率, 进而影响其转染效果, 这对 AAV 的理化特性提出了挑战<sup>[56]</sup>。此外, 内耳淋巴液的沟通能力有限, 尤其是内淋巴液, 这可能直接限制药物注射体积<sup>[57]</sup>。由此可见, 内耳兼具“易靶向”与“难递送”的双重特性。

## 2 内耳精准给药策略的持续探索和优化

为探索安全有效的内耳局部递送策略, 尤其是在基因治疗兴起的背景下, 研究者们借助动物模型对不同内耳注射方法进行了持续探索和优化 (表1)<sup>[50,58-63]</sup>。

耳蜗中阶注射是通过在耳蜗基底转侧壁钻孔, 将药物直接注射至中阶的内淋巴液, 从而提高 AAV 对靶细胞的转染效率与局部表达<sup>[43,64]</sup>。在成年小鼠中, 研究者通过该路径注入携带绿色荧光蛋白 (green fluorescent protein, GFP) 的 AAV 载体, 可转染毛细胞、支持细胞、螺旋韧带以及听神经细胞, 但对较高频率 (32、40 和 45.2 kHz) 听力有损伤<sup>[58]</sup>。除此之外, 通过椭圆囊也可将 AAV9-PHP. B-eGFP 注射至内淋巴液, 转染了 99% 的新生小鼠毛细胞, 且听性脑干反应 (auditory brainstem response, ABR) 和平衡功能检查均未检测出功能损害<sup>[59]</sup>。然而, 内耳膜迷路缺乏通畅的引流途径, 导致其对注射药物产生的体积变化高度敏感。研究表明, 向豚鼠内耳注射人工内淋巴液, 注射体积占内淋巴液体积 23% 时即可导致一过性外毛细胞功能减退, 若进一步增加至 53% ~ 74%, 则可能引起 Reissner 膜破裂, 并导

致外毛细胞功能严重受损<sup>[65-66]</sup>。相比之下,外淋巴液通过耳蜗导水管(cochlear aqueduct, CA)与脑脊液沟通,具备一定的引流和压力缓冲能力,从体积调节角度考虑,外淋巴液可能为更理想的注射靶区<sup>[67]</sup>。

RWM 菲薄易于穿刺,且与耳蜗鼓阶直接延续,成为将药物递送至外淋巴液的重要途径<sup>[49]</sup>。Akil 等<sup>[68]</sup>经 RWM 注射 AAV1-GFP 溶液(1~2  $\mu\text{L}$ )至野生型 P10-P12 小鼠内耳,在内毛细胞及支持细胞可见 GFP 表达且未损伤内耳功能。在新生耳聋小鼠模型中,经此途径递送 AAV 载体可有效转染内耳毛细胞,纠正 *Otof*、*Vglut3* 和 *Tmc1* 等突变,部分或完全恢复 ABR 阈值<sup>[69-71]</sup>。在听觉功能恢复更具挑战性的成年耳聋小鼠模型中,经此途径注射基因治疗药物 AAV1-hOTOF 仍可显著改善听觉功能<sup>[69]</sup>。后续在豚鼠实验中进一步验证了该路径的安全性,仅检测到一过性的外毛细胞功能变化、于 5 h 内恢复<sup>[72]</sup>。鉴于啮齿类动物与人类在内耳解剖结构上存在差异,在临床转化前,研究者利用非人灵长类动物评估了该途径的可行性,即经 RWM 注入恒河猴内耳 10  $\mu\text{L}$  或 30  $\mu\text{L}$  不含载体的磷酸盐缓冲生理盐水(phosphate buffered saline, PBS),随后 8 周,未见听觉及前庭功能受损,支持其作为临床转化路径的潜力<sup>[32]</sup>。但 RWM 可因穿刺损伤导致突发或波动性听力下降与眩晕,对术者操作要求较高<sup>[73-74]</sup>;同时,CA 这一引流通路使部分药物或载体可能进入脑脊液,有小鼠模型在脑部发生非目标转染,提示存在潜在的异位表达风险<sup>[67,75]</sup>。此外,AAV 经 RWM

注射至鼓阶后可能使药物呈现从耳蜗底转至顶转递减的梯度分布,导致低频区转导效率较低<sup>[76]</sup>。为克服药物在耳蜗内分布不均的问题,研究者提出 RWM 注射联合半规管(semicircular canal, SCC)或 OW 开窗的方法。在野生型成年小鼠中,RWM 注射联合 SCC 开窗可使耳蜗顶转内毛细胞转导效率从单纯 RWM 注射的 1.9% 提高至 94.6%,而未损伤听力<sup>[50]</sup>。在非人灵长类动物中,采用 RWM 注射联合 OW 开窗引流,使耳蜗顶转内毛细胞的 AAV 转染率高达 90%<sup>[61]</sup>。尽管这两种联合方法明显提升了 AAV 在耳蜗内的均匀分布,但手术难度也明显增加,它们对手术视野、骨切除精度、开窗与封窗技术均有较高要求,增加了创伤风险,在非人灵长类动物中 RWM 注射联合 OW 开窗出现 1 例同侧轻度面瘫<sup>[61]</sup>。

通过 SCC 递送在克服 AAV 载体耳蜗中分布不均的问题方面显示出独特的优势。药物注入 SCC 外淋巴液后,流经前庭阶与鼓阶,最终抵达 CA,从而实现耳蜗内的均匀分布<sup>[77-78]</sup>。且 SCC 注射在啮齿类动物中无需开放听泡,减少了手术损伤与术后中耳积液风险<sup>[79]</sup>。Isgrig 等<sup>[12]</sup>经后 SCC 注射 AAV8-whirlin 至新生耳聋小鼠内耳,改善了其听觉与平衡功能。但该路径对操作精细度要求较高,需在打开骨性 SCC 的同时确保膜迷路完整,否则内外淋巴液混合将破坏离子稳态,导致不可逆的内耳损伤<sup>[80]</sup>。注射体积可能也受到限制,成年小鼠模型中经 SCC 注射 1  $\mu\text{L}$  液体时听觉功能保持稳定,而 2  $\mu\text{L}$  则引起听力阈值上升与毛细胞损伤,其具体机制仍需进

表 1 内耳给药方式的优势与局限性

给药方式	优势	局限性
全身给药	操作简单微创,临床常用 <sup>[37]</sup>	内耳药物浓度低 <sup>[37-40]</sup> ,系统毒副作用 <sup>[41]</sup>
鼓室内注射	同全身给药	内耳药物浓度低 <sup>[42-44]</sup> ;进入内耳药物剂量不可控 <sup>[47-48]</sup>
内耳局部注射		
中阶注射	药物直接注射至内淋巴液,有望提升病毒载体对靶细胞的转染效率与局部表达 <sup>[43,59,64]</sup>	内耳膜迷路缺乏通畅引流途径,药物注射体积受限 <sup>[65-66]</sup>
椭圆囊注射	同中阶注射	同中阶注射
单纯 RWM 注射	膜性结构 <sup>[49]</sup> ,药物注射至具有引流能力的外淋巴 <sup>[67]</sup>	RWM 穿刺损伤风险 <sup>[73-74]</sup> ,神经系统异位表达风险 <sup>[67-75]</sup> ,药物在耳蜗内分布不均 <sup>[76]</sup>
RWM 注射联合镫骨足板或 SCC 开窗	提升药物在耳蜗内的均匀分布 <sup>[50,61]</sup>	对手术操作精度要求高,增加创伤风险 <sup>[61]</sup>
SCC 注射	不干扰中耳结构,减少了手术损伤与术后中耳积液风险 <sup>[79]</sup> ;提升耳蜗内药物分布均匀性 <sup>[77-78]</sup>	对手术操作精度要求较高 <sup>[80]</sup> ,药物注射体积受限 <sup>[81-82]</sup>
OW 注射	膜性结构 <sup>[63]</sup>	手术难度大,注射针控制不当易损伤球囊引起前庭症状 <sup>[83]</sup>
小脑延髓池注射	具备同时双耳基因治疗的潜力 <sup>[84]</sup>	进入内耳药物剂量不可控,药物在耳蜗内分布不均 <sup>[84]</sup> ;药物神经毒性 <sup>[75,84]</sup>

进一步明确<sup>[81-82]</sup>。因此,提高骨性 SCC 穿刺精度、控制导管插入深度与注射参数、系统评估其安全性是未来研究的重点,有利于推进 SCC 递送策略的应用范围。

除了上述路径,OW 作为另一内耳与中耳的膜性分隔,也被研究者用于内耳注射。经该途径将 Anc80L65-CMV-GFP 注射至成年豚鼠内耳,可转染耳蜗毛细胞(内毛细胞转染率 71% ~ 90%、外毛细胞转染率 42% ~ 81%、前庭毛细胞转染率 64%),并对听力无显著影响<sup>[63]</sup>。在恒河猴模型中,经 OW 注射 PBS 未发现明显的前庭和听觉功能受损,进一步证明了该注射路径的安全性<sup>[32]</sup>。然而,OW 被镫骨足板覆盖增加了手术难度,注射针插入深度与角度控制不当可能会损伤球囊,引起前庭症状<sup>[83]</sup>。

此外,有研究探索了借助脑脊液循环机制实现对内耳的药物递送,他们将携带表达增强型绿色荧光蛋白(enhanced green fluorescent protein, eGFP)基因的 AAV 载体注射至成年小鼠的小脑延髓池(cisterna magna, CM),实现了右耳 49.0% ± 6.5% 和左耳 42.8% ± 9.0% 的内毛细胞转导效率,展示出同时双耳基因治疗的潜力<sup>[84]</sup>。但该路径注射的 AAV 需经 CA 弥散至双耳,实际进入内耳的剂量难以精准把控,使得转染效率表现出从底转到顶转明显衰减的趋势<sup>[84]</sup>。同时,经 CM 注射的 AAV 总剂量高达 10<sup>11</sup> vg 级别(约为局部内耳注射剂量的 3 ~ 4 倍),存在 AAV 剂量依赖性神经系统毒性的风险,可能导致血脑屏障破坏、淋巴细胞浸润及注射区神经元丢失<sup>[75,84]</sup>。

创新给药装置也正在助力局部内耳给药策略的发展。与人工耳蜗结合的递送可通过载药电极或导管在植入时同期给药<sup>[85-88]</sup>,为未来实现耳蜗内基因治疗药物的持久缓释提供了可能。类似地,微泵系统通过可植入装置实现药物的长期程序化输注,有望为慢性听力损失提供持续药物治疗,但其系统集成与长期稳定性仍是临床转化的关键障碍<sup>[89-91]</sup>。多学科交叉从微观层面为内耳给药技术提供了新的思路,如微针可在极小孔径下精确、低创伤地穿透 RWM 进行药物递送,穿刺部位可在短时间(48 ~ 72 h)内愈合,但其推广仍面临材料生物相容性低、制造与操作精度要求高等问题<sup>[92-94]</sup>;超声微泡利用空化效应瞬时可逆地开放 BLB,显著增强静脉全身给药向内耳的转运效率,但空化效应可能造成毛细血管损伤、炎症反应及听觉、前庭功能负担<sup>[95-96]</sup>;磁性靶向策略借助磁场引导载药纳米颗粒在耳蜗内富

集,但其在复杂淋巴液环境中的导航效率与生物安全性仍需深入研究<sup>[97]</sup>。

总之,大量针对局部内耳递送策略的基础研究为该技术向精准、微创、高效方向发展并日趋成熟提供了必要的科学依据。研究者们始终致力于在保护内耳解剖和生理安全性的前提下,持续提升递送效率。未来,探索多维技术的深度融合将为内耳递送策略的优化开辟更多可能性。

### 3 内耳精准给药的临床转化

内耳基因治疗的飞速发展促使局部内耳精准给药策略向临床转化,而临床前研究和人工耳蜗植入经验为此提供了关键参考和指导。在人类,无论是经外耳道还是乳突-面隐窝入路,均可暴露 RWM,而目前动物研究也展示出经此进行内耳注射的良好安全性,因此,经 RWM 显微注射被视为最具临床转化潜力的局部内耳给药策略。目前,其临床应用已使全球多个 OTOF 基因治疗临床试验成功取得一系列突破和进展,但在具体方法上存在差异。

本团队通过前期研发与探索,采用经外耳道耳内镜下 RWM 显微注射联合镫骨足板开窗递送药物 RRG-003(ChiCTR2200063181),该手术和递送方案不仅保障了药物在耳蜗内的均匀分布,也有利于在注射过程中通过观察镫骨足板开窗处溢出的液体确认药物准确注入耳蜗。术后鼓膜外耳道皮瓣切口均可在 4 周内完全愈合,无穿孔或中耳炎等并发症<sup>[19-20]</sup>。同时,首批通过该路径接受单侧基因治疗的 6 例患儿中,5 例在术后 26 周时 0.5 ~ 4 kHz 平均 ABR 阈值恢复至 38 ~ 55 dB HL<sup>[19]</sup>。5 例接受双侧基因治疗的患儿在术后 13 周时平均 ABR 阈值显著改善,并提高了声源定位能力和言语功能<sup>[20]</sup>。Lilly-Akouos 公司采用经外耳道的内耳给药策略递送药物 AK-OTOF(NCT05821959),2 例受试者听力均有改善<sup>[23-24]</sup>。

与上述给药方式不同的是,有团队采用了与人工耳蜗植入相似的经乳突-面隐窝入路进行 RWM 显微注射。Otovia Therapeutics 公司使用该策略向内耳递送药物 OTOV101N + OTOV101C(NCT05901480),术后未见中耳或内耳感染、外淋巴液渗漏等,表明该递送策略总体耐受良好<sup>[21-22]</sup>。该研究的 10 例受试者均观察到不同程度的听力改善,且无前庭功能异常表现<sup>[21-22]</sup>。为保障药物均匀扩散,REGENERON 公司采用经乳突-面隐窝入路 RWM 显微注射联合

外 SCC 开窗递送药物 DB-OTO (NCT05788536), 在 12 例受试者中, 9 例治疗有效, 5 例术后出现可自行缓解的短暂前庭功能异常症状<sup>[25-26]</sup>。SENSORION 公司则采用经乳突-面隐窝入路 RWM 显微注射联合镫骨足板开窗递送药物 SENS-501 (NCT06370351), 3 例受试患儿中 1 例在治疗后 1 个月内即出现听觉行为与发声反应<sup>[27]</sup>。

综合现有的临床试验结果, 内耳给药策略在不同研究中心存在一定差异, 主要体现在手术入路不同和是否联合镫骨足板或外 SCC 开窗。在手术入路选择上, 经乳突-面隐窝路径作为人工耳蜗植入等传统耳科手术入路, 通过切除乳突骨质、开放面隐窝暴露圆窗, 具有操作熟悉、可重复性高等优势<sup>[98]</sup>。经外耳道耳内镜入路, 不需要或仅需切除少许外耳道骨质即可暴露圆窗, 即使联合镫骨足板开窗, 也只需切除部分外耳道后上壁骨质, 具有手术创伤小、恢复快等优势, 并且耳内镜可提供高清手术视野, 有助于直视下进行 RWM 穿刺与注射<sup>[99]</sup>。联合镫骨足板或外 SCC 开窗促进药物在耳蜗内均匀分布的必要性仍有待明确, 但其不容忽视的优势可肉眼判断药物是否准确注入耳蜗。尽管具体给药策略存在以上差异, 但它们总体表现出了令人满意的安全性及有效性结果。

未来, 根据已发布的 HHL 基因治疗国际专家共识<sup>[100]</sup>, 提高不同中心研究的规范化和同质化, 有利于探索和优化更佳的内耳精准给药策略, 使基因治疗在内耳疾病治疗中发挥更大的应用推广价值。

#### 4 内耳外科的崛起助力内耳精准给药

随着基因治疗在内耳疾病中的临床转化不断推进, 传统耳外科的范畴正在被重新定义。基因治疗打开了“内耳外科”的大门, 使得“内耳外科”作为一种新兴的微创手术范式正迅速崛起。传统耳外科以结构重建与功能替代为核心, 如鼓室成形术修复中耳传音结构<sup>[101]</sup>, 人工耳蜗植入绕过受损毛细胞补偿听觉功能<sup>[5]</sup>。然而, 这些手段均未触及内耳疾病的病因学本质, 无法恢复自然听觉。内耳外科的根本突破在于: 通过精准的微创手术路径, 实现治疗药物向内耳的局部、可控、高效递送, 克服了传统全身给药与鼓室内给药因 BLB、RWM 和 OW 通透性限制、药物清除快等问题导致的内耳有效药物浓度不足的瓶颈<sup>[42-43, 48, 102-103]</sup>。这不仅为 HHL 的基因治疗提供了可行的递送通道, 也为多种后天性内耳疾病

(如突发性聋、噪声性聋、梅尼埃病等) 的药物干预与功能保护开辟了新可能。

未来, 内耳外科依托于局部递送路径的进一步成熟与优化, 结合高分辨率影像导航、机器人辅助与内镜技术, 有望实现更加精准、可重复、低创伤的手术操作。其目标不仅是“根治”遗传缺陷, 更包括延缓疾病进展、保留残余听力、修复细胞功能、调控内耳微环境等多元功能。新的治疗药物、生物材料、手术器械和给药装置的不断涌现, 将促使内耳外科成为耳科学的重要组成部分, 推动内耳疾病治疗从“结构修复”迈向“生物治疗”的范式变革。

#### 5 未来展望

内耳精准给药策略的日趋完善为 HHL 基因治疗的成功提供了技术保障, 当前, 以 AAV 为载体的基因治疗已在多项 *OTOF* 相关临床试验中取得了突破性进展。然而, 要实现该内耳给药技术的安全微创与广泛临床应用, 仍需在多个关键领域持续探索与优化。

技术上, 优化手术路径与器械, 如机器人辅助穿刺、可降解微针、智能微泵等, 将有助于提升给药的精准度与安全性, 降低操作创伤<sup>[89, 104]</sup>。在转化层面, 推动跨物种研究(从小鼠、豚鼠到非人灵长类)的系统性药代动力学与安全性评估, 是临床前研究向临床应用过渡的关键<sup>[105-106]</sup>。建立标准化的内耳药物浓度监测方法与功能评估体系, 也将为个体化给药方案的制定提供依据<sup>[107-108]</sup>。临床实践中, 规范内耳给药策略实施流程、强化手术操作规范并明确最佳治疗时间窗是确保患者最大获益的前提<sup>[108]</sup>。在基因治疗方面取得的积极疗效, 催化了“内耳外科”的兴起, 促使我们有信心把内耳精准给药技术拓展至其他内耳疾病(如突发性聋、噪声性聋、老年性聋、梅尼埃病等), 不断丰富“内耳外科”的内涵与应用场景。

多学科融合将是推动该领域发展的核心动力。耳科学、基因治疗、生物材料、影像导航、人工智能等领域的交叉合作, 有望实现“诊断—递送—评估”一体化平台的构建, 最终实现内耳疾病的精准、微创、长效治疗。

综上所述, 内耳精准给药技术正逐步从理念走向现实, 其发展不仅改写了 HHL 的治疗格局, 也正引领耳科学进入“内耳外科”新时代。

## 参考文献:

- [1] Mehra S, Eavey RD, Keamy DG. The epidemiology of hearing impairment in the United States; newborns, children, and adolescents[J]. *Otolaryngol Head Neck Surg*, 2009, 140(4): 461 – 472.
- [2] Tan WJT, Song L. Role of mitochondrial dysfunction and oxidative stress in sensorineural hearing loss[J]. *Hear Res*, 2023, 434: 108783.
- [3] Korver AMH, Smith RJH, Van Camp G, et al. Congenital hearing loss[J]. *Nat Rev Dis Primers*, 2017, 3: 16094.
- [4] Morton CC, Nance WE. Newborn hearing screening—a silent revolution[J]. *N Engl J Med*, 2006, 354(20): 2151 – 2164.
- [5] Carlson ML. Cochlear implantation in adults[J]. *N Engl J Med*, 2020, 382(16): 1531 – 1542.
- [6] Han S, Chen Z, Wang D, et al. Clinical gene therapy restores hearing: A paradigm shift[J]. *Trends Mol Med*, 2025, S1471 – 4914(25)00173 – X.
- [7] Lee NK, Uhler KM, Yoon PJ, et al. Clinical genetic testing for hearing loss: Implications for genetic counseling and gene-based therapies[J]. *Biomedicine*, 2024, 12(7): 1427.
- [8] Landegger LD, Pan B, Askew C, et al. A synthetic AAV vector enables safe and efficient gene transfer to the mammalian inner ear[J]. *Nat Biotechnol*, 2017, 35(3): 280 – 284.
- [9] Zhang T, Zhai R, Liu M, et al. Rapid cochlear gene therapy in adult deaf mice: Vglut3 rescue via AAV8 achieves day-1 hearing restoration[J]. *Mol Ther Methods Clin Dev*, 2025, 33(3): 101539.
- [10] Marcovich I, Baer NK, Shubina-Oleinik O, et al. Optimized AAV vectors for TMC1 gene therapy in a humanized mouse model of DFNB7/11[J]. *Biomolecules*, 2022, 12(7): 914.
- [11] Akil O, Dyka F, Calvet C, et al. Dual AAV-mediated gene therapy restores hearing in a DFNB9 mouse model[J]. *Proc Natl Acad Sci U S A*, 2019, 116(10): 4496 – 4501.
- [12] Isgrig K, Shteamer JW, Belyantseva IA, et al. Gene therapy restores balance and auditory functions in a mouse model of usher syndrome[J]. *Mol Ther*, 2022, 30(2): 975.
- [13] Ivanchenko MV, Hathaway DM, Mulhall EM, et al. PCDH15 dual-AAV gene therapy for deafness and blindness in Usher syndrome type 1F models[J]. *J Clin Invest*, 2024, 134(23): e177700.
- [14] Gu X, Hu X, Wang D, et al. Treatment of autosomal recessive hearing loss via in vivo CRISPR/Cas9-mediated optimized homology-directed repair in mice[J]. *Cell Res*, 2022, 32(7): 699 – 702.
- [15] Xue Y, Hu X, Wang D, et al. Gene editing in a Myo6 semi-dominant mouse model rescues auditory function[J]. *Mol Ther*, 2022, 30(1): 105 – 118.
- [16] Zheng Z, Li G, Cui C, et al. Preventing autosomal-dominant hearing loss in bth mice with CRISPR/CasRx-based RNA editing[J]. *Signal Transduct Target Ther*, 2022, 7(1): 79.
- [17] Cui C, Wang D, Huang B, et al. Precise detection of CRISPR-Cas9 editing in hair cells in the treatment of autosomal dominant hearing loss[J]. *Mol Ther Nucleic Acids*, 2022, 29: 400 – 412.
- [18] Hu S W, Jeong S, Jiang L, et al. PAM-flexible adenine base editing rescues hearing loss in a humanized MPZL2 mouse model harboring an east asian founder mutation[J]. *Nat Commun*, 2025, 16(1): 7186.
- [19] Lv J, Wang H, Cheng X, et al. AAV1-hOTOF gene therapy for autosomal recessive deafness 9: A single-arm trial[J]. *Lancet*, 2024, 403(10441): 2317 – 2325.
- [20] Wang H, Chen Y, Lv J, et al. Bilateral gene therapy in children with autosomal recessive deafness 9: Single-arm trial results[J]. *Nat Med*, 2024, 30(7): 1898 – 1904.
- [21] Qi J, Tan F, Zhang L, et al. AAV-mediated gene therapy restores hearing in patients with DFNB9 deafness[J]. *Adv Sci (Weinh)*, 2024, 11(11): e2306788.
- [22] Qi J, Zhang L, Lu L, et al. AAV gene therapy for autosomal recessive deafness 9: A single-arm trial[J]. *Nat Med*, 2025, 31(9): 2917 – 2926.
- [23] Simons EJ, Germiller JA, Haag O, et al. Clinical development of AK-OTOF gene therapy for OTOF-mediated hearing loss [A]// Agrawal Y, Chen ZY (Co-Chairs). Proceedings of ARO 47th Annual MidWinter Meeting- Late Breaking Presidential Symposium: OTOF Gene Therapy Clinical Trial[C]. [s.l.]:[s.n.], 2024.
- [24] Da Rold C. Gene therapy allows a deaf child to hear for the first time [N/OL]. *Nature News*, 2024 – 02 – 16[2025 – 12 – 09].
- [25] Regeneron Pharmaceuticals, Inc. Latest DB-OTO results demonstrate clinically meaningful hearing improvements in nearly all children with profound genetic hearing loss in CHORD trial[N/OL]. *Regeneron News Release*, 2025 – 02 – 24[2025 – 12 – 09].
- [26] Valayannopoulos V, Bance M, Carvalho DS, et al. DB-OTO gene therapy for inherited deafness[J]. *N Engl J Med*, 2025. doi: 10.1056/NEJMoa2400521. Online ahead of print.
- [27] Sensorion. Sensorion reports new positive clinical results presented at the world congress of audiology 2024[N/OL]. *Sensorion Press Release*, 2024 – 09 – 23[2025 – 12 – 09].
- [28] Moffitt JS, Blanset DL, Lynch JL, et al. Regulatory Consideration for the nonclinical safety assessment of gene therapies[J]. *Hum Gene Ther*, 2022, 33(21 – 22): 1126 – 1141.
- [29] Zhang L, Tan F, Qi J, et al. AAV-mediated gene therapy for hereditary deafness: Progress and perspectives [J]. *Adv Sci (Weinh)*, 2024, 11(47): e2402166.
- [30] Ivanchenko MV, Hanlon KS, Devine MK, et al. Preclinical testing of AAV9-PHP. B for transgene expression in the non-human primate cochlea[J]. *Hear Res*, 2020, 394: 107930.
- [31] Amariutei AE, Jeng JY, Safieddine S, et al. Recent advances and future challenges in gene therapy for hearing loss[J]. *R Soc Open Sci*, 2023, 10(6): 230644.
- [32] Dai C, Lehar M, Sun DQ, et al. Rhesus cochlear and vestibular functions are preserved after inner ear injection of saline volume sufficient for gene therapy delivery[J]. *J Assoc Res Otolaryngol*, 2017, 18(4): 601 – 617.
- [33] Askew C, Chien WW. Adeno-associated virus gene replacement

- for recessive inner ear dysfunction: Progress and challenges[J]. *Hear Res*, 2020, 394: 107947.
- [34] Salt AN, Plontke SK. Principles of local drug delivery to the inner ear[J]. *Audiol Neurootol*, 2009, 14(6): 350–360.
- [35] Iso-Mustajärvi M, Dietz A. Extracting the cochlea from a human temporal bone: A cadaveric protocol [J]. *J Vis Exp*, 2023, (198).
- [36] Nyberg S, Abbott NJ, Shi X, et al. Delivery of therapeutics to the inner ear: The challenge of the blood-labyrinth barrier[J]. *Sci Transl Med*, 2019, 11(482): eaao0935.
- [37] Plontke SK, Meisner C, Agrawal S, et al. Intratympanic corticosteroids for sudden sensorineural hearing loss[J]. *Cochrane Database Syst Rev*, 2022, 7(7): CD008080.
- [38] Chandrasekhar SS, Rubinstein RY, Kwartler JA, et al. Dexamethasone pharmacokinetics in the inner ear: Comparison of route of administration and use of facilitating agents[J]. *Otolaryngol Head Neck Surg*, 2000, 122(4): 521–528.
- [39] Shibata SB, Yoshimura H, Ranum PT, et al. Intravenous rAAV2/9 injection for murine cochlear gene delivery[J]. *Sci Rep*, 2017, 7(1): 9609.
- [40] Nyberg S, Abbott NJ, Shi X, et al. Delivery of therapeutics to the inner ear: The challenge of the blood-labyrinth barrier[J]. *Sci Transl Med*, 2019, 11(482): eaao0935.
- [41] Duan D. Systemic delivery of adeno-associated viral vectors[J]. *Curr Opin Virol*, 2016, 21: 16–25.
- [42] Moatti A, Silkstone D, Martin T, et al. Assessment of drug permeability through an ex vivo porcine round window membrane model[J]. *iScience*, 2023, 26(6): 106789.
- [43] Liu SS, Yang R. Inner ear drug delivery for sensorineural hearing loss: Current challenges and opportunities [J]. *Front Neurosci*, 2022, 16: 867453.
- [44] Saijo S, Kimura RS. Distribution of HRP in the inner ear after injection into the middle ear cavity[J]. *Acta Otolaryngol*, 1984, 97(5–6): 593–610.
- [45] King EB, Salt AN, Eastwood HT, et al. Direct entry of gadolinium into the vestibule following intratympanic applications in Guinea pigs and the influence of cochlear implantation[J]. *J Assoc Res Otolaryngol*, 2011, 12(6): 741–751.
- [46] Ding S, Xie S, Chen W, et al. Is oval window transport a royal gate for nanoparticle delivery to vestibule in the inner ear? [J]. *Eur J Pharm Sci*, 2019, 126: 11–22.
- [47] Dahm V, Gausterer JC, Auinger AB, et al. Evaluation of levels of triamcinolone acetonide in human perilymph and plasma after intratympanic application in patients receiving cochlear implants: A randomized clinical trial[J]. *JAMA Otolaryngol Head Neck Surg*, 2021, 147(11): 974–980.
- [48] Gausterer JC, Saidov N, Ahmadi N, et al. Intratympanic application of poloxamer 407 hydrogels results in sustained N-acetylcysteine delivery to the inner ear[J]. *Eur J Pharm Biopharm*, 2020, 150: 143–155.
- [49] György B, Meijer EJ, Ivanchenko MV, et al. Gene transfer with AAV9-PHP.B rescues hearing in a mouse model of usher syndrome 3A and transduces hair cells in a non-human primate[J]. *Mol Ther Methods Clin Dev*, 2019, 13: 1–13.
- [50] Yoshimura H, Shibata SB, Ranum PT, et al. Enhanced viral-mediated cochlear gene delivery in adult mice by combining canal fenestration with round window membrane inoculation [J]. *Sci Rep*, 2018, 8(1): 2980.
- [51] Mehanna AM, Abdelnaby MM, Eid M. The anatomy and anatomical variations of the round window prechamber and their implications on cochlear implantation: An anatomical, imaging, and surgical study [J]. *Int Arch Otorhinolaryngol*, 2020, 24(3): e288–e298.
- [52] Haubner F, Rohrmeier C, Koch C, et al. Occurrence of a round window membrane rupture in patients with sudden sensorineural hearing loss[J]. *BMC Ear Nose Throat Disord*, 2012, 12: 14.
- [53] Hamamoto M, Murakami G, Kataura A. Topographical relationships among the facial nerve, chorda tympani nerve and round window with special reference to the approach route for cochlear implant surgery[J]. *Clin Anat*, 2000, 13(4): 251–256.
- [54] Sarna B, Abouzari M, Merna C, et al. Perilymphatic fistula: A review of classification, etiology, diagnosis, and treatment [J]. *Front Neurol*, 2020, 11: 1046.
- [55] Necula V, Maniu AA, Ujváry LP, et al. Vertigo associated with otosclerosis and stapes surgery—a narrative review [J]. *Medicina (Kaunas)*, 2023, 59(8): 1485.
- [56] Tan F, Chu C, Qi J, et al. AAV-*ie* enables safe and efficient gene transfer to inner ear cells [J]. *Nat Commun*, 2019, 10(1): 3733.
- [57] Salt AN, DeMott J. Longitudinal endolymph flow associated with acute volume increase in the Guinea pig cochlea[J]. *Hear Res*, 1997, 107(1–2): 29–40.
- [58] Kilpatrick LA, Li Q, Yang J, et al. Adeno-associated virus-mediated gene delivery into the scala media of the normal and deafened adult mouse ear[J]. *Gene Ther*, 2011, 18(6): 569–578.
- [59] Lee J, Nist-Lund C, Solanes P, et al. Efficient viral transduction in mouse inner ear hair cells with utricle injection and AAV9-PHP.B[J]. *Hear Res*, 2020, 394: 107882.
- [60] Liu Y, Okada T, Sheykholslami K, et al. Specific and efficient transduction of cochlear inner hair cells with recombinant adeno-associated virus type 3 vector[J]. *Mol Ther*, 2005, 12(4): 725–733.
- [61] Andres-Mateos E, Landegger LD, Unzu C, et al. Choice of vector and surgical approach enables efficient cochlear gene transfer in nonhuman primate[J]. *Nat Commun*, 2022, 13(1): 1359.
- [62] Suzuki J, Hashimoto K, Xiao R, et al. Cochlear gene therapy with ancestral AAV in adult mice: Complete transduction of inner hair cells without cochlear dysfunction[J]. *Sci Rep*, 2017, 7: 45524.
- [63] Wang J, Zhao L, Gu X, et al. Efficient delivery of adeno-associated virus into inner ear In vivo through trans-stapes route in adult guinea pig[J]. *Hum Gene Ther*, 2022, 33(13–14): 719–728.
- [64] Shibata SB, Cortez SR, Wiler JA, et al. Hyaluronic acid enhances gene delivery into the cochlea[J]. *Hum Gene Ther*, 2012, 23

- (3): 302–310.
- [65] Valk WL, Wit HP, Albers FWJ. Evaluation of cochlear function in an acute endolymphatic hydrops model in the Guinea pig by measuring low-level DPOAEs[J]. *Hear Res*, 2004, 192(1–2): 47–56.
- [66] Valk WL, Wit HP, Albers FWJ. Rupture of reissner’s membrane during acute endolymphatic hydrops in the Guinea pig: A model for ménière’s disease? [J]. *Acta Otolaryngol*, 2006, 126(10): 1030–1035.
- [67] Han S, Xu Z, Wang S, et al. Distributional comparison of different AAV vectors after unilateral cochlear administration[J]. *Gene Ther*, 2024, 31(3–4): 154–164.
- [68] Akil O, Rouse SL, Chan DK, et al. Surgical method for virally mediated gene delivery to the mouse inner ear through the round window membrane[J]. *J Vis Exp*, 2015(97): 52187.
- [69] Zhang L, Wang H, Xun M, et al. Preclinical evaluation of the efficacy and safety of AAV1-hOTOF in mice and nonhuman primates [J]. *Mol Ther Methods Clin Dev*, 2023, 31: 101154.
- [70] Nist-Lund CA, Pan B, Patterson A, et al. Improved TMCI gene therapy restores hearing and balance in mice with genetic inner ear disorders[J]. *Nat Commun*, 2019, 10(1): 236.
- [71] Akil O, Seal RP, Burke K, et al. Restoration of hearing in the VGLUT3 knockout mouse using virally mediated gene therapy[J]. *Neuron*, 2012, 75(2): 283–293.
- [72] Feng SJ, Leong S, Aksit A, et al. Physiologic effects of microneedle-mediated intracochlear dexamethasone injection in the Guinea pig[J]. *Laryngoscope*, 2024, 134(1): 388–392.
- [73] Seo T, Kemmochi A, Koike Y, et al. Case report: Perilymphatic fistula from a round window microfissure[J]. *Front Neurol*, 2023, 14:1281023.
- [74] Cho WS, Koju G, Parajuli S, et al. Round window membrane rupture following blunt force trauma[J]. *Ann R Coll Surg Engl*, 2022, 104(1): e12–e13.
- [75] Stone D, Aubert M, Jerome KR. Breaching the blood-brain barrier: AAV triggers dose-dependent toxicity in the brain[J]. *Mol Ther Methods Clin Dev*, 2023, 31: 101105.
- [76] Shi X, Wu N, Zhang Y, et al. Adeno-associated virus transformation into the normal miniature pig and the normal guinea pigs cochlea via scala tympani[J]. *Acta Otolaryngol*, 2017, 137(9): 910–916.
- [77] Talaei S, Schnee ME, Aaron KA, et al. Dye tracking following posterior semicircular canal or round window membrane injections suggests a role for the cochlea aqueduct in modulating distribution [J]. *Front Cell Neurosci*, 2019, 13: 471.
- [78] Zhao Y, Zhang L, Wang D, et al. Approaches and vectors for efficient cochlear gene transfer in adult mouse models[J]. *Biomolecules*, 2022, 13(1): 38.
- [79] Zhu J, Choi JW, Ishibashi Y, et al. Refining surgical techniques for efficient posterior semicircular canal gene delivery in the adult mammalian inner ear with minimal hearing loss [J]. *Sci Rep*, 2021, 11(1): 18856.
- [80] Lahlou G, Calvet C, Giorgi M, et al. Towards the clinical application of gene therapy for genetic inner ear diseases[J]. *J Clin Med*, 2023, 12(3): 1046.
- [81] Zhao Y, Zhang L, Wang D, et al. Approaches and vectors for efficient cochlear gene transfer in adult mouse models[J]. *Biomolecules*, 2022, 13(1): 38.
- [82] Tao Y, Huang M, Shu Y, et al. Delivery of adeno-associated virus vectors in adult mammalian inner-ear cell subtypes without auditory dysfunction[J]. *Hum Gene Ther*, 2018, 29(4): 492–506.
- [83] Pauw BK, Pollak AM, Fisch U. Utricle, saccule, and cochlear duct in relation to stapedotomy. A histologic human temporal bone study[J]. *Ann Otol Rhinol Laryngol*, 1991, 100(12): 966–970.
- [84] Blanc F, Bemelmans AP, Affortit C, et al. A single cisterna magna injection of AAV leads to binaural transduction in mice[J]. *Front Cell Dev Biol*, 2021, 9: 783504.
- [85] Plontke SK, Götze G, Rahne T, et al. Intracochlear drug delivery in combination with cochlear implants: Current aspects [J]. *HNO*, 2017, 65(Suppl 1): 19-28.
- [86] Chin OY, Diaz RC. State-of-the-art methods in clinical intracochlear drug delivery[J]. *Curr Opin Otolaryngol Head Neck Surg*, 2019, 27(5): 381–386.
- [87] Dhanasingh A, Hochmair I. Drug delivery in cochlear implantation [J]. *Acta Otolaryngol*, 2021, 141(sup1): 135–156.
- [88] Douchement D, Terranti A, Lamblin J, et al. Dexamethasone eluting electrodes for cochlear implantation: Effect on residual hearing [J]. *Cochlear Implants Int*, 2015, 16(4): 195–200.
- [89] Forouzandeh F, Borkholder DA. Microtechnologies for inner ear drug delivery[J]. *Curr Opin Otolaryngol Head Neck Surg*, 2020, 28(5): 323–328.
- [90] Forouzandeh F, Ahamed NN, Hsu MC, et al. A 3D-printed modular microreservoir for drug delivery [J]. *Micromachines (Basel)*, 2020, 11(7): 648.
- [91] Forouzandeh F, Zhu X, Alfadhel A, et al. A nanoliter resolution implantable micropump for murine inner ear drug delivery[J]. *J Control Release*, 2019, 298: 27–37.
- [92] Aksit A, Rastogi S, Nadal ML, et al. Drug delivery device for the inner ear: Ultra-sharp fully metallic microneedles[J]. *Drug Deliv Transl Res*, 2021, 11(1): 214–226.
- [93] Voruz F, Feng SJ, Breil E, et al. Microneedle-mediated intracochlear injection safely achieves higher perilymphatic dexamethasone concentration than intratympanic delivery in Guinea pig[J]. *Drug Deliv Transl Res*, 2025, 15(10): 3595–3606.
- [94] Leong S, Aksit A, Szeto B, et al. Anatomic, physiologic, and proteomic consequences of repeated microneedle-mediated perforations of the round window membrane[J]. *Hear Res*, 2023, 432: 108739.
- [95] Shih CP, Chen HC, Chen HK, et al. Ultrasound-aided microbubbles facilitate the delivery of drugs to the inner ear via the round window membrane[J]. *J Control Release*, 2013, 167(2): 167–174.
- [96] Liao AH, Wang CH, Weng PY, et al. Ultrasound-induced microbubble cavitation via a transcanal or transcranial approach facili-

- tates inner ear drug delivery [J]. JCI Insight, 2020, 5(3): e132880, 132880.
- [97] Ferdous Z, Le TN, Zhang Z, et al. Magnetic targeting of AAV gene therapy for inner ear following systemic delivery: Preliminary findings and transduction pattern in rat cochlea [J]. J Assoc Res Otolaryngol, 2025, 26(5): 553–571.
- [98] Magnan J, Baki F. Cochlear implantation using posterior tympanotomy and cochleostomy [A]//DeSaSouza S. Cochlear Implants: New and Future Directions [M]. Singapore: Springer Nature, 2022: 193–214.
- [99] Zhang LL, Wang J, Gao Z W, et al. A novel delivery approach of clinical inner ear gene therapy [J]. Otol Neurotol, 2025, 46(1): 31–38.
- [100] Fan X, Gao Z, Zhong J, et al. International expert consensus on gene therapy for hereditary hearing loss: Based on clinical trials [J]. Med, 2025: 100886.
- [101] Gutierrez JA, Cabrera CI, Stout A, et al. Tympanoplasty in the setting of complex middle ear pathology: A systematic review [J]. Ann Otol Rhinol Laryngol, 2023, 132(11): 1453–1466.
- [102] Nyberg S, Abbott NJ, Shi X, et al. Delivery of therapeutics to the inner ear: The challenge of the blood-labyrinth barrier [J]. Sci Transl Med, 2019, 11(482): eaa0935.
- [103] Shi H, Li Y, Yin S, et al. The predominant vestibular uptake of gadolinium through the oval window pathway is compromised by endolymphatic hydrops in ménière's disease [J]. Otol Neurotol, 2014, 35(2): 315–322.
- [104] Kashani RG, Henslee A, Nelson RF, et al. Robotic assistance during cochlear implantation: The rationale for consistent, controlled speed of electrode array insertion [J]. Front Neurol, 2024, 15: 1335994.
- [105] Manrique-Huarte R, Linera-Alperi MA de, Parilli D, et al. Inner ear drug delivery through a cochlear implant: Pharmacokinetics in a macaque experimental model [J]. Hear Res, 2021, 404: 108228.
- [106] Yildiz E, Gadenstaetter AJ, Gerlitz M, et al. Investigation of inner ear drug delivery with a cochlear catheter in piglets as a representative model for human cochlear pharmacokinetics [J]. Front Pharmacol, 2023, 14: 1062379.
- [107] Gioacchini FM, Re M, Scarpa A, et al. Proposal of a theoretically feasible method to perform perilymph sampling in clinical settings [J]. Life (Basel), 2024, 14(10): 1323.
- [108] Omichi R, Shibata SB, Morton CC, et al. Gene therapy for hearing loss [J]. Hum Mol Genet, 2019, 28(R1): R65–R79.

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