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1 Recent advances in local drug delivery to the inner ear

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15 Graphical abstract

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18 Abstract

19 Inner ear diseases are not adequately treated by systemic drug administration mainly
20 because of the blood-perilymph barrier that reduces exchanges between plasma and inner
21 ear fluids. Local drug delivery methods including intratympanic and intracochlear
22 administrations are currently developed to treat inner ear disorders more efficiently.
23 Intratympanic administration is minimally invasive but relies on diffusion through middle ear
24 barriers for drug entry into the cochlea, whereas intracochlear administration offers direct
25 access to the cochlea but is rather invasive. A wide range of drug delivery systems or devices
26 were evaluated in research and clinic over the last decade for inner ear applications. In this
27 review, different strategies including medical devices, hydrogels and nanoparticulate systems
28 for intratympanic administration, and cochlear implant coating or advanced medical devices
29 for intracochlear administration were explored with special attention to *in vivo* studies. This
30 review highlights the promising systems for future clinical applications as well as the current
31 hurdles that remain to be overcome for efficient inner ear therapy.

32

33 Abbreviations

34 AIED, autoimmune inner ear disease; BDNF, Brain-derived neurotrophic factor; BPLB, blood-
35 perilymph barrier; BSA, bovine serum albumine; CMAP, Na-carboxymethyl- β -cyclodextrins
36 modified activated polyamidoamine; CMV, cytomegalovirus; FITC, fluorescein
37 isothiocyanate; GMO, glycerol monooleate; HA, hyaluronic acid; HBPL, hyperbranched poly-
38 L-lysine; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; JNK, c-Jun n-
39 terminal kinase; LNC, lipid nanocapsule; NIHL, noise-induced hearing loss; PEG-PCL,
40 poly(ethyleneglycol)-*b*-poly(ϵ -caprolactone); PHEA, poly(2-hydroxyethyl aspartamide);
41 PK, pharmacokinetic; PLGA, poly(lactic-co-glycolic acid); RW, round window; SNHL,
42 sensorineural hearing loss; SPION, superparamagnetic iron oxide nanoparticle; TTI,
43 transtympanic injection.

44

45 Keywords

46 Cochlea, hydrogels, intracochlear administration, intratympanic administration, medical drug
47 delivery devices, nanoparticulate systems.

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