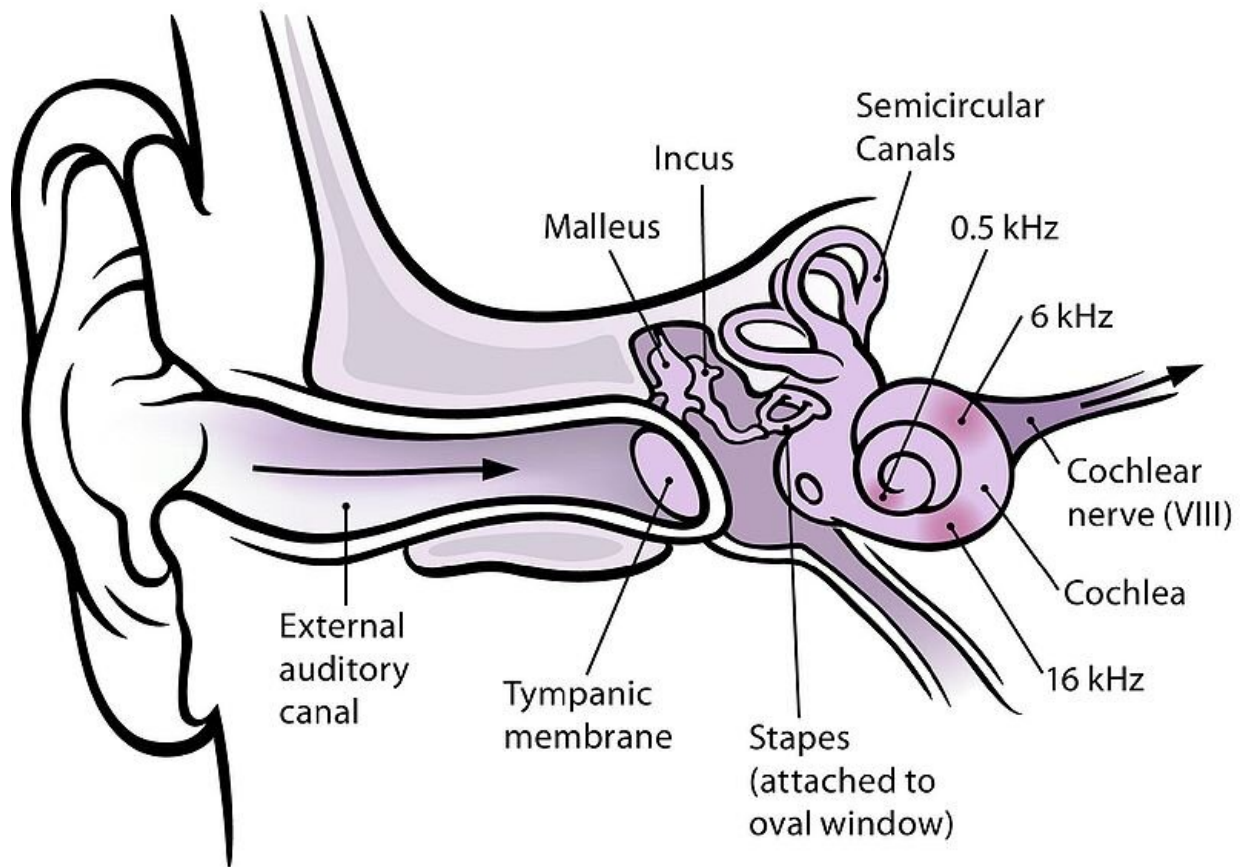


# An unexpected doorway into the ear opens new possibilities for hearing restoration

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A labeled cross-sectional diagram of the human ear. Credit: Chittka L. Brockmann/Wikimedia Commons, [CC BY](https://creativecommons.org/licenses/by/4.0/)

An international team of researchers has developed a new method to

deliver drugs into the inner ear. The discovery was made possible by harnessing the natural flow of fluids in the brain and employing a little understood backdoor into the cochlea. When combined to deliver a gene therapy that repairs inner ear hair cells, the researchers were able to restore hearing in deaf mice.

"These findings demonstrate that cerebrospinal fluid transport comprises an accessible route for [gene delivery](#) to the adult inner ear and may represent an important step toward using gene therapy to restore hearing in humans," said Maiken Nedergaard, MD, DMSc, senior author of the new study, which appears in the journal *Science Translational Medicine*.

Nedergaard is co-director of the Center for Translational Neuromedicine at University of Rochester and the University of Copenhagen. The study was the product of a collaboration between researchers at the two universities and a group led by Barbara Canlon, Ph.D. in the Laboratory of Experimental Audiology at the Karolinska Institute in Stockholm, Sweden.

The number of people worldwide predicted to have mild to complete hearing loss is expected to grow to around 2.5 billion by mid-century. The primary cause is the death or loss of function of hair cells found in the cochlea—which are responsible for relaying sounds to the brain—due to mutations of critical genes, aging, noise exposure, and other factors.

While hair cells do not naturally regenerate in humans and other mammals, gene therapies have shown promise and in separate studies have successfully repaired the function of hair cells in neo-natal and very young mice. However, as both mice and humans age, the cochlea, already a delicate structure, becomes enclosed in temporal bone. At this point, any effort to reach the cochlea and deliver a gene therapy via surgery risks damaging this sensitive area and altering hearing.

In the new study, the researchers describe a little understood passage into the cochlea called the cochlear aqueduct. While the name conjures images of monumental stone architecture, the cochlear aqueduct is thin boney channel no larger than a single strand of hair. Suspected to play a role in balancing pressure in the ear, new study shows that that the cochlear aqueduct also acts as a conduit between the cerebrospinal fluid found in the inner ear and the rest of the brain.

Scientists are developing clearer picture of the mechanics of glymphatic system, the brain's unique process of removing waste first described by the Nedergaard lab in 2012. Because the glymphatic system pumps cerebrospinal fluid deep into [brain tissue](#) to wash away toxic proteins, researchers have been eyeing it as a potentially new way to deliver drugs into the brain, a major challenge in developing drugs for neurological disorders.

Researchers have also discovered that the complex movement of fluids driven by the glymphatic system extend to the eyes and the peripheral nervous system, including ear. The new study represented an opportunity to put the drug delivery potential of the glymphatic system to the test, while at the same time targeting a previously unreachable part of the auditory system.

Employing a number of imagining and modeling technologies, the researchers were able to develop a detailed portrait of how fluid from other parts of the [brain](#) flows through cochlear aqueduct and into the inner ear. The team then injected an adeno-associated virus into the cisterna magna, a large reservoir of [cerebrospinal fluid](#) found at the base of the skull. The virus found its way into the inner ear via the cochlear aqueduct, delivered a [gene therapy](#) that expresses a protein called vesicular glutamate transporter-3, which enable the [hair cells](#) to transmit signal and rescued hearing in adult deaf mice.

"This new delivery route into the ear may not only serve the advancement of auditory research, but also prove useful when translated to humans with progressive genetic-mediated hearing loss," said Nedergaard.

**More information:** Barbara Koch Mathiesen et al, Delivery of gene therapy through a cerebrospinal fluid conduit to rescue hearing in adult mice, *Science Translational Medicine* (2023). [DOI: 10.1126/scitranslmed.abq3916](https://doi.org/10.1126/scitranslmed.abq3916).  
[www.science.org/doi/10.1126/scitranslmed.abq3916](https://www.science.org/doi/10.1126/scitranslmed.abq3916)

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