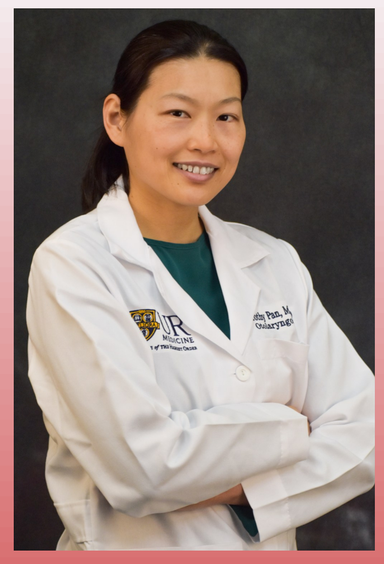
AMERICAN OTOLOGICAL SOCIETY

Dorothy Pan, MD, PhD

Assistant Professor Department of Otolaryngology

University of Rochester



"Characterizing Nanoparticle Transport from the Middle to Inner Ear through the Round Window Membrane "

FELLOWSHIP GRANT 2021

Amount Awarded by AOS: $44,000

PUBLICATIONS:

Pan, D.W.; Kim, J.; Quinones, P.M.; Ricci, A.J.; Applegate, B.E.; Oghalai, J.S. "Cochlear Mechanics are preserved after inner ear delivery of gold nanoparticles." *Int. J. Mol. Sci.* **2025**, *26,* 126.

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Kim, J.; Maldonado, J.; **Pan, D.W.**; Quinones, P.M.; Zenteno, S.; Oghalai, J.S.; Ricci, A.J. Semicircular canal drug delivery safely targets the inner ear perilymphatic space. *JCI Insight*. **2024,** *9,* e173052.

DOI: 10.1172/jci. insight.173052.

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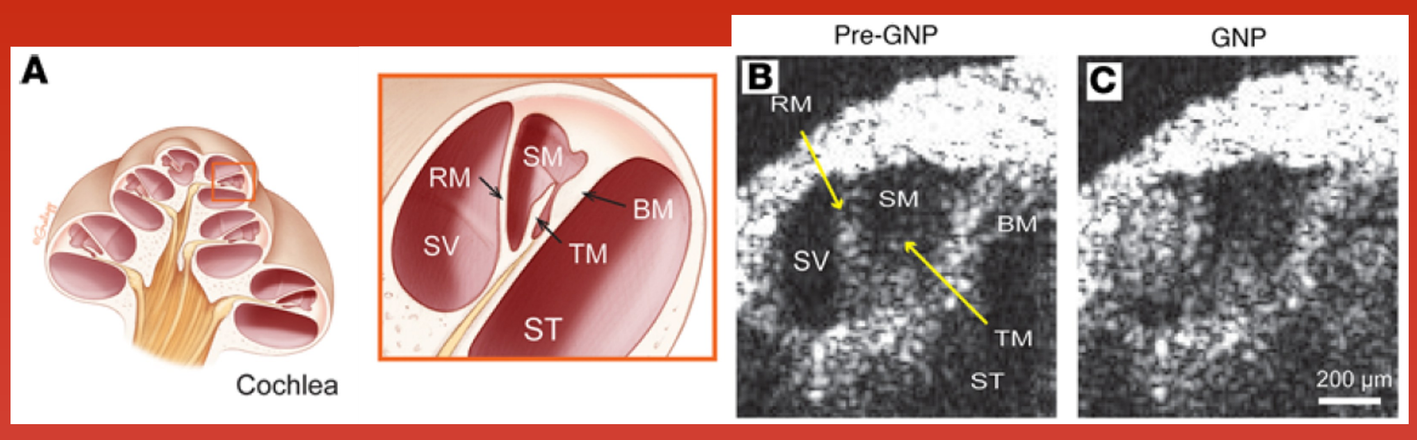
RESEARCH SUMMARY:

Therapeutic delivery to the cochlea is challenging due to its location deeply encased in the temporal bone. Local drug delivery through the tympanic membrane to the middle ear is a minimally invasive technique used clinically. The original goal of the proposed project was to characterize the passage of fluorescently tagged gold nanoparticles (GNPs) through the round window membrane in mice *in vivo* in real time using a 2-photon optical coherence tomography (OCT) microscopy system with the aim of determining the nanoparticle properties which maximize penetration through the round window membrane into the inner ear. Preliminary work seemed promising that this would be achievable, but due to technical limitations we pivoted to performing posterior semicircular canal (PSCC) infusions for nanoparticle delivery directly into the inner ear. We characterized the distribution of GNPs in the cochlea with OCT after PSCC infusion. Furthermore, we wanted to determine whether PSCC infusion affected cochlear mechanics

OUTCOMES:

We showed that PSCC infusion consistently and reliably delivered GNPs throughout the cochlear perilymphatic spaces, including to the apical turn. There were no GNPs seen in the endolymphatic spaces immediately after PSCC infusion. Cochlear mechanics measured at the basilar membrane immediately after and an hour following PSCC infusion of both artificial perilymph and GNPs in artificial perilymph was not affected by precise microsurgical PSCC canalostomy procedure or slow infusion at 0.5 µL/min



In vivo real-time monitoring of gold nanoparticle (GNP) infusion through the PSCC. (**A**) Cross-sectional image of the cochlea with the orange box showing the region outlined in the apical turn rotated to match the OCT images. Cochlear chambers are labeled: scala vestibuli (SV), scala media (SM), and scala tympani (ST). These chambers are separated by Reissner's membrane (RM) and basilar membrane (BM). Tectorial membrane (TM) is within the SM compartment. Optical coherence tomography (OCT) images with the same labeling as panel **A** show (**B**) before GNP (50 nm) infusion and (**C**) after GNP (50 nm) infusion. **Cochlear mechanics are unchanged after stabilized gold nanoparticle (Au50PEG NP) infusion.** Displacement of the basilar membrane, cochlear sensitivity, and phase at the apical turn with characteristic frequency 8 kHz of a representative wild-type CBA/CaJ mouse at (**A**) baseline, (**B**) immediately after Au50PEG infusion, and (**C**) 1 h after Au50PEG infusion showing no significant change in cochlear mechanics after Au50PEG infusion.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

(1) Examine on a cellular level where nanoparticles deposit in the cochlea after PSCC infusion.

(2) Explore targeting nanoparticles to specific cell types within the organ of Corti.

(3) Develop nanoparticles carrying nucleic acids for therapeutic applications

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

Sensorineural hearing loss is a debilitating sensory impairment affecting millions of people worldwide, and treatment is currently limited to devices such as hearing aids and cochlear implants. Next generation therapeutics are being developed to restore inner ear sensory cell function, however delivery of therapeutics remains a challenge. Nanoparticles are a viable carrier for many types of therapeutics and can be infused directly into and throughout the inner ear for delivery without affecting cochlear function. Direct infusion of nanoparticles into the inner ear is a viable method to deliver therapeutics to the inner ear for treatment of sensorineural hearing loss