AMERICAN OTOLOGICAL SOCIETY

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(PGY-3/Research)

"Microneedle-Assisted Intracochlear Glucocorticoid Delivery and Sequential Proteomic Characterization "

RESEARCH GRANT 2021

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PUBLICATIONS:

Leong S, Aksit A, Szeto B, Feng SJ, Ji X, Soni RK, Olson ES, Kysar JW, Lalwani AK (2023). Anatomic, Physiologic, and Proteomic Consequences of Repeated Microneedle-Mediated Perforations of the Round Window Membrane. Hear. Res. 432: 108739.

Leong S, Feng SJ, Aksit A, Olson ES, Kysar JW, Lalwani AK (2023). Microneedles Facilitate Small-Volume Intracochlear Delivery Without Anatomic or Physiologic Injury. Otol. Neurotol. 44(5): 513-519.

Feng SJ, **Leong S**, Aksit A, Hébert D, Olson ES, Kysar JW, Lalwani AK (2024). Physiologic Effects of Microneedle-Mediated Intracochlear Dexamethasone Injection in the Guinea Pig. Laryngoscope. 134(1): 388-392.

RESEARCH SUMMARY:

The laboratory has developed 3D-printed microneedles via two-photon polymerization (2PP) lithography that can perforate the guinea pig round window membrane (RWM) in vivo without causing hearing loss. This study aimed to assess the feasibility of repeated diagnostic aspiration and direct glucocorticoid injection into the inner ear via hollow microneedle technology.

OUTCOMES:

Repeated microneedle perforation of the RWM is feasible, allows for complete healing of the RWM, and minimally changes the proteomic expression profile. Thus, microneedle-mediated repeated aspirations in a single animal can be used to monitor the response to inner ear treatments over time.

Microneedle-mediated intracochlear delivery of small volumes relative to the volume of the scala tympani is feasible, safe, and does not cause HL in guinea pigs; however, injection of large volumes induces high-frequency HL. Injection of small volumes of a fluorescent agent across the RWM resulted in significant distribution within the basal turn, less distribution in the middle turn, and almost none in the apical turn. Microneedle-mediated intracochlear injection opens the pathway for precision inner ear medicine. Direct intracochlear delivery of dexamethasone via microneedles results in temporary shifts in hearing thresholds that resolve by 5 hours, thus supporting microneedle technology for the treatment of inner ear disorders.

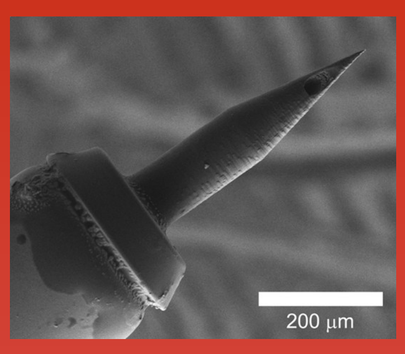

Figure 1. Scanning electron microscope image of a single-lumen hollow microneedle. A 200 µm scale bar is displayed for reference.

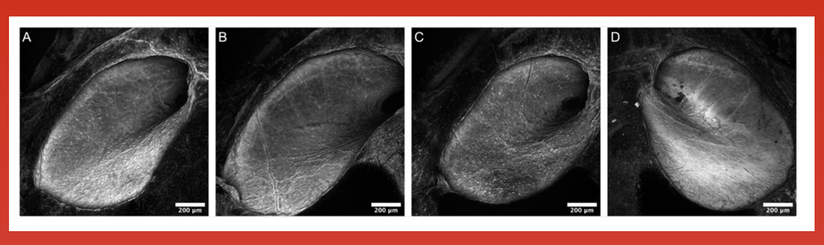

Figure 2. Confocal images of RWMs 48 hours after microneedle-mediated injection of 1.0 µL (A), 2.5 µL (B), and 5.0 µL (C) of artificial perilymph, 100x magnification. A confocal image of an unperforated RWM is displayed for comparison (D). A 200 µm scale bar is displayed for reference. No residual perforation, inflammation, or scarring is noted in any of the images.

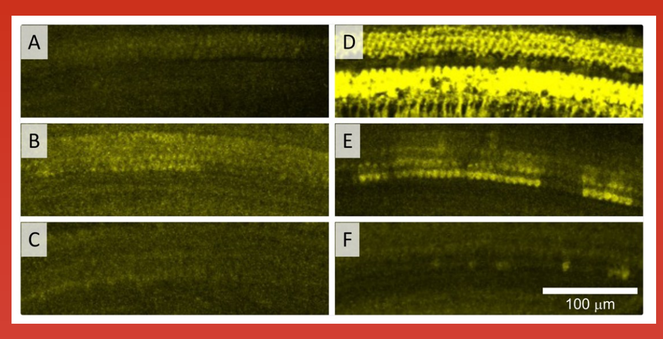

Figure 3. Confocal images of the basal (A), middle (B), and apical (C) turns of a non-injected cochlea vs. the basal (D), middle (E), and apical (F) turns of a cochlea injected with 1.0 µL of 70 µM FM 1–43 FX, 100x magnification. Samples were fixed 1 hour following FM 1–43 FX injection. A 100 µm scale bar is displayed for reference. Following FM 1–43 FX injection, fluorescence of outer hair cells, inner hair cells, and neurons is observed in the basal turn; fluorescence of outer and inner hair cells is observed in the middle turn; little fluorescence is observed in the apical turn. No significant fluorescence above background is noted in the comparison cochlea.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

The laboratory has investigated microneedle-mediated intracochlear injection of gene therapy and gadodiamide contrast. In summary: Small volumes of siRNA and Lipofectamine can be effectively delivered to cochlear structures using microneedles, paving the way for atraumatic cochlear gene therapy.

Intracochlear gadodiamide enables controllable and efficient contrast delivery with significantly lower contrast dosage, making it a viable alternative for contrast-enhanced cochlear MRI.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

Microneedle-mediated intracochlear delivery of therapeutics is feasible, safe, and does not cause hearing loss in guinea pigs. This technique may facilitate inner ear gene therapy among other otologic treatments.