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Novel 3D-Printed Microneedles Enable Controlled Perforations in Mouse Round Window Membranes: Insights for Human Applications

Michelle Yu, M.D., M.S. [1], Daniella R. Hammer, M.S.[2], Liana Sargsyan, M.D. [1], Eugenie Breil, M.D.[1], François Voruz, M.D.[1], Anil Lalwani, M.D.[1], Jeffrey Kysar, Ph.D.[2]

[1]Department of Otolaryngology—Head & Neck Surgery, Columbia University Irving Medical Center and NewYork-Presbyterian, New York, NY
[2]Department of Mechanical Engineering, Columbia University

Scan me for an audio walkthrough!
Rationale & Background: 0:15
Objective 1: 1:27
Objective 2 (left): 2:34
Objective 2 (right): 4:05
Conclusion and Discussion: 4:35

RATIONALE & BACKGROUND

Inner ear therapeutics is a growing field of study with promising pharmacologic and technologic advances, particularly gene therapy. Delivery to the inner ear, however, is impeded by cochlea's bony housing. **3D-printed microneedle** technology has enabled access to the cochlea via the **round window membrane (RWM)** with precision and versatility, providing an avenue for diagnosis and treatment of inner ear diseases (**Fig 1**)[1]

Objectives of this study:
(1) To engineer a microneedle design suitable for use in mice, a model organism for gene therapy
(2) To characterize the mechanical properties of the RWM and microneedle

The overarching goal of this study is to demonstrate **adaptability of the microneedle** technology for varying **anatomic constraints** and **mechanical demands**, which will be applied in the future to **human inner ear access**.

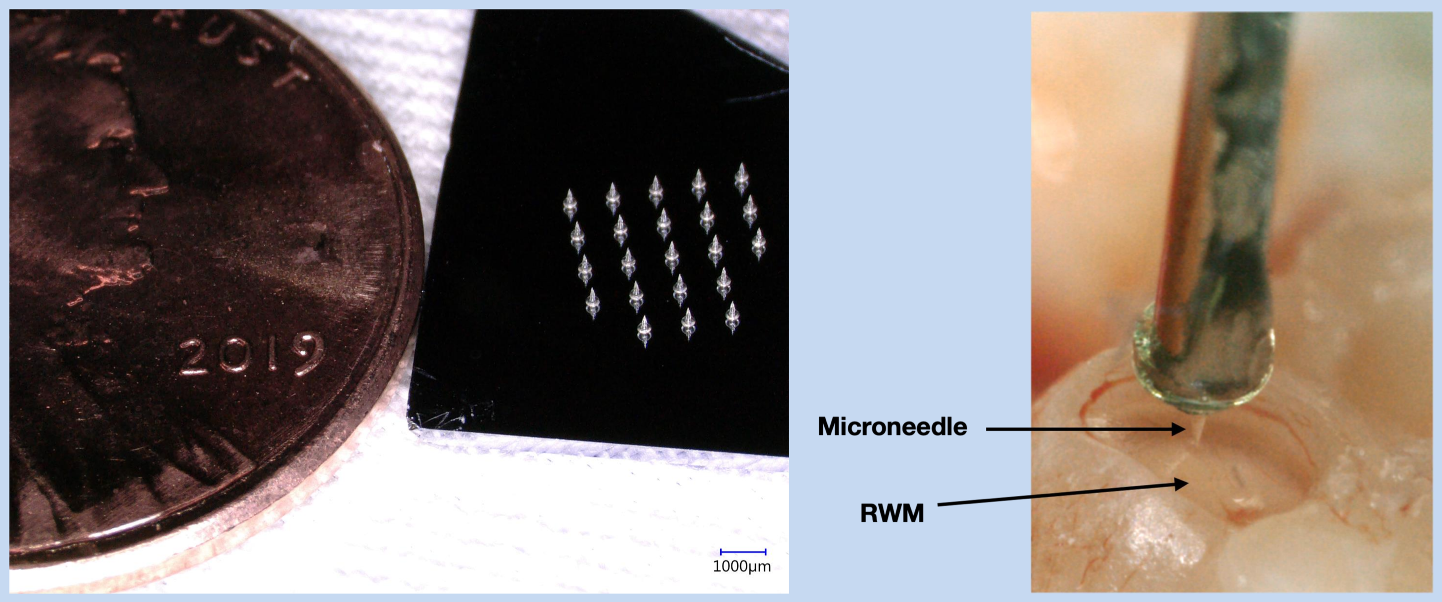


Figure 1. On the **left** is a photo of 3D-printed microneedle tips designed for guinea pigs with a penny for scale. On the **right** is an example of an in vitro perforation of a guinea pig RWM (approximately 1000 μm in its greatest dimension) with one of these microneedles.[2]

Objective 1: MICRONEEDLE DESIGN

Methods: Through the engineering design process, mouse cadaveric studies were performed serially with multiple prototype rounds of various microneedles. Designs were evaluated by two surgeons experienced in rodent ear surgery.

Results:
- Anatomic characterization: mouse RWM is **smaller** and is set **deeper** within a bony niche compared to guinea pig RWM (Fig 2)
- Microneedle adaptations: designs required a **smaller diameter** but **longer shaft** to accommodate the anatomy (Table 1, Fig 3)

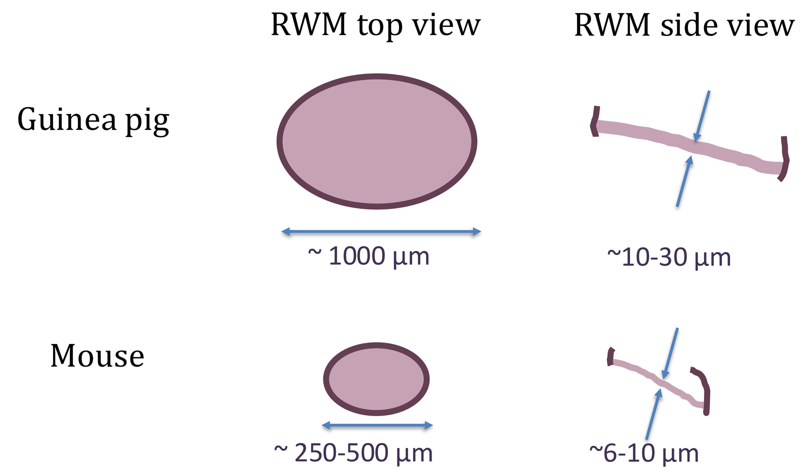


Figure 2. Comparison between guinea pig and mouse RWM anatomy

Microneedle design changes:

Shaft diameter	↓
Shaft length	↑
Sharpness	Unchanged
Mounting needle size	↓

Table 1. Constraints placed on microneedle design for new anatomy

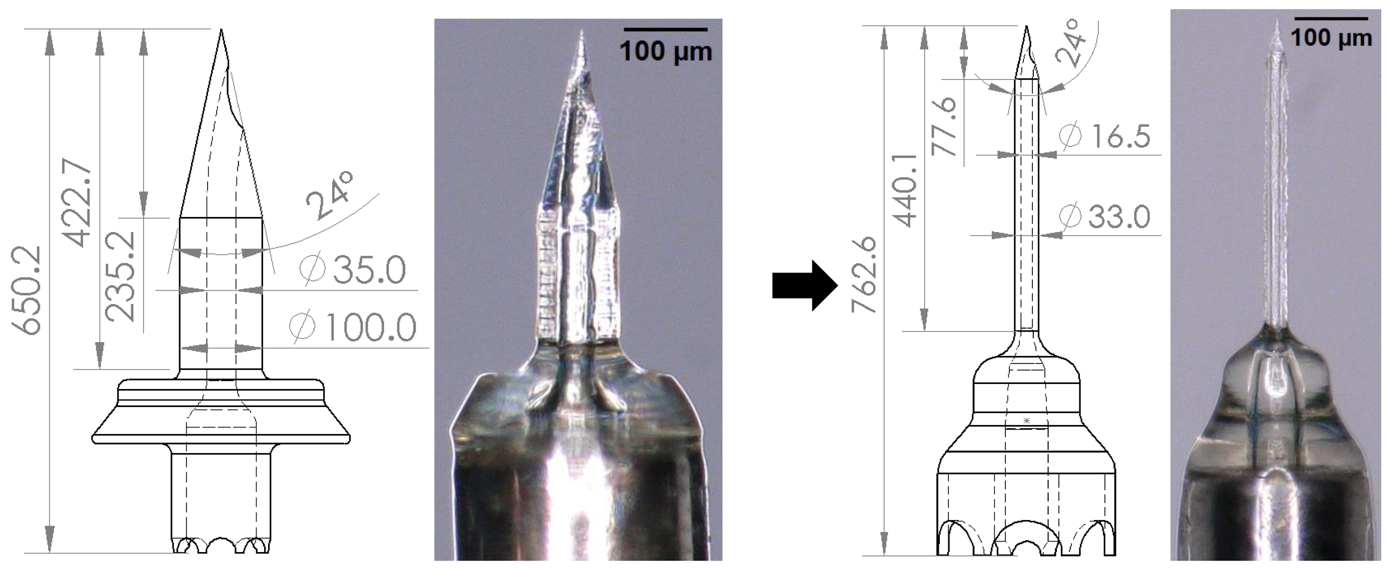


Figure 3. Microneedle designs for **guinea pig (left)** versus **mouse (right)** anatomy, determined by cadaveric studies and evaluated by two surgeons experienced in rodent ear surgery.

Objective 2: EXAMINING MECHANICAL PROPERTIES

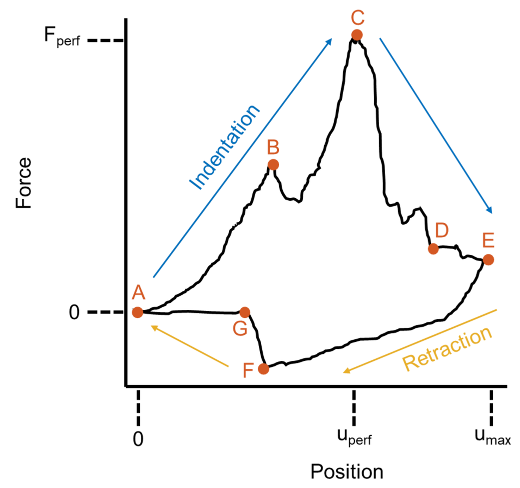
Characterizing mechanical properties of RWM perforation

Methods: Forces produced by mouse RWM perforation *in vitro* were measured with a micro-indenter with a force sensor.

Results: Perforations produced forces of 1.4±0.3 mN and occurred at a depth of 159±27 μm (Fig 4, 5, 6; Table 2).

Sample #	Force (mN)	Depth (μm)
1	1.6	121
2	1.1	183
3	1.6	143
4	1.2	165
5	1.7	183
Mean (SD)	1.4 (0.3)	159 (27)

Table 2. Measured perforation force (mN) and perforation depth (μm).



Scan me to see a video of perforation and how the force curve correlates!

Figure 4. Example force curve during perforation A: needle pushing on membrane, B: needle enters membrane, C: entire bevel completes insertion, D: friction of membrane on needle shaft, E: begin withdrawing. F: needle pulls on membrane on its way out, G: completes contact with membrane.

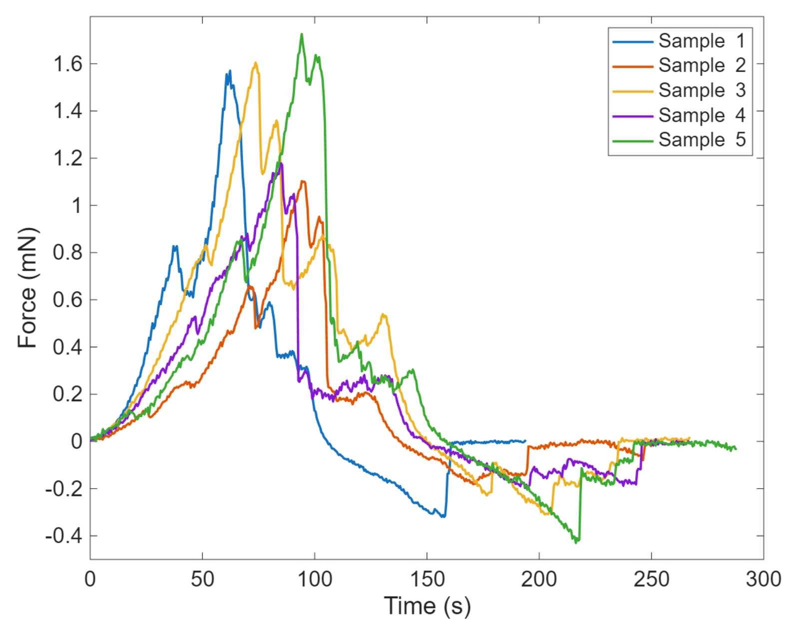


Figure 5. Force (mN) applied by the microneedle to the RWM over time (s).

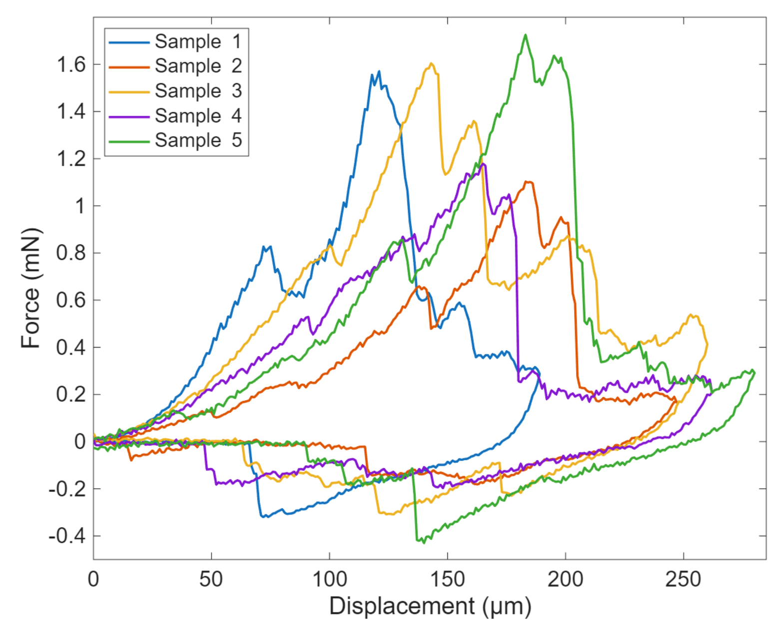


Figure 6. Force (mN) applied by the microneedle on the mouse RWM plotted over displacement (μm) of the needle. The curves plotted here all possess stereotypical transition points labeled in Figure 4.

Examining perforation shape and microneedle durability

Methods: RWMs were imaged with rhodamine B staining and confocal microscopy after perforation. Microneedles were imaged with scanning electron microscope (SEM).

Results: RWM perforations were **lens-shaped** and a predictable size, approximately the **diameter of the microneedles (33±1 μm x 11±0.6μm; n=3)** (Fig 6A). Microneedles had **minimal blunting** or bending, which demonstrates their durability (Fig 6B).

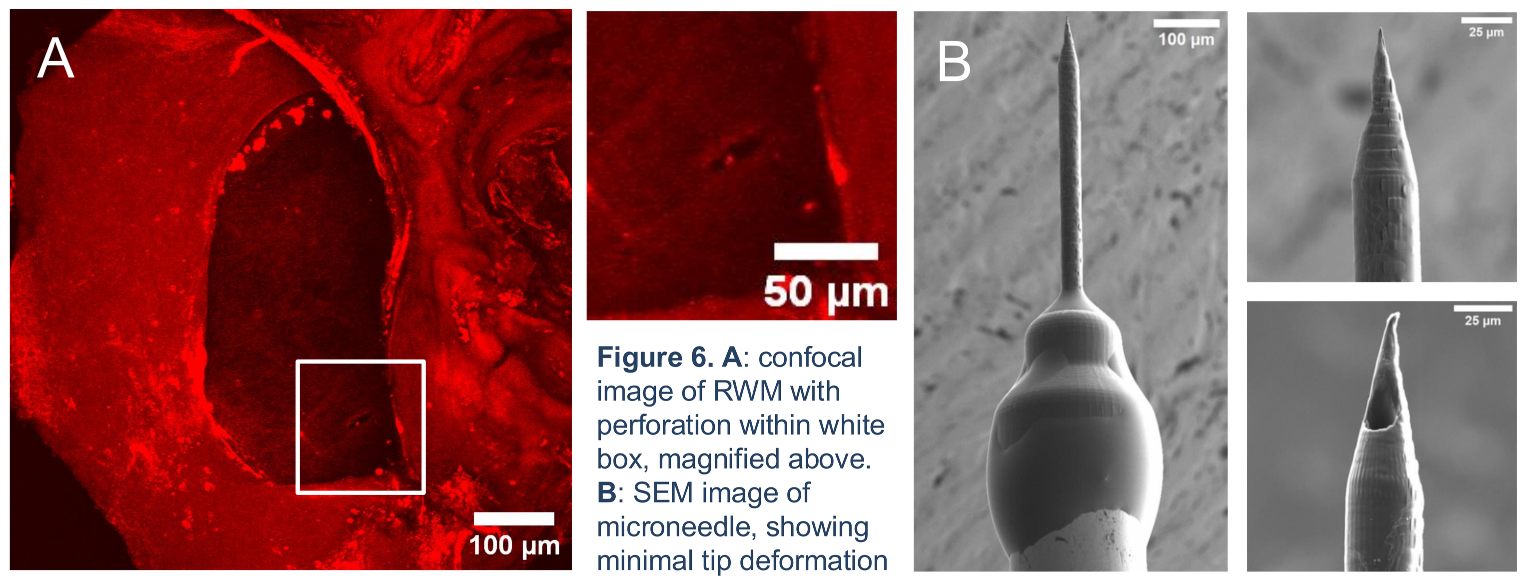


Figure 6. A: confocal image of RWM with perforation within white box, magnified above. **B**: SEM image of microneedle, showing minimal tip deformation

CONCLUSION & DISCUSSION

We successfully engineered a novel microneedle design for constraints presented by mouse RWM, which contributes to our confidence in designing microneedles specific to human RWM anatomy (varying size and niche depth). In addition, perforation forces and shapes obtained were reproducible and similar to data obtained in prior work on guinea pigs[1-3]. Characterization of RWM properties contributes to the body of knowledge that will aid in inner delivery technology for humans.

Contact

Michelle Yu, MD MS
Fellow, Medical University of South Carolina
Email: yumi@musc.edu
Phone: (949) 878-7802

References

1. Szeto B, Aksit A, Valentini C, Yu M, Werth EG, Goeta S, Tang C, Brown LM, Olson ES, Kysar JW, Lalwar Novel 3D-printed hollow microneedles facilitate safe, reliable, and informative sampling of perilymph from guinea pigs. Hear Res. 2021 Feb;400:108141.
2. Aksit A, Arteaga DN, Arriaga M, Wang X, Watanabe H, Kasza KE, Lalwani AK, Kysar JW. In-vitro perforat the round window membrane via direct 3-D printed microneedles. Biomed Microdevices. 2018 Jun 8;20(2
3. Yu M, Arteaga DN, Aksit A, Chiang H, Olson ES, Kysar JW, Lalwani AK. Anatomical and Functional Consequences of Microneedle Perforation of Round Window Membrane. Otol Neurotol. 2020 Feb;41(2):e e287.

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