Title: Cage implants for in vivo mechanistic analysis of levonorgestrel release from PLGA microneedles

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Abstract Body

Introduction: Long-acting contraceptive microneedle (MN) patches present greater access to enduring contraception (1). A systematic methodology to evaluate the *in vivo* performance of MNs and its correlation with *in vitro* characterization may provide valuable feedback for formulation optimization (2).

Methods: MNs were prepared by casting a diglyme/water (95%/5%, w/w) solution of poly(lactic-co-glycolic acid) (PLGA)/LNG (60%/40%, w/w) onto a polydimethylsiloxane (PDMS) mold, followed by casting a second solution of PVP-K30/sucrose (18%/18% in water, w/w) upon drying. A silicone cage sealed by stainless steel mesh (38-μm opening), inside which MNs were placed, was designed to facilitate MN retrieval *in vivo*. *In vitro* release studies were conducted by placing silicone cages encapsulating MN patches in 25% (v/v) (ethanol)/(PBS(pH 7.4)) at 37 °C. *In vivo* assays were performed by implanting silicone cages encapsulating MNs subcutaneously in the flanks of rats. MNs at different time points were retrieved from both *in vitro* and *in vivo* and studied for diffusivity modeling, morphology, and polymer degradation by BODIPY uptake/confocal microscopy, electron/confocal microscopy, and GPC, respectively.

Results: A 20 × 20 array of MNs encapsulating LNG (1.53 ± 0.08 mg) was manufactured (Fig. 1A) and enabled long-acting release of LNG for up to 28 days *in vitro* (Fig. 1B). A silicone cage was introduced to directly retrieve MNs *in vivo* after skin retrieval proved difficult. Cage containment and reduced shaking speed slightly decreased *in vitro* release (Fig. 1B). Confocal imaging of MNs retrieved *in vitro* (Fig. 1D) displayed a clear diffusive gradient for analysis by diffusion models. SEM and confocal images suggested that matrix degradation started at the lower part of the MN, which abutted the aqueous backing during preparation. (Figs. 1E, F).

Conclusion: We confirmed the feasibility of retrieving MNs from *in vitro* and *in vivo* assays by modifying a silicone cage system that was previously developed by our group for characterizing PLGA microspheres (2). Insights from investigating the release mechanism of LNG from PLGA MNs may facilitate optimizing LNG/MNs.

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References: (1) Li, W. et al. Science Advances 2019: 5, eaaw8145. (2) Doty, A. C. et al. Biomaterials 2016: 109, 88–96.

Presenter Biography: Tao Zheng is a graduate student in the Department of Pharmaceutical Sciences, University of Michigan. He focuses on PLGA controlled release systems.

Learning Objective: Understand *in vitro-in vivo* characterization of levonorgestrel-PLGA microneedles.

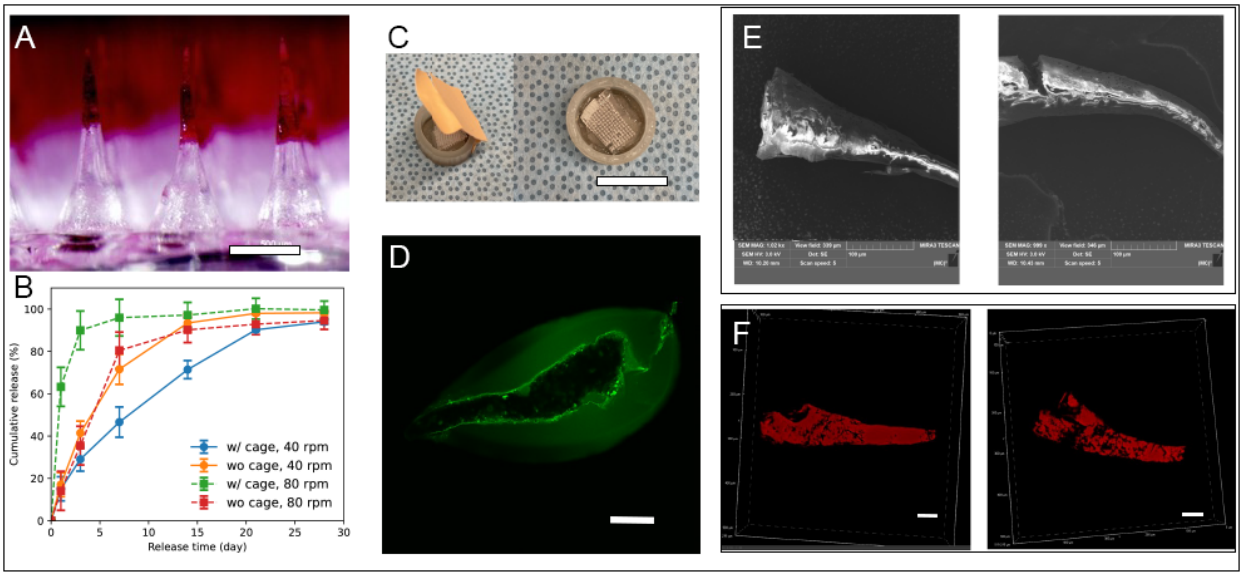

Figure 1 (A) Bright-field microscopy of MNs. The red tips, containing Rhodamine B for better visualization, represented the PLGA matrix encapsulating LNG. Scale bar, 500 µm. (B) *In vitro* cumulative release of LNG from PLGA matrix MNs, mean ± SD (n = 3). (C) MN patch placed in the silicone cage system for retrieval from *in vitro* and *in vivo* assays. Scale bar, 1.5 cm. (D) Confocal image of MN on day 1 of *in vitro* release after incubation with BODIPY. Scale bar, 150 µm. (E) SEM and (F) confocal images of MNs retrieved on day 7 (left) and day 21 (right) from cages implanted *in vivo*. Scale bars, 100 µm.