# Supplementary Materials

## Efficient delivery of nucleic acid molecules into skin by combined use of microneedle roller and flexible interdigitated electroporation array

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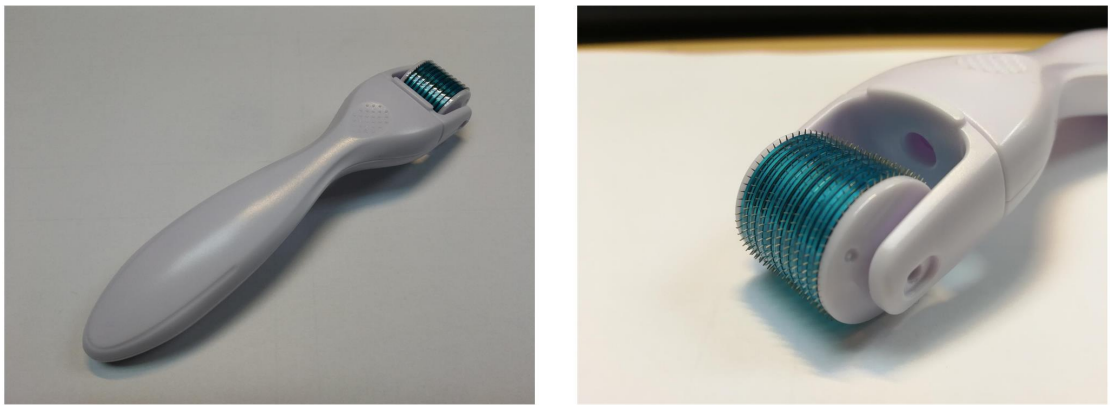

**Figure S1. The picture of the commercial microneedle roller** (DRS Dermaroller System 600, Derma Roller System, Ltd., Genmany). There are 10 rows on the head, with 60 needles per row. The space between rows is 2 mm. The derma roller comes in several different needle lengths depending on the treatment. In this paper, 0.5-mm-long, 1.0-mm-long and 1.5-mm-long models are used.

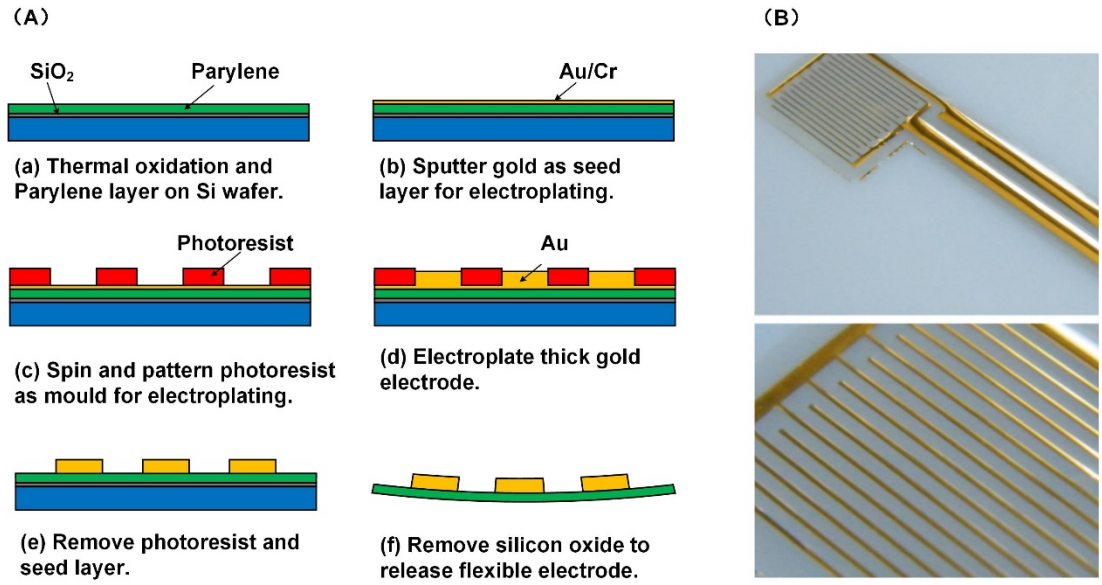


**Figure S2. The details of the fabrication of the FIEA.** (A) Process of the fabrication of the Parylene-based flexible patch with 10 μm thick electroplated golden electrode. (B) The details of the flexible electrode. To achieve uniform distributed electric field, the microelectrode is designed as rectangular interdigital profile. The width of the microelectrode is 200 μm, while the spacing is 500 μm. The effective area is 10 by 10 square millimeter.

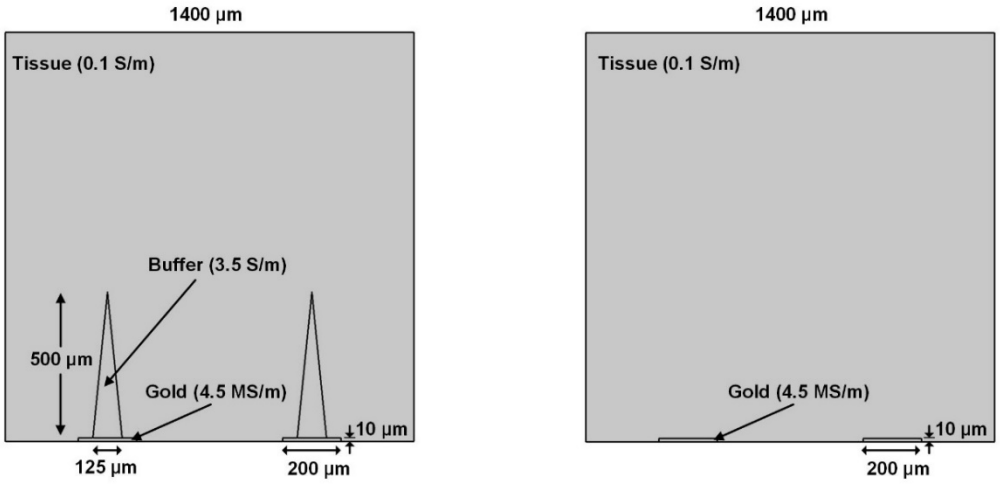


**Figure S3. The model of the electric field analysis.**

The simplified model is shown in Figure S3. A square two-dimensional domain of the tissue had a 10 μm thick gold electrode applied on the bottom as the right half of Figure S1 shows. To simplify the model, we treated that the electric conductivity of the tissue was homogeneous everywhere, and the high-resistance corneum was ignored. The conductivity of the gold and tissue was set as 4.5 MS/m and 0.1 S/m, respectively.[1] If using the proposed method in this paper, the effect of the microneedle roller could cause a series microchannel in the skin as shown in left of Figure S1. The geometric shape of the microchannel was cone with 125 μm diameter and 500 μm height, and they were connecting with the gold electrode.[2]

The model utilized the Electric Currents module to fully capture the electric field contribution to solve the following equations:

$$\nabla \cdot \boldsymbol{J} = Q_j$$

$$\boldsymbol{J} = \sigma \boldsymbol{E} + \boldsymbol{J_e}$$

$$\boldsymbol{E} = -\nabla V$$

Here $\boldsymbol{J}$ denotes the current vector (A) and $\boldsymbol{E}$ represents the electric field vector (V/m). $Q_j$ is electric charge (C), $V$ is potential (V).

The boundary condition: The left electrode was set as 50 V, and the right electrode was set as Ground. The other boundaries were set as electric insulation except two vertical boundaries, and they were defined as periodic boundary to simulate the actual situation better.

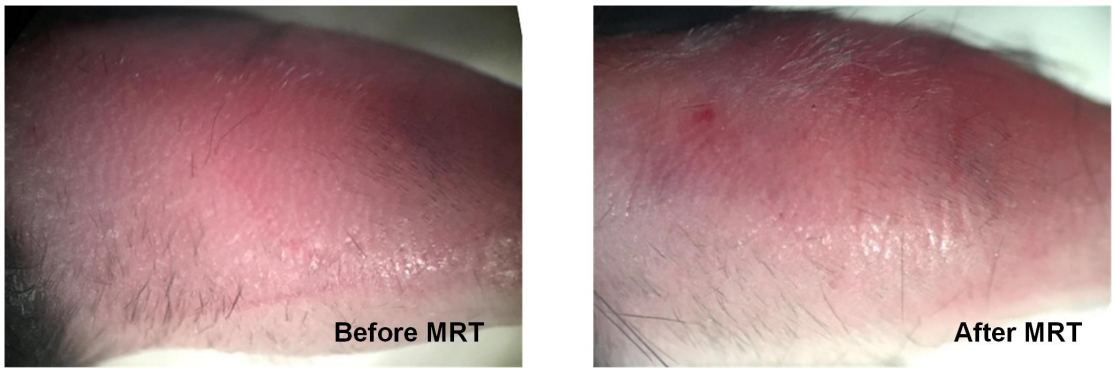


**Figure S4. The skin surface before and after microneedle roller treatment (MRT).**

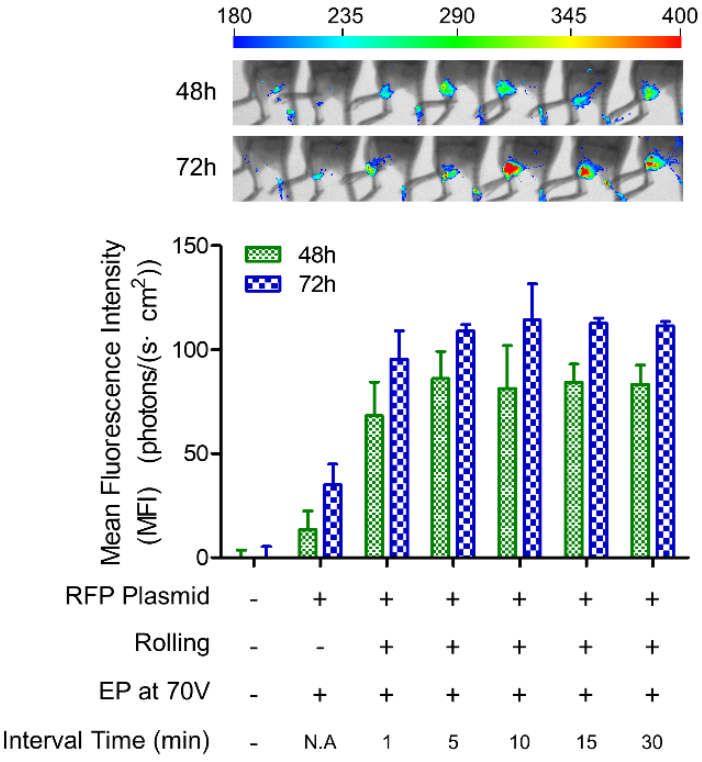


**Figure S5. The relationship of RFP plasmid delivery efficacy and the interval time between microneedle and FIFA treatment.**

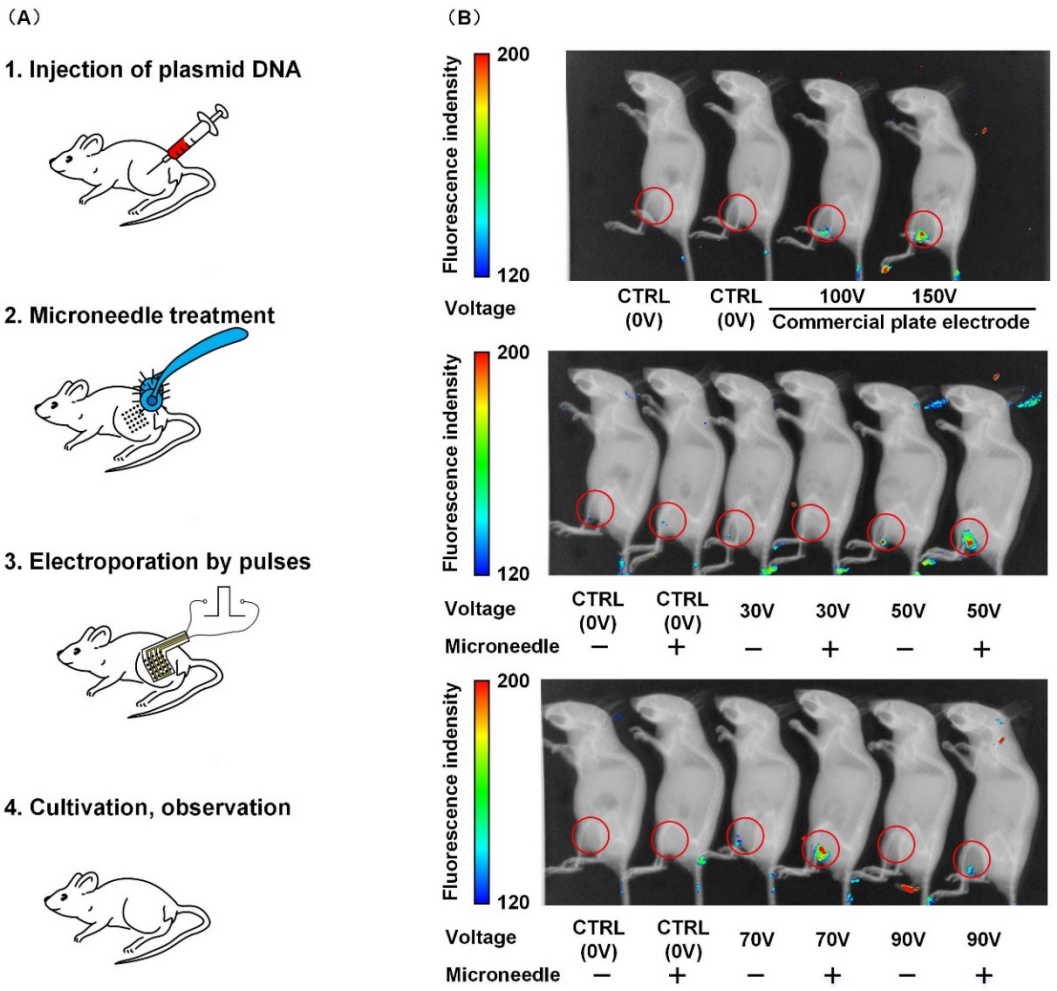


**Figure S6. Experiment to verify sufficient electric field could be generated under the skin by penetrating high-resistance stratum corneum.** (A) The process of the in vivo muscle electroporation utilizing microneedle roller and flexible electroporation electrode. (B) Whole-body fluorescence images of the control mice and ten mice whose thigh received different treatments for RFP plasmid transfection *in vivo*. Red circles represent the electroporated area (5 pulses, 10ms duration, 1s interval)

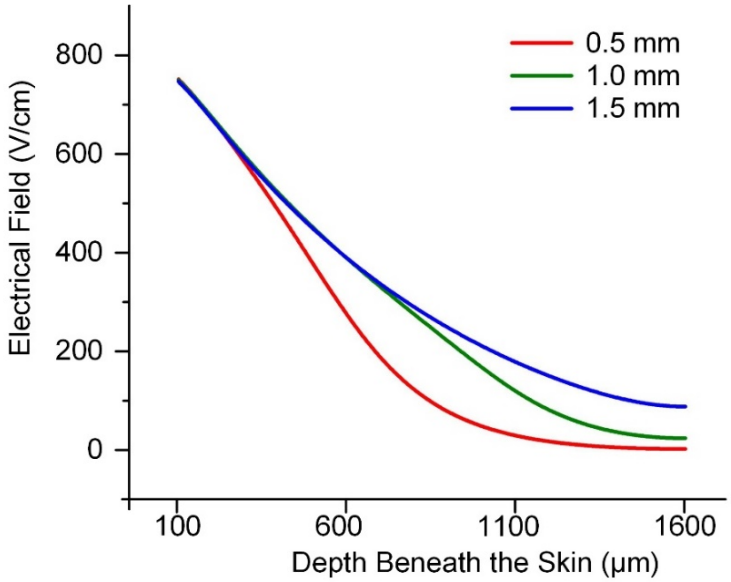


**Figure S7. The distribution of electric field beneath the skin (100 μm - 1600 μm) under treatment with the microneedle rollers of different length.** The model is analogously set up as previously described, but different in the geometric height of the microchannel. Red, olive and blue curves represent the electric field strengths on the centerlines in the middle of adjacent microchannel with 0.5 mm, 1.0 mm and 1.5 mm height, respectively.

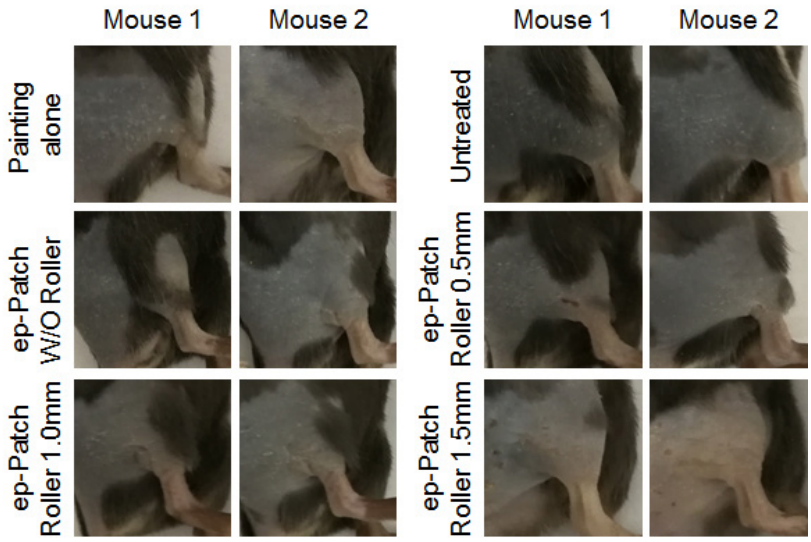


**Figure S8. Mouse images acquired at day 5 after electroporation of Cy5-labelled siRNA.** It was shown that the skin was healthy, the color of pre-depilated skin was gray or black, suggesting hair growth cycle has switched from telogen, to catagen or anagen. Accordingly, some hair has regrown out from the skin.

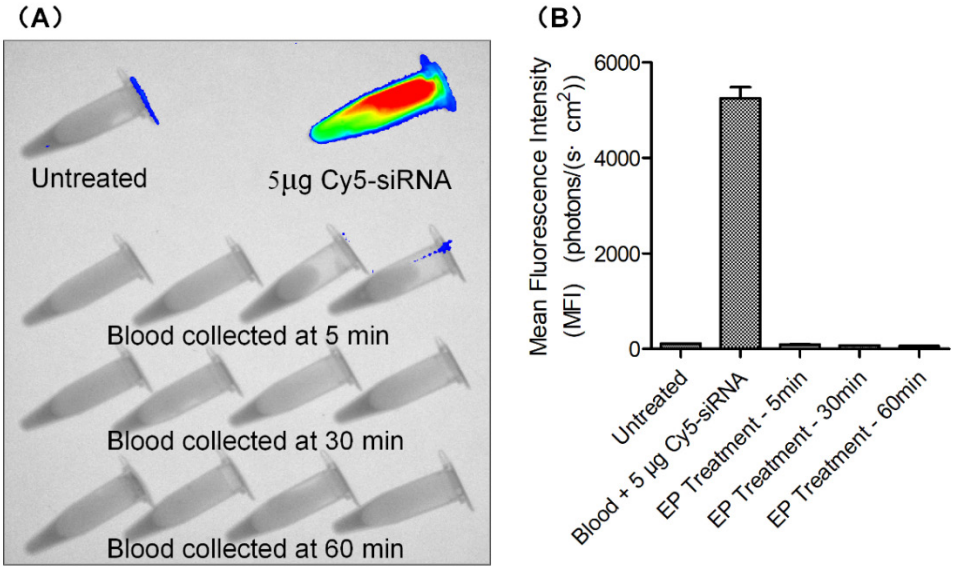


**Figure S9. The diffusion of the drug into the blood vessels assay.** (A) Fluorescence image of the blood collected from the electroporated mice after 5 minutes, 30 minutes and 60 minutes. (B) Quantitative analysis of the mean fluorescence intensity of different groups.

**References:**

1. Zhang X, Hu N, Chen X, Fan T, Wang Z, Zheng X, et al. Controllable cell electroporation using microcavity electrodes. Sensor Actuat B-Chem. 2017; 240: 434-42.

2. Badran MM, Kuntsche J, Fahr A. Skin penetration enhancement by a microneedle device (Dermaroller®) in vitro: Dependency on needle size and applied formulation. Eur J Pharm Sci. 2009; 36: 511-23.