Determining Vaccination Status in the Developing World using Microneedle-Delivered Fluorescent Microparticles

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Statement of Purpose: Vaccines have been shown to be exceptionally safe and effective, yet each year 1.5 million people die due to vaccine-preventable infectious disease [1]. Challenges in terrain and availability of adequate tools in resource constrained settings often limit the effective distribution of vaccines, which can lead to reduced vaccine coverage rates [2]. One key barrier to improving vaccine coverage rates in low-resource settings is the lack of accurate immunization records. Because centralized databases of medical records do not exist in these areas, healthcare workers often rely on verbal communication with parents to determine vaccination status, which is often inaccurate leading to missed opportunities to vaccinate and wasted resources when additional unnecessary doses of vaccine are administered. To address this issue, we have developed an on-patient medical record using long-lived fluorescent microparticles, microneedles, and an adapted smartphone to determine vaccination status in the developing world. Our platform is designed to deliver both the vaccine and fluorescent particles in one form factor to streamline the administration process and be detectable for up to five years using a minimally-adapted smartphone.

Methods: A platform consisting of copper-based quantum dots (QDs) with emission in the near-infrared (NIR) were synthesized, characterized, and encapsulated at 60% loading (w/w) into poly(methyl methacrylate) microparticles. In parallel, microneedle molds were created using two-photon polymerization and soft lithography. QD-containing fluorescent microparticles were then loaded into the polydimethylsiloxane molds, back-filled with an aqueous solution of sucrose and poly(vinyl alcohol), and dried. After removal from the molds, the resulting microparticle-loaded microneedles were administered to Wistar rats, resulting in dissolution of the microneedle tip and microparticle delivery into the dermis. Rats were longitudinally imaged using an LED and NIR-adapted smartphone to quantify the retention of fluorescent particles residing in the skin.

Results: Over 100 QD formulations were tested and down-selected based on the wavelength of their emission peak, quantum yield, and photostability. Our top QD candidate, S10C5H, exhibited peak emission at 886 nm, a quantum yield of 30.2%, and a retention of 13 ± 3% of its initial intensity after 5 years of simulated sun exposure through skin. Various microneedle geometries were tested using computational modeling and empirical mechanical testing. A final microneedle geometry consisting of a 750 µm cone atop a 750 µm cylinder was chosen based on xix-factor optimization for resistance to mechanical failure and deliverable volume. Fluorescent microparticle delivery in rats resulted in resulted in a signal-to-noise ratio in excess of 500:1 immediately after administration and remained high throughout the experiment. Three unique signals composed of eight markings each were able to be automatically detected using a machine learning algorithm for the duration of the six-month experiment. Co-administration of the Salk inactivated polio vaccine type 2 in microneedles with or without encapsulated QDs elicited total and neutralizing titers that were statistically similar to each other and to a subcutaneous injection of vaccine, demonstrating that the particles do not inhibit vaccine efficacy. In addition, gross examination and histological evaluation of tissue indicated good biocompatibility with little, if any, inflammation and fibrous encapsulation persisting after the resolution of mechanically induced inflammation associated with microneedle administration.

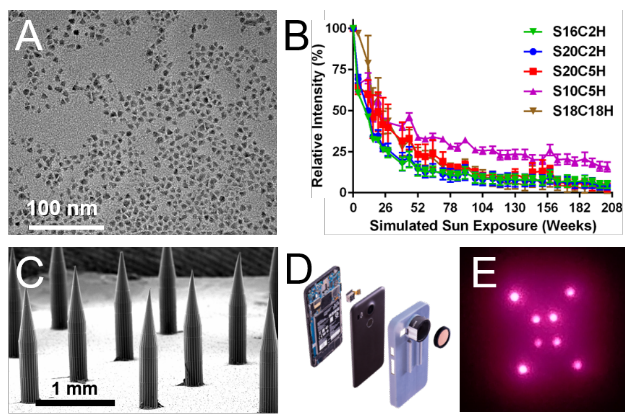

Figure 1. Near-infrared quantum dot synthesis, evaluation, and application. (A) Transmission electron microscopy image of copper-based quantum dots. (B) photostability of quantum dots under simulated sun exposure through skin. (C) Scanning electron microscopy image of microneedles. (D) Adapted smartphone with internal near-infrared filter removed and long-pass filters added. (E) “X” pattern detected using the adapted smartphone following microneedle administration to rats.

Conclusions: We have developed a biocompatible, photo-stable QD formulation that can be delivered into the dermis using a microneedle patch to store information about an individual’s vaccination status on the patient themselves. This would be particularly useful in areas of the developing world that do not have reliable medical records in order to dramatically reduce missed opportunities to vaccinate and thereby improve vaccination coverage. In addition to avoiding missed opportunities to vaccinate at the level of the individual, this platform can also provide population-wide data to enable vaccination campaigns to better allocate and distribute their limited resources. **References:** [1] Black RE. Lancet. 2010;375:1969-87. [2] McHugh. J Control Release. 2015;219:596-609.