A Photo-sensitive Polymer Base-layer for Quick-Release of Multi-layer Films from Polymer Microneedle Arrays for Transcutaneous Vaccine Delivery

Peter C. DeMuth[1], Younjin Min[1], Paula T. Hammond,[1,2] Darrell J. Irvine[1,2,3,4]

[1]Massachusetts Institute of Technology, Cambridge, MA, 02319; [2]Koch Institute for Integrative Cancer Research at MIT, Cambridge, MA, 02139; [3]Howard Hughes Medical Institute, Chevy Chase, MD, 20815, USA; [4]Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA 02139

Statement of Purpose: We have recently reported the application of layer-by-layer (LbL) deposition for the self-assembly of hydrolytically degradable multi-layer thin films encapsulating plasmid DNA (pDNA) on the surface of biocompatible microneedle arrays *(DeMuth P C, Adv Mat. in press)*. Upon application to the skin of mice these films deliver pDNA locally within the skin over a period of 24 hours from the microneedle surface. Here we present a new approach for the deposition of multi-layer films designed to provide rapid delamination upon application *in vivo*, thus allowing for bulk transfer of films into the skin for subsequent degradation and delivery following microneedle removal. Specifically, we have employed a light sensitive photoresist as a base-layer for film deposition which undergoes a chemical transition from an insoluble to water-soluble state mediating the rapid delamination of overlying films in aqueous conditions. This approach represents a general strategy for the rapid delamination-based delivery of intact films from surfaces that is bio-friendly and generally applicable.

Methods: Microneedle arrays have been fabricated as previously reported *(DeMuth P C, Adv Mat. in press)*. Carboxylated and biotinylated poly(o-nitrobenzyl-methacrylate-methylmethacrylate-poly(ethylene glycol) methacrylate) (PNMP) was synthesized as previously reported *(Doh J, JACS; 126:9170-9171)*. PNMP was deposited onto silicon wafers or poly(L-lactide) (PLA) microneedle arrays by spin coating or spray deposition. Biotin-conjugated PNMP was labeled using fluorescent streptavidin (SAv). Multi-layer films were then deposited on PNMP by LbL processing using branched poly(ethyleneimine) (BPEI)-polyacrylic acid (PAA), protamine sulfate (PS)-poly(4-styrene sulfonate) (SPS), or pDNA-poly-β-amino ester (PBAE). Films were then UV irradiated and tested for delamination from silicon and PLA microneedles using optical/confocal laser scanning microscopy (CLSM).

Results: We have observed uniform deposition of PNMP photoresist polymer onto silicon and PLA microneedles through spin and spray deposition respectively. Specifically, surface profilometry indicated regular thickness on silicon, and SEM as well as CLSM of fluorescent SAv-labeled biotin-PNMP showed conformal coating on PLA microneedles. Subsequent LbL deposition of (BPEI/PAA), (PS/SPS), or (PBAE/pDNA) onto PNMP base-layers exhibits regular film growth as measured using surface profilometry (***Fig. 1)*** and CLSM imaging of fluorescently labeled pDNA on PLA microneedles (***Fig 2)***. Following film deposition by LbL the UV irradiation-mediated chemical transition of PNMP

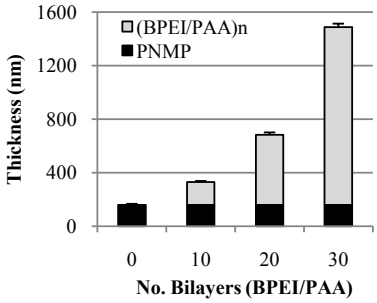

Figure 1: *Growth of BPEI-PAA multi-layer films on PNMP base-layers.*

was monitored through FTIR measurement of a characteristic nitro-benzyl peak (~1530 cm-1) that is cleaved from PNMP to give the hydrophilic form of the polymer. These results indicate that UV-processing of the PNMP base-layer can be completed even after LbL film deposition. Further results have confirmed the ability of PNMP base-layers to mediate rapid film delamination following UV irradiation and exposure to physiological conditions. Specifically, (BPEI/PAA) and (PBAE/pDNA) films were observed to delaminate after 2 minutes incubation in PBS, following 30 minutes UV exposure.

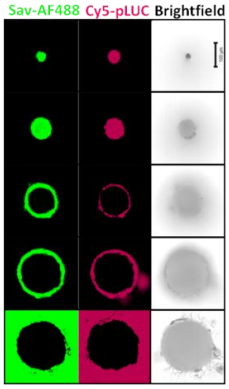

Figure 2: *Biotin conjugated PNMP is spray deposited onto PLA microneedles. The figure shows CLSM z-stacks taken along the length of one individual microneedle of a skin patch, showing SAv fluorescent signal from biotinylated PNMP and Cy5 labeled pDNA assembled by LbL on the PNMP base-layer.*

Conclusions: The application of a UV-processible photo-resist as a base-layer supporting subsequent LbL deposition for quick release of intact multi-layer films has been described. These base-layers have been deposited on silicon as well as PLA microneedles and have been observed to support regular LbL film growth, to complete a UV-mediated cleavage and resulting chemical transition from hydrophobic to hydrophilic, and ultimately to mediate rapid delamination of overlying films upon rehydration. To our knowledge, this is the first reported demonstration of a light-sensitive base-layer to create rapidly detachable multi-layer films. Further studies will explore the application of this materials system for rapid bulk transfer of multi-layer films from microneedles upon application to the skin for vaccine delivery.