

## **"Controlled Release Microneedle Technologies for the Enhanced Immunogenicity of Subunit Vaccines"**

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The poor efficacy of subunit protein vaccines, which typically consist of a protein antigen and a molecular adjuvant, has recently been improved by completing multiple injections of the vaccine with an exponential dosing profile over time. The hypothesis is that as viruses replicate in a host organism, they shed exponentially increasing quantities of pathogen associated molecular patterns (PAMPs) and viral protein, and replicating this pattern during vaccination allows scientists to better mimic the immune response elicited by an actual infection. Instead of completing multiple injections, a promising alternative is to complete a one-time application of a microneedle device to the skin that controllably releases the vaccine to mimic this exponential pattern to manipulate the immune system into providing strong humoral and cellular mediated protection. A number of different novel microneedle constructs have been created in this thesis towards this end.

Membrane microneedles consist of tips with a polymeric core that contains vaccine that's encapsulated within a crosslinked layer-by-layer film. The three component film acts as a tunable diffusional barrier to vaccine release. Poly( $\gamma$ -propargyl l-glutamate) (PPLG) polymer grafted with maleimides was used to make microneedles that function based on the same concept except that the tip's surfaces are chemically crosslinked with poly(ethylene glycol) dithiol to enable controlled release. Importantly, degradable ester bonds are incorporated into the network to allow for tunability. Finally, poly(vinyl alcohol) microneedles were vapor-phase crosslinked to form reversible acetal bonds, and these constructs were also characterized and shown to allow for controlled release. Several other constructs were also generated. The work presented herein involves the microneedle design, fabrication, and characterization of these constructs with various experimental set-ups and techniques.