Reducing Inflammation to Implanted Neural Electrodes

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Statement of Purpose:

Implanted neural electrodes have the potential to restore functionality to patients with spinal cord injuries and sensory loss while playing a key role in brain-machine interfaces (BMIs)[1]. A significant hurdle to developing BMIs is the short lifespan of implanted electrodes due to tissue response of the brain around the implant. Several major factors are involved in this response including scar formation, inflammation, and neuronal cell death around the electrode site after implantation.[2,3] Scar formation from astrocyte and microglial recruitment creates a physical barrier around electrodes which prevents electrical signals from reaching the electrode surface. Inflammatory response can lead to further recruitment of astrocytes while also releasing cytokines that may increase neuronal cell death. These factors combined lead to shorter functional electrode lifespan. Previous work has indicated that introducing a non-fouling coating alone does not provide a sufficient change to improve the tissue response to implanted electrodes, and there is evidence to suggest that the inflammatory response plays a major role in the continuing tissue response. We believe that incorporation of materials that reduce inflammation may allow implanted electrodes to maintain longer functionality *in vivo*.

Methods:

Silicon wafer samples were coated using dip coating. Si wafer samples were incubated for one hour with 2.5% silane-PEG-maleimide in DMSO then rinsed with 100% ethanol followed by PBS. Samples were dipped in peptide crosslinker with flanking thiols (which interact with maleimide group) for two minutes, rinsed with PBS, incubated in PEG-mal for two minutes, and rinsed with PBS. The dip-coating cycle was repeated to achieve the desired number of layers. Thickness of PEG-mal coatings was determined by ellipsometry measurements performed in a liquid cell. For *in vitro* cell adhesion analysis, coated and uncoated samples were incubated with mixed glial cells (astrocytes and microglia) in medium w/ serum and stained after 24h with Live/Dead (Life Technologies, Inc.) to analyze cell spreading on the surface.

Results:

Coating thickness analysis using hydrated ellipsometry indicated a linear increase in film thickness with a 120 nm thickness for the 6-layer films. The multi-layer coating approach allows flexibility in building complex films that can be further modified by incorporating anti-inflammatory agents. Cell adhesion experiments indicated significantly reduced cell adhesion with increasing layers of the PEG-maleimide coating.

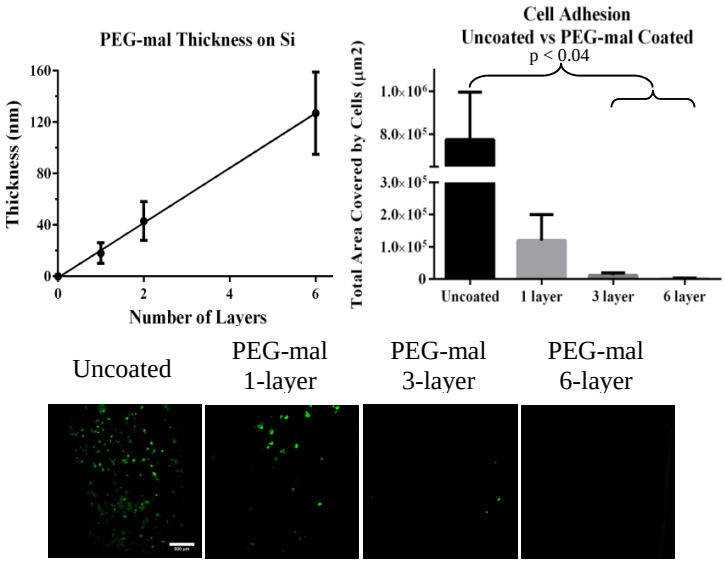

Figure 1. Thickness of the PEG-mal coating on Si (top left, linear regression R^2=0.999). Significantly lower cell spreading on the PEG-mal coated Si, 6 layers has lowest cell spreading (top right). Variable cell adhesion on uncoated Si vs. multi-layer PEG-maleimide coated Si (bottom, scale = 500μm).

There was significantly reduced cell adhesion on PEG-maleimide coated samples compared to uncoated controls, with significantly lower cell adhesion present on the 6-layer coatings. Results from our previous experiments have indicated that passive coatings alone may not provide sufficient modification to overcome the challenges involved with improving the tissue response to implanted electrodes[4]. Studies to determine the release characteristics of anti-inflammatory agents from the PEG-mal coating *in vitro* are ongoing. Additionally, studies are ongoing using a rat model to study the *in vivo* response of the cortex to implanted electrodes to compare uncoated and PEG-mal coatings with anti-inflammatory agents.

Conclusions:

We have developed a PEG-based coating for silicon electrodes. Thickness characterization indicated a 120nm coating for 6-layer films and cell adhesion experiments indicated reduced cell adhesion and cell spreading on silicon substrates coated with PEG-maleimide. Current studies are ongoing to analyze release of anti-inflammatory agents *in vitro* and the tissue response to implanted electrodes *in vivo.*

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References: [1]Schwartz A. Neuron. 2006;52:205-220. [2]Turner J. Exp Neurol. 1999;156:33-49. [3]Zhong Y. Brain Res. 2007;1148:15-27. [4]Gutowski SM. JBMR-A. 2013; (*DOI:* 10.1002/jbm.a.34799).