The use of Extracellular Matrix Coatings to Immunomodulate the FBR in Rat Brain

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Statement of Purpose: Microelectrode recording devices show promise to provide volitional control of prosthetic devices by recording neuronal activity from single isolated neurons. However, these devices perform inconsistently over long indwelling periods, presumably due to the foreign body response (FBR, dominated by neuroinflammatory sequela. Available evidence has shown that decellularized extracellular matrix (ECM) derived from various tissue sources is capable of modulating the activation state of macrophages and accelerating wound healing. Here we investigate the utility of various cell-specific ECMs as immunomodulatory biomaterial coatings for neural recording devices.

Methods: Open-cell polyurethane foams (Tecoflex) were fabricated, pretreated with fibronectin and seeded with either mesenchymal stem cells, fibroblasts, astrocytes or glial precursors and cultured for several weeks[1]. Following culture, the cells and polymer were removed using a weak aprotic solvent and the remaining cell-derived material was rinsed in DI water, frozen and lyophilized. The ECM was characterized by Mass Spectroscopy and immunohistochemical methods. Planar silicon microelectrode arrays were coated with acid solubilized ECM solutions by dip coating. In some cases ECM coated substrates were examined for macrophage activation *in vitro*. For *in vivo* analysis, coated electrodes and uncoated controls were implanted stereotactically in motor cortex of adult male Sprague-Dawley rats. After a 8-week indwelling period, animals were transcardially perfused and their brains post-fixed in 4% paraformaldehyde. The brains were then sectioned and the FBR was characterized using markers of macrophage activation (ED-1), blood product (IgG) and implant-associated neuronal death (NeuN).

Results: ECM was harvested from all cell types as shown by Mass spectroscopic and immunohistochemical analysis that contained collagen, fibronectin, growth factors and a variety of glycosaminoglycans (GAGs). In general, the freeze dried product was a white lacy solid that could be ground into a powder and bought into solution under acidified conditions. Fig 1 shows the electrode coated with ECM derived from primary astrocytes. Macrophage activation assays showed that coated substrates were capable of maintaining microglia in a non-activated morphology. Eight weeks after implantation coated perfused rat brains showed evidence of less reactivity than uncoated controls (Fig 2). Detailed histological analysis is ongoing and will be reported at the meeting.

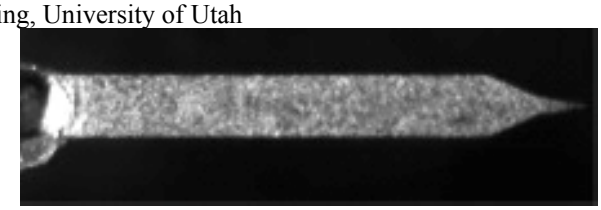

Figure 1: A 300μm wide monolithic silicon electrode coated with an astrocyte-derived extracellular matrix.

Conclusions: Our studies have shown that variable cell-sources create ECM rich in fibronectin and laminin, which contain important platelet adhesion motifs, and that conditioning with growth factors and mechanical stimuli can alter the relative concentration of these proteins within the matrix. Vascular damage following implant-induced injury contributes to the inflammatory burden by releasing soluble factors, cytokines and serum proteins associated with secondary neuronal cell death. By accelerating hemostasis we expect to see minimized blood product accumulation and down-regulated macrophage activation. Initial implant surgeries have proven the feasibility of our approach and on-going research is selecting sources of ECM that show enhanced hemostatic ability and immunomodulatory potential.

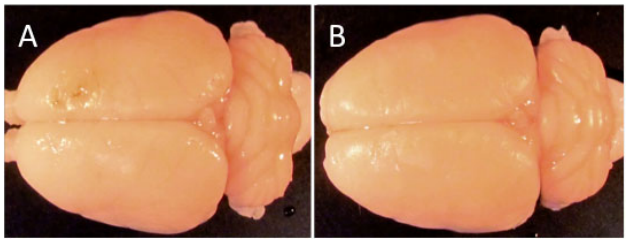

Figure 2: Stereoscopic brain images from a) uncoated and b) coated electrode implants. A trend of increased blood products in the brain parenchyma and tissue loss was observed with uncoated electrodes, indicating a potential immunomodulatory ability of ECM coatings.

References:

(Wolchock JC. Biomaterials. 2010;31:9595-9603)