Bioresponse of Mammalian Kidney to Implantation of Polymeric Materials

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Statement of Purpose: Biomaterials can modulate regenerative outcomes in tissue engineering or regenerative medicine applications by facilitating cell attachment and delivery and by providing a physical substrate for tissue infiltration[1]. This study investigated host tissue responses to intra-renal injection of natural and synthetic biomaterials in rodent kidney to identify candidate biomaterials for forming cell/biomaterial composites with bioactive renal cell populations[2]. The ultimate goal of this research is to develop Neo-Kidney Augment prototypes that delay the need for dialysis and improve renal function in patients with chronic kidney disease.

Methods: Natural biomaterials included gelatin and hyaluronic acid (HA). Synthetic biomaterials included polycaprolactone (PCL) and poly-lactic-*co*-glycolic acid (PLGA). Candidate biomaterials were evaluated in two discrete physical conformations: homogenous, spherical beads or heterogenous and non-uniform particles. PCL and PLGA beads (**Figure 1, left**) were prepared using a modified double emulsion (water/oil/water) solvent extraction method. Gelatin beads were purchased (Cultispher-S®, Sigma-Aldrich, St. Louis, MO). PLGA particles were prepared using a solvent casting porogen leaching technique; gelatin and HA particles were prepared from cross-linked, lyophilized foam (**Figure 1**, **right**). Two injections of 35 µl of loosely packed biomaterials were delivered to the left kidney parenchyma of 3 month old Lewis rats. Histopathologic evaluation of formalin-fixed sections of kidney tissue at 1 and 4 weeks post-injection was conducted using a semi-quantitative grading severity scale from 0 (absent) to 4 (marked) of inflammation, tissue/cellular in-growth, neo-vascularization, material degradation, and fibro-cellular responses. Overall scores were calculated as the ratio of % positive to % negative response (the higher the overall score the superior outcome).

Results:

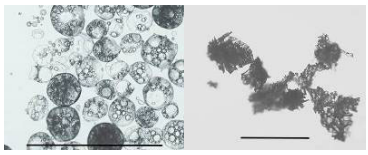

Figure 1. Representative images of PLGA beads (left) and gelatin particles (right). Scale bars = 1 mm

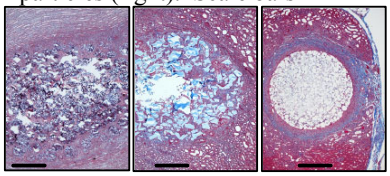

Figure 2. Histopathologic evaluation performed on biomaterial candidates – representative 40X images of kidneys harvested 1 week post-implantation, sections stained with Masson's Trichrome. Materials composed of polymers of natural origin, such as gelatin (left) and HA (center) were associated with milder fibro-cellular response and chronic inflammation, and greater cellular in-growth, neo-vascularization, biomaterial degradation, and necessary inflammation required for tissue healing and integration when compared to the synthetic biomaterials, such as PLGA (not shown) and PCL (right – note organized fibrous encapsulation).

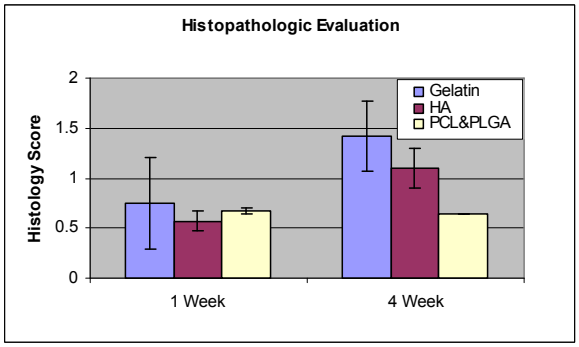

Figure 3. Summary of histopathologic evaluation scoring. Scores were averaged by material composition (mean±SD). The synthetic materials (PLGA and PCL) scored the lowest, and gelatin materials generally scored higher than HA materials. This trend is most pronounced at the 4 week time point. Due to factors unrelated to the material injections, not all the samples tested at 1 week were available for analysis at 4 weeks. The number of samples that are included in the gelatin, HA, and synthetic groups are 3, 4, 3 at 1 week and 2, 3, 1 at 4 weeks, respectively.

Conclusions:

- Biomaterials of natural origin (e.g., gelatin or HA) elicited minimal tissue responses when evaluated 4 weeks post-injection
- Active are studies investigating the *in vivo* effect of bioactive renal cell/biomaterial composites to kidney tissue histology and function in established animal models of chronic renal disease.

References:

1. Basu J. Trends Biotechnol. 2010; 28 (10): 526-33
2. Presnell SC. Tissue Eng Part C. 2010, in press

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