Hyaluronic acid modified surfaces for the reduction of the inflammatory response

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Statement of Purpose: Polymeric biomaterials trigger the foreign body reaction resulting in adsorption of blood proteins and platelets, monocyte/macrophage adhesion and the release of pro-inflammatory cytokines, all of which contribute to clinical complications post-implantation and the ultimate failure of these materials. We have previously shown surface modifications that decrease the foreign body reaction with potential to increase the long-term success of these materials.[1] The naturally occurring glycosaminoglycan hyaluronic acid has also been shown to prevent protein adsorbtion, creating a bioinert blood-contacting surface. In this study, we investigate the hypothesis that hyaluronic acid (HA) would create a bifunctional surface coating biocompatible with blood contacting surfaces. Clinical applications of this technology would include polymeric vascular implants and medical devices that come in contact with blood, such as grafts, catheters and cardiopulmonary bypass tubing.

Methods: Poly vinyl chloride (PVC) surfaces were modified with both HA[2] and CD47[1] (individually and combined) and tested via the Chandler Loop Assay[1] (Figure 1) . Cell attachment was quantified via imaging the inner surface of the tubing. Hyaluronic acid hydrogel scaffolds and microgels were fabricated and presented to THP-1cells to assess monocyte attachment, which was quantified via cell counting.

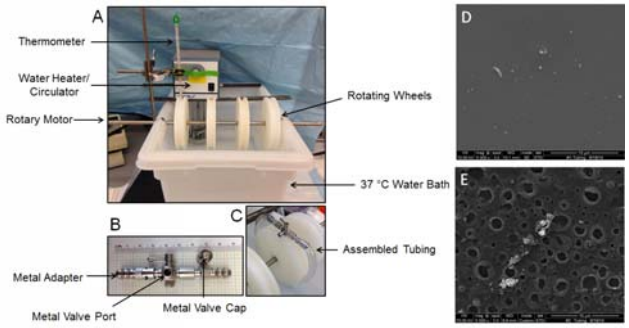

Figure 1. (A-C). Chandler Loop Assay. Whole blood exposure through PVC tubing, rotated at 37°C (D). Unmodified PVC tubing. (E) HA-modified PVC tubing.

Results: Cell attachment to PVC tubing following Chandler Loop Assay exposure for 3 hours decreased when HA was added to the blood in the form of microgels (Figure 2A) as well as coated directly onto the PVC tubing (Figure 2B). Cell attachment was further decreased when CD47 was attached to the HA coating (Figure 2B).

In vitro THP-1 cell attachment was decreased following monocyte activation over 3 days when cells were exposed to HA in the form of microgels (Figure 3A) and three-dimensional hydrogels (Figure 3B). Attachment, and thus monocyte activation was further decreased when three-dimensional HA hydrogels were modified with CD47 (Figure 3B).

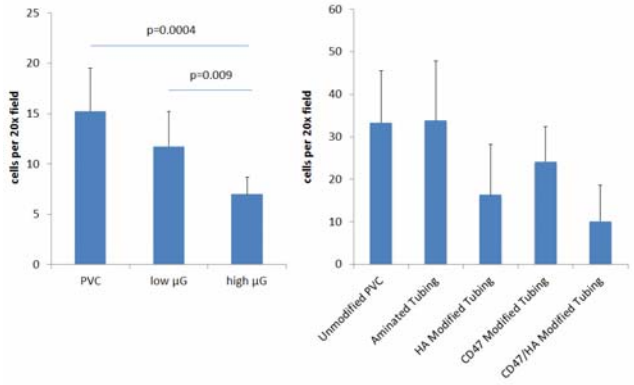

Figure 2. Cell attachment following Chandler Loop assay exposure to whole blood. (A) Hyaluronic acid hydrogels. (B) Hyaluronic acid coated PVC tubing.

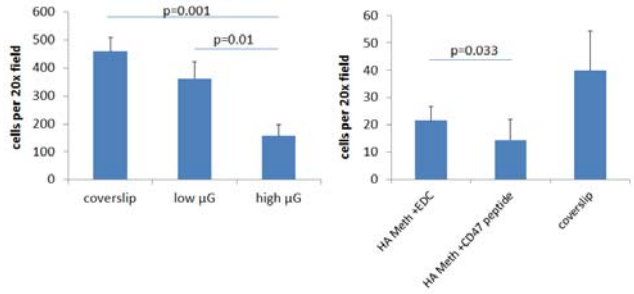

Figure 3. *In vitro* THP-1 cell attachment assay. (A) HA microgels. (B) HA hydrogels.

Conclusions: These results demonstrate the ability of HA to decrease monocyte activation and cell attachment in both an *in vitro* study as well as whole blood exposure in a Chandler Loop Assay.

References:

1. Finley, M. J. *et al.* Diminished adhesion and activation of platelets and neutrophils with CD47 functionalized blood contacting surfaces. *Biomaterials* **33,** 5803–5811 (2012).

2. Eckmann, D. M., Tsai, I. Y., Tomczyk, N., Weisel, J. W. & Composto, R. J. Hyaluronan and dextran modified tubes resist cellular activation with blood contact. *Colloids Surfaces B Biointerfaces* **108,** 44–51 (2013).