Novel High-Throughput Polymer Bio-Compatibility Screening Designed For SAR (Structure Activity Relationship): Application For Evaluation Of BioLinx Polymer System For Cardiovascular Drug Eluting Stents

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Statement of Purpose:

The definition of biocompatibility has been evolving in conjunction with the continuing development of materials used in medical devices. The current paradigm for a material to be considered biocompatible is to exhibit the properties of being biologically non-toxic and support cell growth and viability. Introduction of drug-eluting-stents (DES) has resulted in significant improvement in the long-term outcome of percuteneous coronary interventions. However, drug eluting stents are not without risk, and concerns have been raised with regard to DES in the context of vascular inflammation, endothelial dysfunction and late stent thrombosis [1]. Generally, the release of drugs from DES is controlled by a polymeric coating that is retained on the stent post drug elution. Biocompatibility of the polymeric coating can therefore influence subsequent vascular healing [2]. These factors prompted us to extend our definition of polymer biocompatibility to include the extent of inflammatory and thrombotic effect that the polymer may exert on adjacent cells.

Here we describe the development of high-throughput biocompatibility screening relying on the concept that surface composition of the biomaterial dictates its hydrophilicity, which in turn determines its biocompatibility. The assay platform we designed for evaluation of polymer scaffolds allows for differentiation between polymers based on their ability to provoke an inflammatory response in vascular cells. The data generated in these assays provides a structure-activity relationship (SAR) profile to the polymer chemists to guide polymer design in the context of biocompatibility. We have also applied this methodology to evaluate a novel polymer system (BioLinx) designed in-house, for cardiovascular drug eluting stents.

Methods:

96 well plates were coated with various hydrophobic and hydrophilic compositions of polymers as also a blend of these polymers developed for DES (drug eluting stents). We studied the interaction of monocytic and vascular (smooth muscle and endothelial) cell types with these polymers, utilizing Taq Man based gene-profiling and FACS-BD Cytokine Array/ELISA for the evaluation of inflammatory cytokine production, as well as analyzing monocyte adhesion to polymers. In addition, these polymers were compared for their effect on the viability of endothelial and vascular smooth muscle cells.

Results/Discussion:

In our study we discovered clear differences in monocyte adhesion and induction of markers for inflammation (such as IL-8 and MCP-1) and thrombosis (Tissue Factor and PAI-1) between the evaluated polymers. These differences aligned with the corresponding hydrophobicity/ hydrophilicity profiles of these polymers, as indicated by measurements of their contact angle and nitrogen content. The most biocompatible polymer blend, BioLinx, features a hydrophilic surface and minimal adhesion of monocytes, with no induction of inflammatory and thrombotic markers.

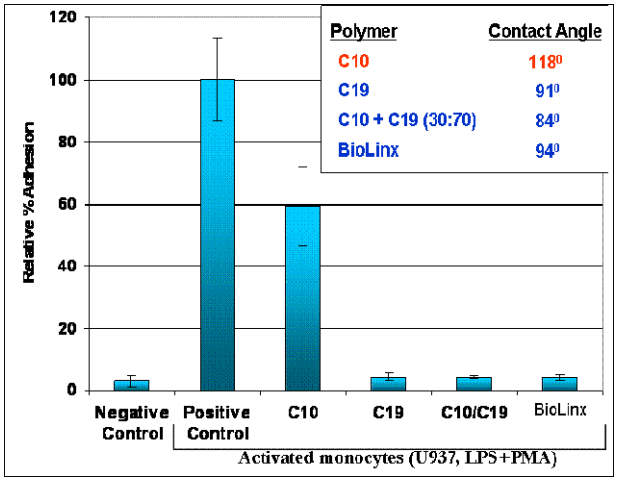

Figure 1. Contact angle measurement (upper right hand corner of graph) is a convenient method to determine relative hydrophilicities of surfaces. Activated monocytes (above graph) do not bind to polymer blends containing the hydrophilic component C19.

Conclusions:

We designed a high-throughput platform for polymer screening that allows for the evaluation of multiple parameters related to vascular cell activation, in particular inflammation and thrombosis.

The screening results indicate that polymer coatings with hydrophilic surfaces are more biocompatible than hydrophobic surfaces since they elicit minimal inflammatory/thrombotic responses in vascular cells. The proprietary hydrophilic polymer blend, BioLinx, developed for cardiovascular drug eluting stent coatings is biocompatible as determined by these assays.

References:

[1] M. Joner et al , J Am Coll Card. 2006. 48:193

[2] R. Virmani et al, Coronary Artery Disease 2004. 15:313.