Native Endothelium Mimicking Nanomatrix for Drug Eluting Stent Applications

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Statement of Purpose: The main goal of this study is to develop an innovative strategy for next generation drug eluting stents (DES) using native endothelium mimicking self-assembled peptide amphiphile (PA) nanomatrices. Deployment of stents is a major therapeutic technique for treatment of cardiovascular diseases. The requirement for new generation stents is caused by characteristic limitations of conventional stents. Bare metal stents (BMS) suffer from intimal hyperplasia and poor endothelialization, leading to restenosis. DES was designed to deliver drugs that tackle the shortcomings of BMS. However, DES has been associated with late stent thrombosis which may be due to lack of endothelialization. This study utilizes two different PAs to develop an endothelium mimicking stent coating: PA-YIGSR which contains endothelial cell adhesive YIGSR ligand and PA-KKKKK which contains nitric oxide (NO) donors.

Methods: PA-YIGSR and PA-KKKKK were separately synthesized using F-moc Chemistry and mixed in a 9:1 molar ratio to produce PA-YK[1]. NO producing PA-YK-NO was developed by reacting pure NO gas with PA-YK solution. PAs were self-assembled into nanofibers by solvent evaporation and verified for self-assembly with TEM. NO release from PA-YK-NO was studied using Greiss assay. Human Umbilical Vein Endothelial Cells (HUVECs) and Human Aortic Smooth Muscle Cells (AoSMCs) behaviors on PA-YK-NO was evaluated by Proliferating Cell Nuclear Antigen (PCNA) staining. Platelet attachment on the collagen, PA-YK, and PA-YK-NO was investigated with mepacrine labeled human blood. Preliminary animal studies were conducted by implanting PA-YK-NO coated stents in a rabbit iliac artery. ANOVA analysis was performed to evaluate statistical significance.

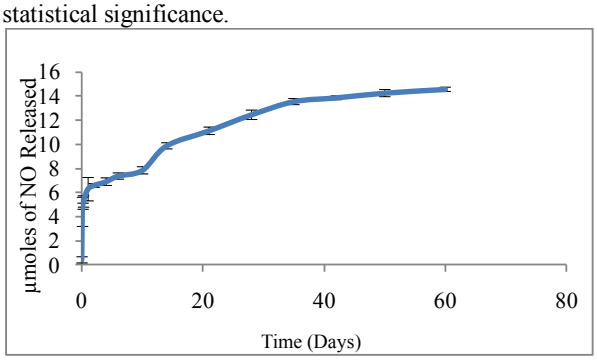

Figure 1. The NO release profile from PA-YK-NO over a 2 month period.

Results: Successful self-assembly of all PAs into nanofibers (8 nm - 10nm) was confirmed by TEM. NO release from the PA-YK-NO nanomatrix was studied, and an initial burst release, followed by sustained release was observed over a 2 month period (*Figure 1*). PA-YK-NO showed significantly higher proliferation of HUVECs and significantly lower proliferation of AoSMCs when compared to PA-YK. PA-YK was also found to limit platelet attachment compared to the positive control, collagen I. PA-YK-NO further prevented platelet attachment. This result indicates that PA-YK-NO may have potential to enhance endothelialization, prevent intimal hyperplasia, restenosis and prevent thrombosis. Preliminary rabbit studies showed that stents were successfully deflated, stent coatings are stable, minimal inflammation was observed, and no thrombosis was found as shown in *Figure 2*.

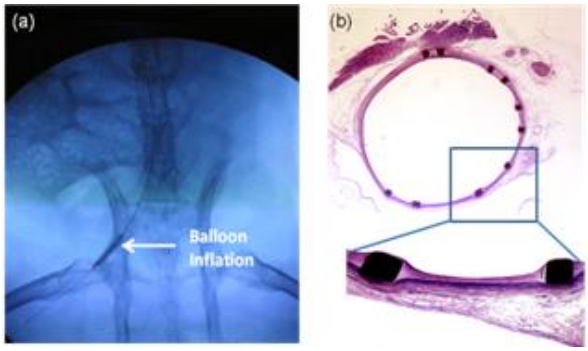

Figure 2. (a) Balloon inflation to deploy stent in rabbit iliac artery. (b) Histology section of PA-YK-NO coated stents after 4 weeks of implant.

Conclusions: We have successfully developed a nitric oxide releasing native endothelium mimicking nanomatrix that promotes endothelial cell proliferation but limits platelet adhesion and smooth muscle cell proliferation. Effectively, this nanomatrix possesses the potential to promote endothelialization but limit intimal hyperplasia, restenosis and thrombosis. Preliminary rabbit studies showed that the nanomatrix coating displayed stability under blood flow. Endothelialization was evident and neointimal proliferation and thrombosis were limited. Currently, the ability of this nanomatrix to recruit endothelial progenitor cells and promote their differentiation is being studied. This nanomatrix could have a great potential to improve clinical patency of DES as a coating by enhancing endothelialization while reducing restenosis and thrombosis.

References:

1. Kushwaha *et al*, Biomaterials 2010 ; 31 :1502-1508

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