



Multilayer vascular grafts based on collagen-mimetic proteins

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ABSTRACT

A major roadblock in the development of an off-the-shelf, small-caliber vascular graft is achieving rapid endothelialization of the conduit while minimizing the risk of thrombosis, intimal hyperplasia, and mechanical failure. To address this need, a collagen-mimetic protein derived from group A *Streptococcus*, Sc12.28 (Sc12), was conjugated into a poly(ethylene glycol) (PEG) hydrogel to generate bioactive hydrogels that bind to endothelial cells (ECs) and resist platelet adhesion. The PEG-Sc12 hydrogel was then reinforced with an electrospun polyurethane mesh to achieve suitable biomechanical properties. In the current study, initial evaluation of this multilayer design as a potential off-the-shelf graft was conducted. First, electrospinning parameters were varied to achieve composite burst pressure, compliance, and suture retention strength that matched reported values of saphenous vein autografts. Composite stability following drying, sterilization, and physiological conditioning under pulsatile flow was then demonstrated. Sc12 bioactivity was also maintained after drying and sterilization as indicated by EC adhesion and spreading. Evaluation of platelet adhesion, aggregation, and activation indicated that PEG-Sc12 hydrogels had minimal platelet interactions and thus appear to provide a thromboresistant blood contacting layer. Finally, evaluation of EC migration speed demonstrated that PEG-Sc12 hydrogels promoted higher migration speeds than PEG-collagen analogs and that migration speed was readily tuned by altering protein concentration. Collectively, these results indicate that this multilayer design warrants further investigation and may have the potential to improve on current synthetic options.

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1. Introduction

Approximately 1.4 million patients require arterial prostheses each year in the USA alone [1]. Existing options for vascular grafts have limited clinical success with an associated cost exceeding US\$25 billion. The current gold standards, autologous saphenous veins and mammary arteries, are not available for up to 20% of patients due to disease, trauma, or anatomic abnormalities [2,3]. Cadaveric saphenous vein allografts are readily available but require processing prior to implantation, which induces damage to the endothelial layer and a loss of properties. In addition, allografts have associated immunological concerns [4–8]. Synthetic grafts made of polyethylene terephthalate (PET) and expanded polytetrafluoroethylene (ePTFE) are viable options for large diameter applications (>4 mm); however, thrombogenicity and low compliance cause re-occlusion in small-caliber vessels [9,10]. Such complica-

tions limit the use of these synthetic grafts in coronary artery bypass surgeries, which account for one-third of the arterial prosthesis procedures performed each year [1,11]. The urgent clinical need for off-the-shelf, small diameter vascular prostheses has prompted researchers to investigate biomimetic grafts with properties that more closely match those of native blood vessels [12–15].

For a graft to be effective as an off-the-shelf arterial prosthesis, it must avoid cell harvesting and construct pre-culture, which delay treatment and increase cost [16–19]. Thus, generation of the luminal endothelial cell (EC) layer critical to inhibiting platelet aggregation and smooth muscle cell hyperproliferation must occur following implantation. Therefore, rapid endothelialization has been identified as a critical element in the development of off-the-shelf vascular prostheses to prevent small-caliber graft re-occlusion [16,20]. In vivo graft endothelialization appears to involve EC migration from graft anastomoses as well as endothelial progenitor cell adhesion and migration. Thus, the ability to promote cell migration is critical to graft endothelialization. Collagen was

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