Fabrication and testing of vascular grafts with biomimetic microstructure that match the compliance of natural blood vessels

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Introduction: There exists a need for better small diameter vascular grafts due to poor patency rates of current prostheses, along with associated morbidity and limited quantities of autologous grafts [1]. Differences in radial compliance between vascular grafts and the native vessel have been shown to cause intimal hyperplasia and thus luminal narrowing [1]. It is hypothesized that a synthetic vascular graft that mimics the histological structures and matches the compliance of natural blood vessels would have increased patency. Our lab developed technologies to fabricate thin nanofiber arrays oriented in a composite with interlacing wavy and aligned configurations similar to the arrangement of collagen and elastin nanofibers in natural blood vessels (Figure 1). These composites have highly tuneable mechanical properties similar to natural vascular tissue. Tubular vascular grafts assembled from these thin nanofiber arrays (Figure 2A) maintained their biomimetic morphology and mechanical properties.

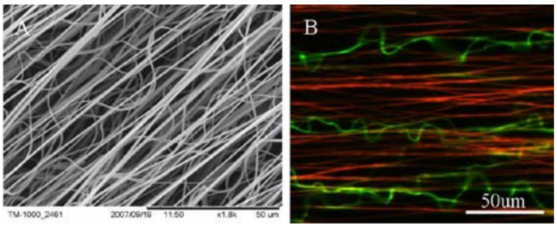

Fig. 1: (A) SEM Image (B) Flourescent Image of thin composite fiber sheets with interlacing waved (PCL) and straight fibers (PU).

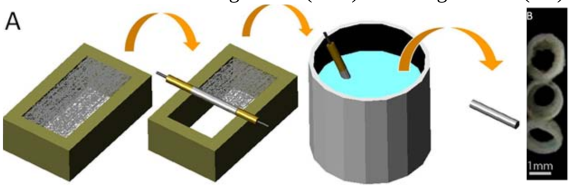

Fig. 2: (A) Schematic of fabrication procedure (B) From top to bottom: biomimetic graft, control graft, rabbit carotid explants.

Material/Methods: Polyurethane (PU) and nylon nanofibers were electrospun and assembled into straight/wavy composites sheets. Amine terminated polyethylene-glycol (PEO-NH_2) was added to the electrospinning solutions to facilitate surface functionalization. Several thin nanofiber sheets were rolled around a dry gelatin coated mandrel with fiber alignment in the circumferential direction. A randomly aligned nanofiber layer was electrospun from a PU/PEO-NH_2 solution for the inner and outer most layers so that no seams were exposed. The nanofiber graft was dried and removed from the mandrel by gelatin dissolution in water. A carboxyl-to-amine crosslinking reaction was performed to attach heparin to the surface of the nanofibers in the graft. Graft microstructure was examined by SEM and graft mechanical properties were measured using a Cell-Scale Biotester. Heparin incorporation was examined by Toulidine Blue assay and XPS. Several grafts were implanted in the carotid artery of rabbits to evaluate their performance as vascular grafts.

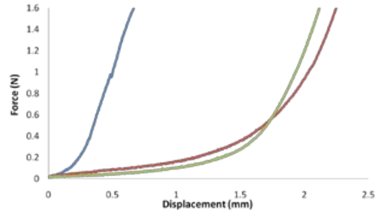

Fig. 3: Force vs. displacement for ring samples of biomimetic (red), and control grafts (blue), and rabbit carotid explants (green)

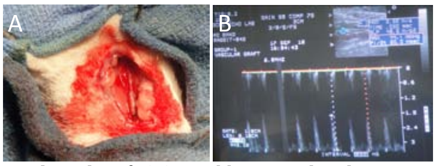

Fig. 4: Implanted graft (A) in rabbit carotid replacement model and ultrasound Doppler monitoring the graft after 3 months of implantation is showing normal pulse (B).

Results/Discussion: Tubular grafts with bimimetic straight/wavy microstructure or control grafts with only straight fibers were successfully fabricated with overall appearance and diameter similar to native rabbit carotid artery (Figure 2B). Interestingly, because very thin layers were used in the rolling procedure no adhesive was needed. It is hypothesized that electrostatic interactions and physical entanglements provided structural adhesion. SEM confirmed that biomimetic microstructure was preserved in tubular grafts, while control grafts maintained a straight fiber microstructure. Mechanical testing confirmed that grafts maintained non-linear J-shaped mechanical behavior exhibited by natural blood vessels. Mechanical behavior of a graft optimized to match the rabbit carotid artery is displayed in Figure 3. No observed reduction in strength was observed during 100 cycle fatigue testing at physiological loads. Heparin attachment to the functionalized nanofibers was confirmed by Toulidine Blue assay and XPS. Grafts were robust enough to withstand the mechanical rigors of implantation and did not leak. Restoration of blood flow thorough the carotid artery for at least 3 months was confirmed after surgery.

Conclusions: Robust tubular nanofiber grafts with biomimetic microstructure were successfully fabricated. The mechanical behaviour of these grafts was matched to the rabbit carotid artery and they were successfully implanted. This versatile novel technology may be used to fabricate vascular grafts with the appropriate mechanical properties to improve the patency.

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References:

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2. Sum-Tim et al. Ann Thorac Surg, 68, 2298-305, 1999