Transcatheter Tissue-Engineered Vein Valve

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Introduction: Venous valve disease, also referred to as chronic venous insufficiency (CVI), is a painful and debilitating condition affecting over 7 million patients annually in the United States.[1] Current treatment costs exceed $1 billion per year, and lifetime disease management expenses typically approach $40,000 per individual. The condition occurs when one or more of the small, one-way valves in the saphenous or popliteal veins fails, allowing blood to pool in the lower leg. Common causes of valve failure are chronically high venous blood pressure, or blockage by a blood clot (thrombus). Treatment options for individuals who develop CVI, especially in deep veins, are generally are limited to compression stockings. More recently developed treatment methods include microsurgical valve repair [2] and autologous transplantation [3]; however, these approaches tend to offer only short-term improvements for most patients. To date, fixed-pericardium based vein valve has been investigated in clinic with short-term positive results[4]. To address this unmet need, we have developed a transcatheter venous valve by growing engineered tissue in the form of a bileaflet valve directly don a nitinol stent, with subsequent tissue decellularization.

Material and Methods: A custom 3D-printed mold was used to cast a fibroblast-seeded fibrin gel (Fig. 1a). A commercial vascular nitinol stent (eV3) was placed in the annulus of the mold when the gel was cast to allow for tissue growth around the stent as well as in the two leaflet channels (Fig. 1b). The valve was cultured for 3 weeks and then decellularized using SDS/Triton-X/DNAase sequential washes. It was evaluated for hydrodynamic properties in a custom pulse duplicator with 1Hz pulse-flow of 200 ml/min and baseline pressure of 50 mmHg. The associated mean and peak systolic pressure gradients were measured. Additionally, the vein valve was seeded with blood-outgrowth endothelial cells in a rotating flask chamber then incubated for 24 hr. The tissue was stained for an endothelial marker (CD31) to evaluate cell adhesion and monolayer formation.

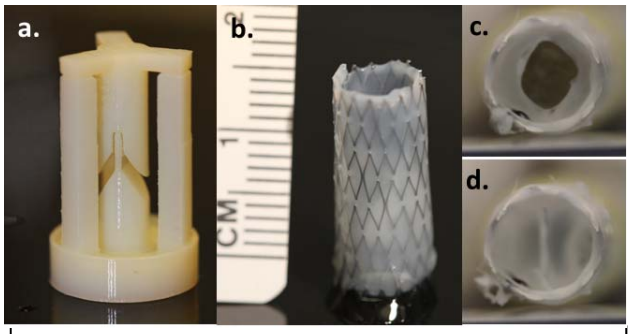

Figure 1. a. 3D printed valve mold, **b.** Nitinol stent embedded into engineered tissue, and **c.** End on view of engineered vein valve in open (top) and closed (bottom) position.

Results and Discussion: The engineered tissue of the vein valve grew around the nitinol stent embedded within the valve root (Fig. 1b). The stent was well integrated into the cell-produced matrix by visual inspection and confirmed by histology. The valve opened and closed under cyclic pressure, with images at fully open and close positions shown in Figure 1c. Hydrodynamic testing showed peak systolic pressure gradient of 1 mmHg and mean gradient of 0.3 mmHg. The very low pressure drop is ideal for the venous system where resistance needs to be minimized. To address hemocompatibility, a major obstacle for attempts at prosthetic vein valves using synthetic materials due to low blood flow rates, this vein valve was seeded with endothelial cells, and staining revealed formation of a monolayer of spread cells on the leaflet surfaces (Fig. 2a&b).

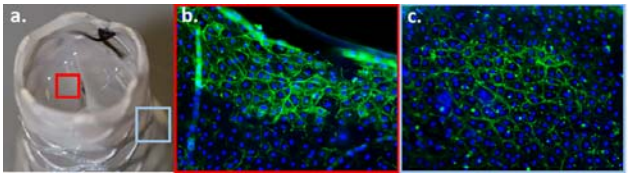

Figure 2. a. Top view of engineered vein valve with red and box showing area of endothelialization in **b.** leaflet region, and **c.** root region.

Conclusion: These preliminary data show promise for growing engineered tissue directly on a stent in a bileaflet valvular geometry to develop a vein valve that could eventually be deployed using a transcatheter approach. With previously demonstrated regenerative capacity of our cell-produced matrix[5] and the ability to endothelialize this engineered vein valve could be a viable solution to restore normal venous flow in CVI patients.

References:

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