Tunable Hydrogel System for the Development of Tissue Engineered Vascular Grafts

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Statement of Purpose: The mechanical properties of materials used for tissue engineered vascular grafts have the potential to influence cell phenotype and morphology, as well as extracellular matrix production and organization. Additionally, application of physiological transmural strain and pressure profiles have beneficial affects on the mechanical integrity of developing grafts. For these reasons, we present the use of poly(ethylene glycol) (PEG) hydrogels with tunable mechanical properties and integrated biofunctionality in a pulsatile flow bioreactor system for the improvement of tissue engineered vascular grafts.

Methods: The base polymer PEG diacrylate (PEGDA), as well as cell adhesive PEG-RGDS, and proteolytically degradable PEG-LGPA-PEG were synthesized as described previously (1). Polymers were dissolved in HBS, mixed with a photoinitiator, and placed in rectangular glass molds for photopolymerization upon exposure to long wavelength UV light. The resulting hydrogels were subjected to swelling analysis for mesh size calculation and uniaxial tensile tests to determine elastic moduli.

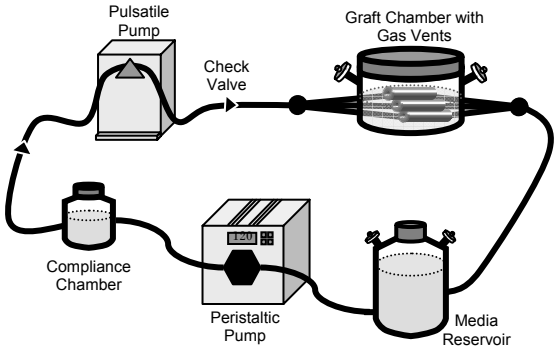

Figure 1. Pulsatile Flow Bioreactor System

A pulsatile flow bioreactor system (above) was designed and evaluated using tubular hydrogels formed in cylindrical molds. Grafts were placed in a custom glass chamber and subjected to flows of 120 mL/min at 5 dynes/cm^2 shear and a pressure profile of 120/75 mmHg and 120 beats per min. Transmural strain in the grafts was calculated from analysis of digital images obtained during flow. Cell-laden grafts were created by homogenously mixing smooth muscle progenitor cells with the PEG polymers prior to gelation. Grafts were cultured under flow conditions for 8 wks. Samples were assayed for cellularity and extracellular matrix production by standard methods and compared to static controls.

Results / Discussion: Varying the molecular weight and solution concentration of PEGDA in hydrogels allows the formulation of materials with a range of mechanical and diffusive properties as shown in the table below. When subjected to flow-induced pulsatile strain in the physiological bioreactor system, the hydrogels experience radial strains of 2.9 – 10.7% depending on composition of the hydrogel. This range includes several potential matrices with strains greater than 5%, which has been shown to induce a positive response by vascular graft cells.

Tunable Properties of PEGDA Hydrogels

PEGDA Formulation	Mesh (Å)	Modulus (kPa)
3400 MW, 0.1 g/mL	27.2 ± 1.0	107.8 ± 2.1
6000 MW, 0.1 g/mL	34.4 ± 0.5	80.6 ± 2.3
10000 MW, 0.1 g/mL	50.5 ± 2.2	49.1 ± 1.4
20000 MW, 0.2 g/mL	108.9 ± 0.3	27.0 ± 1.3
Degradable*, 0.1g/mL	39.1 ± 0.9	59.3 ± 4.1

**Degradable gel is 70% 6000 MW and 30% PEG-LGPA-PEG*

Of note, although these gels provide varying mechanical environments for vascular graft cells, the adhesive properties of the scaffolds can be maintained by controlling the amount of PEG-RGDS present, allowing study of a single variable in the experimental setup. In contrast, with scaffolds formed from materials such as fibrin or collagen, changes in the solution concentration alter both the stiffness of the matrix and the number of adhesive ligands present.

Analyses of constructs cultured under pulsatile flow conditions show improved cellularity and collagen production when compared with static controls. These results support the addition of mechanical conditioning during the development of tissue engineered vascular grafts.

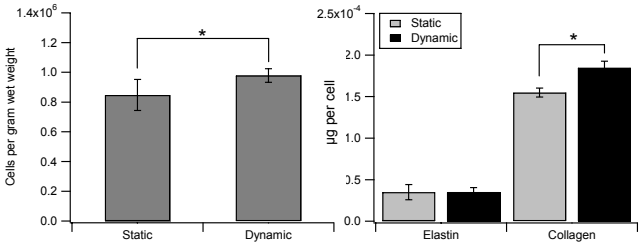

Figure 2. Cellularity and ECM results for PEG hydrogels cultured under pulsatile flow conditions. * $p < 0.05$.

Conclusions: Systematic modulation of PEGDA hydrogel composition results in a range of potential vascular grafts that have varying mechanical and diffusive properties. These hydrogels contain specific peptide moieties which allow cell adhesion and enzyme mediated degradation of the polymer matrix during culture. A pulsatile flow bioreactor was designed to provide physiologically relevant pressure and flow profiles and appropriate transmural strain and was shown to improve the biological response of encapsulated cells. Information gained through these studies will help determine the ideal parameters for vascular graft applications.

1. Mann BK. Biomaterials. 2001;22:2045-51.