Drug-encapsulated super stiff poly(ethylene glycol) hydrogel for stem and progenitor cell mobilization

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Statement of Purpose: Injectable and biodegradable hydrogels have been increasingly studied for sustained drug delivery. However, it remains a challenge to attain desired delivery rate at injection sites due to local tissue pressures exerted on the soft hydrogels. Furthermore, there is often limited controllability of stiffness and degradation rates, which are key factors required for achieving desired drug release rate and therapeutic efficacy. This study presents a stiff and metastable poly(ethylene glycol) diacrylate (PEGDA)-poly(ethylene imine) (PEI) hydrogel which exhibits an elastic modulus equivalent to bulk plastic materials, and controllable degradation rate independent of its initial elastic modulus. Such unique stiffness was attained from the highly branched architecture of PEI, and the decoupled controllability of degradation rate was achieved by tuning the non-equilibrium swelling of the hydrogel. Furthermore, a single intramuscular administration of granulocyte colony stimulating factor (GCSF, half-life = 2-4 hours)-encapsulated PEGDA-PEI hydrogel significantly increased the yield of expanded CD34+ and CD31+ endothelial progenitor cells (EPCs) as compared to daily bolus administrations.

Title Drug-encapsulated Super Stiff Poly(ethylene glycol) hydrogel for Stem Cell Mobilization

Methods: To prepare the PEGDA-PEI hydrogels, aqueous solutions of PEGDA (molecular weight (Mw) ≈ 400, Polysciences) and PEI (MW ≈ 2000, Sigma-Aldrich) were thoroughly mixed and incubated at room temperature for 2 minutes. Elastic moduli of the synthesized hydrogels were characterized with a mechanical testing system (MTS Insight). Imaging of water diffusion through the hydrogel was carried out using magnetic resonance imaging (600 MHz Varian Unity/Inova nuclear magnetic resonance (NMR) spectrometer). *In vitro* and *in vivo* protein releases were characterized with encapsulated fluorescent bovine serum albumin with the latter being conducted on murine models. Cytotoxicity assay was conducted with chicken chorioallantoic membrane assays and stem cell mobilization with GCSF was conducted with porcine models.

Results: Hydrogels consisting of PEGDA and PEI, termed as PEGDA-PEI hydrogels, were formed through Michael reactions between PEGDA and branched PEI. Overall, compressive moduli, E_0, of the PEGDA-PEI hydrogels were controlled from 1 to 8 MPa, which are one to two orders of magnitude higher than elastic moduli of the conventional pure PEGDA hydrogels. Water diffusivities, D, and E_0 can be decoupled by varying PEI and PEGDA concentrations (Fig. 1). Injection of the GCSF-encapsulated hydrogels elevated the number of mononuclear cells in circulation one day after administration as compared to single bolus injection of GCSF. After three passages of the mobilized cells, there were more stem cells expressing CD34 markers for the 'GSCF-encapsulated hydrogel' condition as compared to all other conditions (Fig. 2).

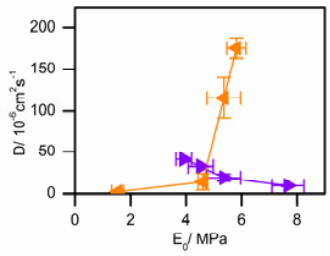

Figure 1. Increasing the PEI concentration of the hydrogels at a given PEGDA concentration of 20 % resulted in the increase of both E_0 and D (-◀-). In contrast, increasing the PEGDA concentration of the hydrogels at a given PEI concentration of 10 % led to the inverse dependency between D and E_0 (-▶-).

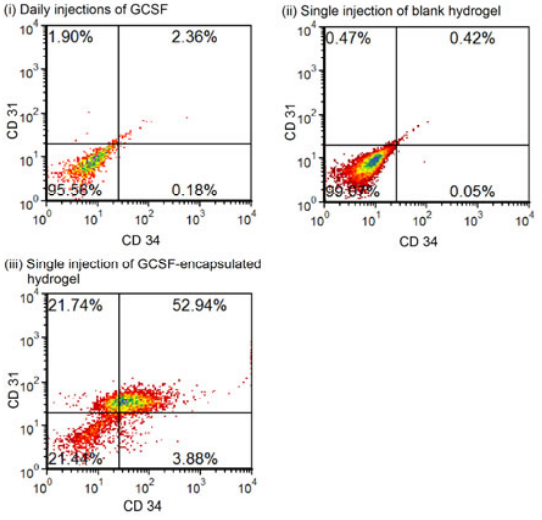

Figure 2. The conditions were (i) daily bolus injections of 0.3 mg of GCSF for four days, (ii) single injection of blank hydrogel, and (iii) single injection of 1.2 mg of GCSF encapsulated within the hydrogel. Administration of GCSF-encapsulating hydrogel resulted in the largest fraction of culture-expanded CD34-expressing stem cells as compared with other conditions.

Conclusions: Overall, the results of this study demonstrate that the stiff and metastable PEGDA-PEI hydrogels allowed the decoupled control of degradation rates and stiffness. This hydrogel system was successfully used as an injectable drug delivery system enabling sustained mobilization of stem and progenitor cells into circulation despite short half-life of GCSF. The unique stiffness of the hydrogel was attained from the highly branched architecture of PEI and the decoupled controllability of degradation rate was achieved by tuning the number of protonated amine groups of the hydrogel.