A Dynamically Disassembling Filamentous Scaffold for Sustained Micellar Delivery

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Statement of Purpose: Stimuli responsive polymers provide an opportunity to develop platform technologies that dictate the spatiotemporal control over the release of diverse payloads. Herein, we describe the development of a novel, photoresponsive scaffold composed of self-assembled poly(ethylene glycol)-*bl*-poly(propylene sulfide) (PEG-*bl*-PPS) nanostructures. The molecular weight ratio of the hydrophilic PEG and hydrophobic PPS blocks dictates the morphology of the self-assembled nanostructures, which include solid core micelles, vesicular polymersomes, and high aspect ratio filomicelles (FMs) [1]. Incorporating low percentages of functionalized block copolymers (BCPs) into the FM assemblies enabled their crosslinking into macroscopic scaffolds. The inherent oxidation sensitivity of PPS permitted the manipulation of the hydrophilic:hydrophobic block ratio and the subsequent transition from filamentous to spherical micelles. Stable encapsulation of the ROS-generating photooxidizer ethyl eosin within the hydrophobic core of the PEG-*bl*-PPS structures provided light-mediated changes in nanostructure morphology, and consequently, the dissasembly of the scaffold into monodisperse micellar vehicles, capable of achieving sustained transport and targeting of diverse payloads to specific cell populations.

Methods: PEG_{45}-*bl*-PPS_{44} was prepared by end-capping the living ring-opening polymerization of propylene sulfide with monomethyl ether-PEG_{45}-mesylate. Vinyl sufone (VS)-PEG_{45}-*bl*-PPS_{44} was prepared from hydroxy-PEG_{45}-*bl*-PPS_{44} using divinyl sulfone and sodium hydride. Both polymers were characterized using H^1 NMR and gel permeation chromatography. FMs, with or without encapsulated ethyl eosin, were prepared via thin film rehydration in 1xDPBS. Crosslinked filamentous scaffolds were prepared by mixing 10% w/v FM solutions exhibiting varying percentages of VS-PEG_{45}-*bl*-PPS_{44} with 8-arm PEG-thiol. The impact of crosslinking density was confirmed through rheological analysis on a parallel plate rheometer. Scaffold photodegradation was induced through exposure to visible light for between six and 24 hours. Mass loss was determined following removal of the supernatant and lyophillization of the remaining scaffold. Induced micellization was confirmed through UV/Vis spectrophotometry, cryogenic electron microscopy (cryoTEM) and dynamic light scattering (DLS). Near infrared fluorescence (NIRF) imaging was used to compare the difference in indocyanine green (ICG) signal over time for the subcutaneous (SC) injection of free ICG and ICG-loaded FMs.

Results: PEG_{45}-*bl*-PPS_{44} FMs prepared at 10% w/v solutions were successfully crosslinked into macroscopic scaffolds through the addition of 8-arm PEG-thiol (Figure 1A). Scaffolds incorporating 10%, 20%, and 30% of the functionalized BCPs and encapsulating ethyl eosin at 0.75% by mass were produced. Increasing the percentage of functionalized BCP led to an increase in resistance to scaffold degradation (Figure 1B). We hypothesized that scaffold degradation was due to the transition from filamentous to spherical micelles. Analysis of the scaffold supernatant following irradiation via UV/Vis spectrophotometry revealed an increase in PEG-*bl*-PPS absorbance over time. DLS analysis confirmed the presence of micellar structures, whose heterogeneity increased with incorporation of functionalized BCP (Figure 1C). NIRF imaging (Figure 1D) was used to compare the change in ICG signal over time for free ICG and ICG-loaded FMs following SC injection. The presence of ICG two weeks post-injection (Figure 1E) indicated that FMs could be used for the formation of a nanoparticle releasing SC depot.

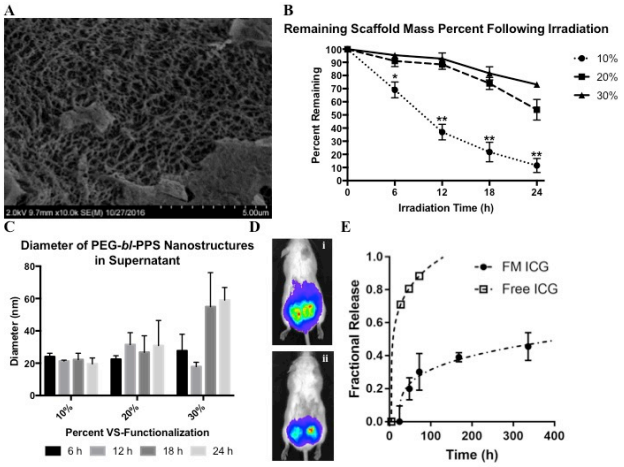

Figure 1. A) CryoSEM image of crosslinked FM scaffold. B) Degradation of ethyl eosin loaded FM scaffolds following exposure to visible light (n=3). C) Diameter of PEG-*bl*-PPS micelles released from degraded FM scaffolds (n=3). D) NIRF images depicting ICG-loaded FM depots i) 0 hours and ii) 314 hours post-injection. E) Fractional release of ICG from injection site.

Conclusions: PEG-*bl*-PPS nanostructures can be effectively crosslinked into macroscopic scaffolds. Stable encapsulation of a photosensitizer, such as ethyl eosin, imparted the ability to trigger photodegradation of the scaffold. Scaffold degradation can be varied through incorporation of functionalized BCPs within the assemblies. Degradation was due to the transition from structural FMs to monodisperse micelles. Biodistribution of released micellar delivery vehicles will continue to be studied for both non-crosslinked FM depots and *in situ* crosslinked FM scaffolds.

References: Cerritelli S. *Langmuir*, 2009; 25.19: 11328-11335.