Biodegradable Photoluminescent Polylactide and Polylacide-*co*-glycolide

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Statement of Purpose: The use of degradable polymers such as polylactide (PLA), polylactide-*co*-glycolide (PLGA) has generated huge scientific and economic impact on a number of biomedical applications including drug delivery, tissue engineering, medical implants, and diagnostic imaging in the past few decades. In recent years, fluorescence imaging has become a powerful tool for *in vivo* non-invasive tracking and evaluation of biomaterials. Traditional fluorescent imaging agents such as organic dyes and quantum dots suffer from long-term toxicity and severe photo-bleaching, thus are not suitable for *in vivo* applications. Our lab has recently developed a new family of polymers, biodegradable photoluminescent polymers (BPLPs), without using any organic dyes or quantum dots [1]. Taking advantages of both BPLPs and FDA-regulated PLA/PLGA, here we developed a new series of biodegradable photoluminescent polylactones (BPLPL) copolymers (such as BPLP-PLA, BPLP-PLGA) that exhibited tunable photoluminescent properties.

Methods: A two-step reaction was conducted to synthesize BPLP-PLA or BPLP-PLGA. First, BPLPs were synthesized according to our previous method [1] by reacting citric acid, aliphatic diols, and amino acids. Next, lactide or lactide/glycolide monomers and BPLP were added into a dry glass tube at various ratios. 0.05 wt% of Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) were added into the tube followed by 3 cycles of vacuum and purging with nitrogen, then the glass tube was sealed. After the reaction at 140°C for PLA and 180°C for 2 hrs then 160°C for various times for PLGA respectively, the resulting copolymers were dissolved in chloroform and precipitated in cold ethanol. The polymer structures and molecular weight were characterized by ^{1}H-NMR, FT-IR, and GPC. The photoluminescent properties (excitation/emission spectra and the quantum yield) of polymers were characterized under a fluorospectrometer. Tensile mechanical tests were conducted on an Instron mechanical tester. *In vitro* degradation tests were performed in PBS at 37°C. *In vitro* cytocompatibility was evaluated by seeding NIH 3T3 fibroblasts on polymer films, followed by measuring cell viability by MTT assay.

Results: The representative synthesis of BPLP-PLGA copolymers is shown in Figure 1. Both BPLP-Cys and BPLP-Ser were used to initiate the copolymerization. BPLP-PLA, BPLP-PLGA(50/50), BPLP-PLGA(75/25), and BPLP-PLGA(85/15) were all synthesized through ring-opening polymerization with various BPLP to LA/GA ratios. BPLP-PLA and BPLP-PLGA copolymers inherited strong inherent photo-stable fluorescence from BPLP pre-polymers. The fluorescence intensities decreased with increasing PLA or PLGA chain lengths. Interestingly, the quantum yield of the copolymers did not decrease significantly upon increasing PLGA chain (from 20% to 15%), while the BPLP-PLA exhibited higher quantum yield (>30%). Mechanical tests revealed that BPLP-PLA and BPLP-PLGA copolymers had similar tensile strength and Young's modulus compared to PLA and PLGA. However, the elongation at break of copolymers was significant lower than that of PLA and PLGA. The degradation profiles were evaluated *in vitro* by measuring fluorescence decay over time and verified by mass loss. *In vitro* cell viability tests also suggested BPLP-PLA and BPLP-PLGA were as cytotocompatible as PLA and PLGA.

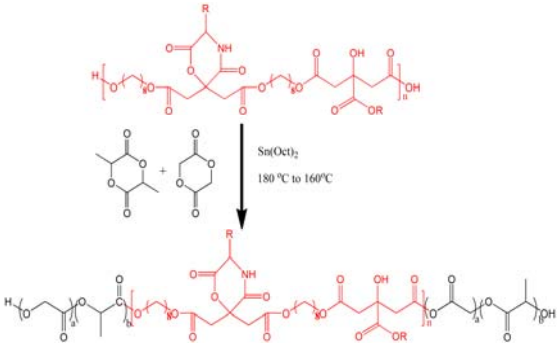

Figure 1. Schematic of synthesis route of BPLP-PLGA.

Conclusions: We have synthesized biodegradable photoluminescent polylactone exemplified by BPLP-PLA and BPLP-PLGA copolymers without using photobleaching organic dyes or cytotoxic quantum dots. These polymers showed tunable photoluminescence, mechanical properties and degradation rate. The introduction of BPLP in polylactones did not comprise their cytocompatibility and represents an innovation on the widely used FDA-regulated polylactones. BPLPL should serve as promising candidates in many biomedical applications where fluorescence imaging and sensing have gained increasing roles.

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References: 1. Yang, J., et al., Development of aliphatic biodegradable photoluminescent polymers. Proc. Nat. Acad. Sci., 2009. 106: p10086-10091.