Methodology of Biodegradable Photoluminescent Polymer Development

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Statement of Purpose: Biodegradable polymers have been made into theranostic nanoparticles conjugated/encapsulated with imaging agents for targeted cancer drug delivery and diagnosis. The traditional fluorescence imaging agents including organic fluorescence dyes and inorganic quantum dots bring concerns on photobleaching or toxicity thus preventing them from being used in *in vivo* bioimaging. In order to obtain in-situ and real-time information on the scaffold degradation and tissue infiltration/regeneration in vivo without traumatically explanting samples or sacrificing animals, it is expected that the biodegradable polymers used in tissue engineering should serve as not only suitable implant materials, but also as non-invasive *in vivo* bioimaging probes. However, such degradable polymers have not been previously reported. None of the previous biodegradable polymers can intrinsically emit fluorescence for *in vivo* imaging without using exogenous organic dyes or quantum dots. Given the versatile needs for various types of biodegradable polymers in biomedical engineering and biological sciences, we develop a methodology for developing various types of biodegradable photoluminescent polymers and investigate the micro/nanofabrication and their bioimaging applications *in vitro* and *in vivo*.

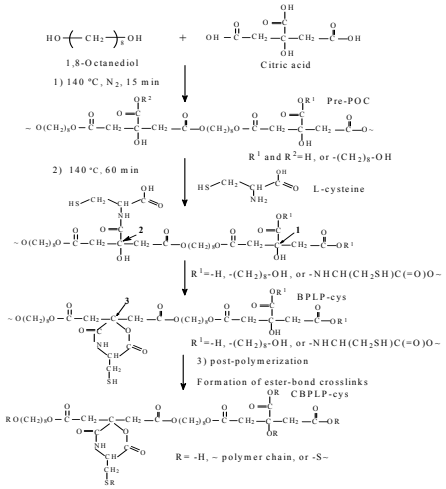

Fig. 1 Synthesis of representative BPLPs.

Methods: We have recently synthesized a series of biodegradable photoluminescent polymers (BPLPs) based on citric acid, 1, 8-octanediol, and 20 essential amino acids via a convenient condensation reaction (Fig. 1).[1] BPLPs can be further thermally crosslinked into elastomeric BPLPs. These polymers offer advantages over traditional organic fluorescent dyes due to high quantum yields (up to 62.33%), tunable fluorescence emission (up to 725 nm), photostability, excellent cytocompatibility *in vitro*, and minimal chronic inflammatory responses *in vivo*. It was believed that the formation of a 6-member ring when the carboxylic acid, alpha carbon, and amino moieties of the amino acid bend back to join the polymer backbone was responsible for the unique fluorescence properties (Fig. 1). The amino acid side chain influences both fluorescence frequencies and quantum yield. In this paper, we designed multiple types of biodegradable photoluminescent polymers by introducing the 6-member ring structure in the polymer designs.

Results: *Synthesis of water-soluble BPLP (WBPLP):* In order to obtain a water-soluble BPLP, the 1,8-octanediol has been replaced by polyethylene glycol. The hydrophilicity of PEG segment ensures the water-solubility of WBPLP. PEGs with different molecular weight have been used for synthesis. *Synthesis of photocrosslinkable BPLP (PCBPLP):* In order to make the BPLP photocrosslinkable, the double bond containing monomer, maleic acid has been incorporated into BPLP. Citric acid has been partially replaced by maleic acid. The double bond containing polymer chain can be crosslinked by different initiators including photoinitiators and redox initiators. *Synthesis of urethane doped BPLP (UBPLP):* The extension of a polyester chain with diisocyanate has been proven to be an effective way to increase the mechanical property of the polymer.[2] The BPLP has been extended with 1,6-Hexamethylene diisocyanate (HDI). Different molar ratios between BPLP and HDI have been used. UBPLP shows a tensile mechanical strength up to 50 MPa and an elongation up to 400%. BPLP, WBPLP, PCBPLP, and UBPLP all emit fluorescence brightly at various wavelengths. BPLPs can be made into nanoparticles (biodegradable polymeric "quantum dots") for cellular labeling and imaging. We further demonstrated that BPLP nanoparticle-labeled cells and 3-D porous tissue engineering scaffolds could be imaged *in vitro* and *in vivo*.

Conclusion: We have developed a methodology to synthesize various types of biodegradable photoluminescent polymers by introducing a fluorescent 6-member ring in polymer designs. This methodology enables us designing biodegradable photoluminescent polymers with desired functionalities (mechanical properties, degradability, and photoluminescence) at will. The development of biodegradable photoluminescent polymers holds great promises in theranostic drug delivery, fluorescence-based sensing and detection, and tissue engineering.

References:

1. Yang J. Proc Nat Acad Sci USA. 2009;106;10086-10091.
2. Dey J. Biomaterials 2008, 29: 4637-4649.