Biodegradable Thermal-Responsive Dual-Imaging Enabled Nanoparticles

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Statement of Purpose: Current cancer management is dedicated in developing new techniques for earlier diagnosis and controlled drug delivery. Common diagnostic modalities such as magnetic resonance imaging (MRI), positron emission tomography, and optical imaging all individually have different limitations such as low sensitivity, low spatial resolution, toxicity of contrast agents, and inaccurate diagnosis. Dual-/multi-modal imaging systems may overcome these limitations by taking advantages of various individual techniques. For instance, MRI provides exceptional tissue contrast, penetration depth, and high spatial resolution, whereas fluorescence imaging provides high sensitivity. Previously, we have developed the first biodegradable photoluminescent polymers (BPLP) that can be used as a imaging agent and a carrier for contrast agents and drugs [1, 2]. In addition, thermal responsive polymers such as polyvinylcaprolatam (PVCL) have been widely used as smart materials to control drug delivery in response to the environmental stimuli. In this study, we develop BPLP-PVCL copolymer into biodegradable multifunctional nanoparticles (NPs) capable of MRI, fluorescence imaging, and temperature-controlled drug release. These NPs are expected to aid in the detection of cancers at their early stages and to achieve higher therapeutic efficiency.

Methods: First, BPLP was synthesized using PEG200, citric acid, and L-serine following our previously developed protocols [1]. Further, conjugation of BPLP with allylamine was performed using the carbodiimide chemistry. BPLP-Allylamine was added into water solution with VCL, SDS and bisacrylamide. Gadolinium (Gd)-loaded nanogels were prepared by adding Gd-diethylene triamine pentaacetic acid and sonicating the mixture to homogeneity. Thereafter, free radical polymerization was conducted under nitrogen for 4 hours. The end product was dialyzed and lypholized to obtain BPLP-PVCL/Gd NPs. Resulting NPs were subjected to FTIR, TEM, and DLS measurements. Fluorescence spectroscopy, confocal microscopy, and MRI phantom imaging were used to identify the dual-imaging capabilities. In vitro cytotoxicity, cell uptake, drug release, and phamarceutical effects were also performed.

Results: BPLP-PVCL NPs was synthesized by emulsion polymerization. The compositions of the copolymers were confirmed by FTIR. The sizes of BPLP-PVCL NPs are in the range of 200nm-250nm, and they are stable in serum and PBS solutions. Two different NPs with lower critical solution temperatures (LCSTs) at 41 and 45°C were synthesized, namely BPLP-PVCL41 and BPLP-PVCL45. Upon being heated above LCSTs, both BPLP-PVCL nanoparticle suspensions turn into turbidity. Both nanoparticles exhibited strong fluorescence (Fig.1). After 4 weeks of incubation in PBS, both NPs lost more than 40%wt. BPLP-PVCL NPs exhibited no significant toxicity with concentrations lower than 250μg/ml to fibroblasts and normal prostate epithelial cells. *In vitro* studies showed that prostate cancer cells PC3 were able to uptake our NPs, while BPLP-PVCL41 showed relatively higher uptake efficiency. Both fluorescent confocal imaging and MR phantom imaging (Fig.1) demonstrated that our biodegradable NPs were able to label PC3 cells. In addition, doxorubixin was loaded within NPs. The rates of drug release were higher at a temperature higher than the LCSTs, which are higher than physiological body temperature. Drugs released from NPs were also effective to kill prostate cancer cells *in vitro*.

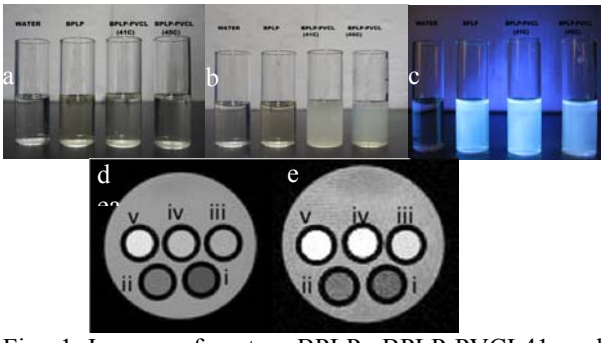

Fig. 1 Images of water, BPLP, BPLP-PVCL41 and BPLP-PVCL45 solutions under (a) 25°C, (b) 45°C, and (c) UV light. (d) and (e) are MR phantom images of BPLP-PVCL41 and BPLP-PVCL45 with Gd loaded. iii, iv, v are nanoparticle concentrations of 0.5, 1, and 2 mg/ml. i and ii are controls without Gd.

Conclusions: We synthesized biodegradable fluorescent thermo-responsive nanoparticles by copolymerizing BPLP and PVCL. These cytocompatible degradable nanoparticles showed dual-imaging modalities to label cancer cells as well as temperature-triggered drug release profiles. BPLP-PVCL nanoparticles are promising candidates for theranostic drug delivery.

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References: 1. Yang, J., et al., Proc. Nat. Acad. Sci., 2009. 106: p10086. 2. Wadajkar, A.S. et al. Adv. Healthcare Mat., 2012. 1: p450.