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Synthesis of Poly (Styrene Sulfonate) Coated Gd^{3+} Poly (Lactide-Co-Glycolic Acid) Perfluoro Bromide Nanoparticles for Stem Cell Monitoring Using Magnetic Resonance Imaging

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Abstract. *Magnetic resonance imaging (MRI) is one of best imaging technologies to monitor transplanted stem cells, because of its high anatomical resolution and safety. In this study, we aim to synthesize Poly (styrene sulphonate) coated Gd^{3+} - Poly (lactide co glycolic acid) Perfluorooctyl Bromide nanoparticles (PSS-coated Gd^{3+}@NPs) for stem cell labeling using both ^{1}H and ^{19}F MRI. At a weight ratio 20 of PLGA/ Gd^{3+}, NPs have a spherical shape with the hydrodynamic size at 180 nm with zeta potential at -53 mV. In vitro, we obtain the intended T1 relaxation acceleration of water on ^{1}H MRI. The NPs have low toxicity to the human mesenchymal stem cells (hMSC) up to 1 mg/ml. They could internalize into the stem cells via caveolae-mediated endocytosis efficiently, confirmed by flow cytometry analysis, and gives a good contrast in both channels ^{1}H and ^{18}F MRI scans. In conclusion, our NPs have shown a great potential as a dual-contrast agent in MRI for stem cell monitoring.*

Keywords*: MRI contrast agent, gadolinium, perfluorooctyl bromide, stem cell monitoring*

1. Introduction

Rising incidence of degenerative diseases such as osteoarthritis and neurological disorders has pressed the demand for regenerative therapies in countries with aging population. The treatment of these diseases often consists of several approaches. Among them, stem cell therapy, which involves transplantation of stem cells to the patient, is one of the potential methods in regenerative medicine that could assist the treatment of such diseases. Transplanted stem cells will alter into targeted cells in order to cure and replace the damaged cells. However, for safety and prognostic reasons, the transplanted stem cells need to be tracked and monitored *in vivo*.

Magnetic resonance imaging (MRI) is a versatile imaging technique that provides a tool for monitoring the stem cells after transplantation. Prior to transplantation, stem cells are labeled with contrast agents such as super paramagnetic iron oxides nanoparticles (SPION), Gadolinium containing compounds, or fluorinated nanoparticles in order to be detected using MRI [1-4]. Among these three contrast agents, SPION is mostly used for its high sensitivity in ^{1}H MRI and its ability to create a negative contrast (darkness) in the images. However, the signal of the SPION labeled stem cells can be confused with other tissues having inherently low T2 relaxation times, such as hemorrhage, bone, and air. Moreover, the magnetic susceptible effects of SPION labeled cells can also result in a blooming artifact that surpasses the size of an individual cell, thereby obscuring surrounding anatomy [5-7]. Alternatively, the use of Gadolinium-chelates, which are commonly used intravenous contrast agents to create positive contrast (brightness) in ^{1}H T1 weighted MRI, poses some challenges for medical applications due to their low sensitivity, weak uptake efficiency, and the high toxicity of Gd^{3+} chelates [4]. Fluorinated compounds, usually called tracers rather than contrast agents, provide high nuclear magnetic sensitivity [8-10] without exerting interference with the intrinsic signal sources.

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