Title: Lanthanide nanoparticles as vascular contrast agents for micro-CT

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Structured Abstract:

Introduction

Vascular development is extensively studied in small animals. Micro-CT is routinely used to study the vasculature and it requires a high-attenuating contrast agent to remain in the blood pool during in vivo imaging (i.e. tens of minutes). This can be achieved by using polymer-encapsulated nanoparticles exceeding 10 nm in diameter. Although nanoparticle agents exist for micro-CT, they are predominantly based on iodine, which has a low atomic number. Superior CT contrast can be achieved using lanthanides (e.g. Er). While lanthanide-based contrast agents are used clinically in MRI, they are composed of small molecules (<1 nm) that exit the blood pool of small animals within seconds. Thus, the purpose of this work is to develop and characterize an in vivo vascular contrast agent composed of polymer-encapsulated erbium nanoparticles (ErNP) exceeding 10 nm in size.

Methods

A series of polymers were studied to identify and prepare ErNP that remained stable in a mouse blood mimic and had comparable Er content as commercially-available agents (i.e. 100 mg/mL). The ErNP size and Er content were characterized using standard chemical techniques.

Using 0.2 mL of the ErNP (100 mg/mL of Er) dissolved in normal saline, male C57BL/6 mice (m=25-30 g) were injected subcutaneously (n=2) and intravenously (n=3) via the tail vein. The animals that were injected subcutaneously were sacrificed for gross tissue examination.

The biodistribution of the ErNP was observed by micro-CT. Micro-CT images were obtained using the GE Locus Ultra (London, ON), where 1000 views (16 ms per view) were acquired at 80 kVp, 55 mA over 360° and reconstructed using a cone-beam reconstruction algorithm to a voxel size of 150 × 150 × 150 μm. Images were analyzed using MicroView (Parallax Innovations, London, ON) and CT contrast was reported in Hounsfield Units (HU).

Results

The synthesized ErNP had an average size of 171 ± 3 nm with low size dispersity, which was confirmed by microscopy. The optimized formulation was also measured to be able to encapsulate 100 mg/mL of Er.

After subcutaneous administration, the ErNP remained to localize in the injection site for up to a week. No signs of irritation or necrosis were observed in the subcutaneous tissue upon gross examination. In the blood pool of the animals that were intravenously injected, contrast enhancements of over 250 HU were observed for up to an hour.

Discussion

ErNP that were larger than 10 nm in size with high Er loading were successfully synthesized. The ErNP did not irritate subcutaneous mouse tissue for up to a week, and remained stable and inert. In the blood pool, contrast enhancement was observed for up to an hour, which exceeds in vivo micro-CT requirements. This work represents the development of the first lanthanide-based contrast agent that is targeted for in vivo micro-CT. No such agent has been synthesized previously.