Novel Solid Lipid Nanoparticles (SLNs) Encapsulated with Gd-DOTA for Contrast-Enhanced MRI

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Introduction: Solid lipid nanoparticles (SLNs) have emerged as an efficient, non-toxic, and versatile colloidal drug carrier system that avoids some of the disadvantages of liposomes and polymeric nanoparticles. Because SLNs are composed of physiological lipids, they tend to show high compatibility and biodegradability and have lower risk of the acute and chronic toxicity that is often associated with polymeric nanoparticles. Also, because SLNs are comprised of a solid lipid core instead of an aqueous core, they offer better protection against chemical degradation to their drug cargo than liposomes, and also facilitate sustained drug release due to the zero-order kinetic breakdown of the solid lipid matrix[1]. While many studies have reported SLN encapsulation of therapeutic agents, very few have reported encapsulation of diagnostic agents, especially those for imaging applications[2]. Using a water/oil/water (W/O/W) microemulsion method, we have encapsulated Gadolinium-DOTA (Gd-DOTA), a T1-weighted contrast agent, into SLNs. We have previously shown that these SLNs have a longer blood half-life in mice compared to free Gd-DOTA. Intracerebroventricular (ICV) injection of the Gd-loaded SLNs in mice confirms the ability for these particles to shorten T1 and provide positive contrast *in vivo* using T1-weighted imaging.

Methods: Gd-DOTA was loaded into SLNs using a water/oil/water (W/O/W) microemulsion method[3] and the resulting SLNs were characterized with dynamic light scattering (DLS) for size determination, with inductively coupled plasma mass spectrometry (ICP-MS) for Gd content, and with a Bruker Minispec relaxometer (1.4T, 37°C) for relaxivity properties (r1). T1-weighted MRI (3D gradient echo images, TR/TE/Alpha = 25/2/30°, 156 x 156 x 203 μm^3, 7T Varian) was then used to observe the positive contrast enhancement generated after ICV injection of Gd-loaded SLNs.

Results: DLS measurements have verified a size-controllable synthesis of a Gd-loaded SLNs with a unimodal, Gaussian distribution (Fig. 1a) using a modification of the W/O/W method[4], and have also confirmed the size stability over time in solution (Fig. 1b). ICP-MS analyses of dialysis experiments have confirmed that Gd-DOTA is not being released from the SLN matrix over time in the absence of brain lipases (Fig. 1c). ICP-MS has also confirmed a Gd-DOTA:lipid molar ratio = 0.09 ± 0.03 after Gd-DOTA encapsulation into SLNs. Relaxivity measurements (1.4 T, 37°C) indicate a smaller r1value (~2.5 $mM^{-1}sec^{-1}$) for the Gd-loaded SLN in comparison to free Gd-DOTA (~3.5 $mM^{-1}sec^{-1}$), which can likely be attributed to the inaccessibility of water to Gd-DOTA when encapsulated inside the SLN core. ICV injection of the Gd-loaded SLNs confirms the ability for these particles to provide positive contrast enhancement *in vivo* with T1-weighted MRI (Fig. 1d,e).

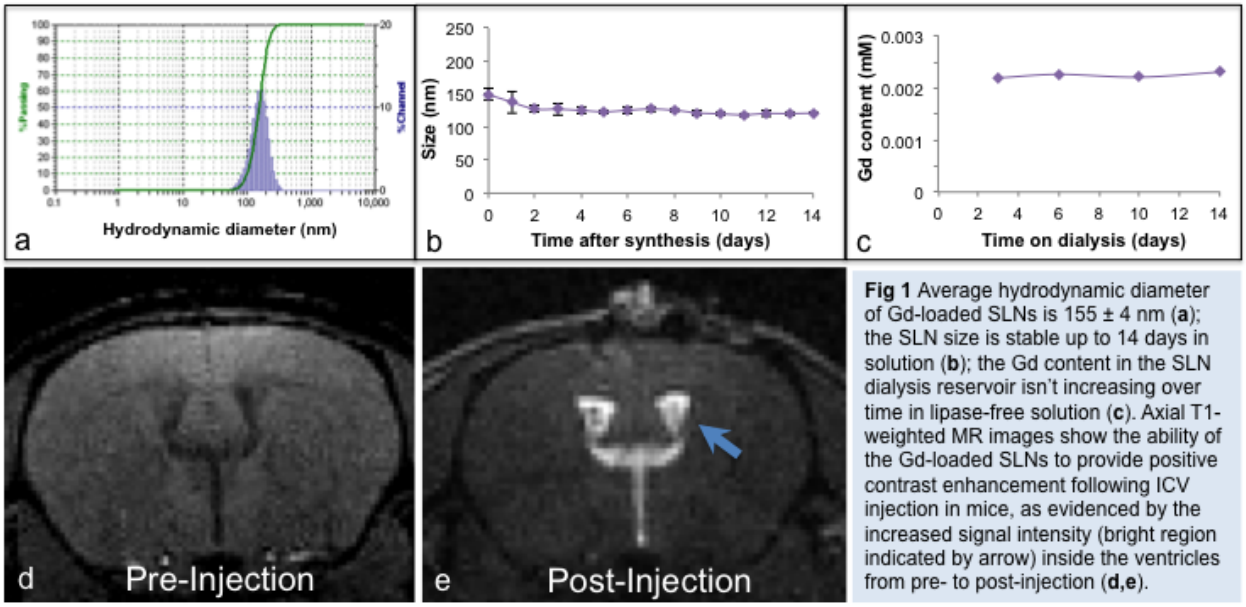

Fig 1 Average hydrodynamic diameter of Gd-loaded SLNs is 155 ± 4 nm (**a**); the SLN size is stable up to 14 days in solution (**b**); the Gd content in the SLN dialysis reservoir isn't increasing over time in lipase-free solution (**c**). Axial T1-weighted MR images show the ability of the Gd-loaded SLNs to provide positive contrast enhancement following ICV injection in mice, as evidenced by the increased signal intensity (bright region indicated by arrow) inside the ventricles from pre- to post-injection (**d**,**e**).

Conclusions: We showed that SLNs can be loaded with Gd-DOTA and can shorten T1 to provide T1-weighted contrast *in vivo*. These Gd-loaded SLNs show different relaxivity (r1) and blood clearance properties than free Gd-DOTA. Serving as stable, long-circulating, biocompatible T1 contrast agents, these Gd-loaded SLNs offer the potential to facilitate T1-weighted imaging *in vivo* for a wide variety of applications. Furthermore, these SLNs can be radiolabeled[4] to provide high-sensitivity, high-resolution dual-modality diagnostics with positron emission tomography (PET) and magnetic resonance imaging (MRI).

References/Acknowledgements: [1]Kaur, I.P., et al., *Journal of Controlled Release*, 2008. [2]Blasi, P. et al., *Adv Drug Deliver Rev*, 2007(6), 454. [3]Zhen, L. et al., *Chem Res Chinese* U, 2010. [4]Andreozzi, E. et al., *Bioconjugate Chemistry*, 2011. We thank the France-Berkeley Fund for their financial support.