Towards the Implementation of Hyperpolarized, Functionalized Silicon Nanoparticles as In Vivo Colorectal Molecular Imaging Agents

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Purpose: There is an ever-growing need for accurate and effective colonoscopies to detect inflammation and neoplastic growths in the lower gastrointestinal tract, such as polyps, diverticulosis, and cancer. Conventional colonoscopies carry risks of gastrointestinal perforation and are often limited by individual patient tolerance. While 'virtual' colonoscopies are non-invasive, they are limited by radiation exposure, movement artifacts and low sensitivity due to susceptibility gradients caused by air-tissue interfaces. Very recently *in-vivo* MR imaging of hyperpolarized ^{29}Si nuclei in silicon nanoparticles (SiNP) has been demonstrated [1]. In this technique, the hyperpolarization (HP) of the ^{29}Si nuclear spins is generated by low temperature dynamic nuclear polarization (DNP) and takes advantage of electronic defect sites that naturally occur at the surface of the SiNPs, so no additional radicals are required for HP [2]. SiNPs have extremely long spin-lattice relaxation times that range from minutes to many hours depending on particle size and materials properties [3] and the polarization characteristics do not appear to be affected by surface functionalization or the *in-vivo* environment. SiNPs are being investigated for many biomedical applications due to their favorable *in-vivo* biocompatibility and biodegrability [4] and are amenable to a range of surface modification techniques for drug loading and targeting [5]. The HP process increases the detection sensitivity by ~4-5 orders of magnitude and this, coupled with the abnormally long signal decay time (~40 minutes, allowing a >1 hour time window for imaging) [1], makes hyperpolarized SiNPs uniquely capable of serving as high-impact MRI contrast agents. We aim to further develop HP SiNPs as viable molecular imaging agents for the early diagnosis of colorectal polyps and tumors.

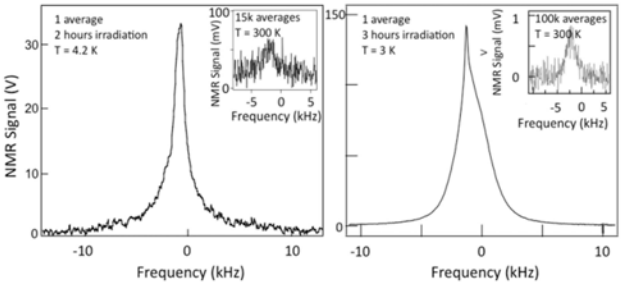

Fig. 1. Low temperature ^{29}Si NMR spectra of HP SiNPs with sizes (a) d_0 ~60 nm (b) 2 um. *Insets*: thermally polarized signal showing ~10^3 enhancement in SNR.

Methods: We have investigated a range of commercially available SiNPs with varying average mean diameters (~20 nm to ~2 um). The particles are surface functionalized with aminopropyltriethoxysilane (APTES) and polyethylene glycol (PEG) to improve biocompatibility. The reactive amine group on the APTES molecule allows for further functionalization steps for targeting. A home-built DNP polarizer, with *in situ* NMR spectroscopy to monitor polarization dynamics, is located adjacent to an animal MRI system (7T Bruker). ^{29}Si spectroscopy is performed in the polarizer using a saturation recovery sequence. Co-registered [^{1}H:^{29}Si] imaging is performed using a dual coil setup. A ^{1}H volume coil is used for sample placement and anatomical imaging, while a custom built surface coil (38 mm ID) is used for HP ^{29}Si imaging and spectroscopy of the abdominal region of the mouse models. ^{29}Si imaging is performed with a variable flip angle RARE sequence (1.8 ms TE; 6.25 cm FOV; MTX: 32 x 32).

Results: Figure 1 shows HP ^{29}Si spectra for SiNPs 60 nm and 2um in diameter, demonstrating an increase in polarization of at least 3 orders of magnitude. Figure 2 shows ^{29}Si MRI images of a cylindrical phantom of 2 μm SiNPs recorded 0 min (a) and 30 min (b) after the phantom was placed in the imager. A α = 10° pulse was used for (a) while α = 90° pulse was used for (b).

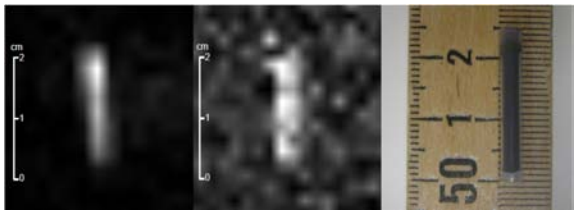

Fig. 2. MRI of HP ^{29}SiNPs (a): immediately after ~4 hrs DNP, and (b): 30 min after (a). RARE sequence with initial 10°(a) and 90° (b) tipping angles. (c) Photo of SiNP phantom.

Discussion: We have successfully hyperpolarized SiNPs ranging in size from 20 nm to 2 um and demonstrated that these particles can be transported to the 7 T imager for imaging without a significant loss of polarization. MRI using the 7 T scanner appears to deliver almost an order of magnitude improvement in SNR when compared to previous studies at 4.7 T for the same polarization parameters due to improvements in electromagnetic shielding. *In situ* NMR of the DNP process will allow additional optimization of experimental parameters, including temperature, microwave frequency (and modulation characteristics), and DNP time for a variety of particle sizes, porosities, and surface functionalities. For animal studies, the functionalized HP SiNPs (~100 mg) will be dissolved in phosphate-buffered saline and injected into murine models with colorectal polyps and tumors [*Lkb 1*$^{+/-}$ and *Apc (min*$^{+}$*)*], as well as normal mice. Early-stage polyps should provide the ideal test bed for demonstrating the efficacy of HP SiNPs for early detection of abnormal growths that may result in colorectal cancer, as well as to probe the transformative phase between polyp and tumor--an important stage that is not currently well-characterized. When translated to the clinic, patients will benefit from reduced incidence of invasive procedures, improved accuracy of active surveillance, and greatly enhanced ability to identify recurrences following treatment.

References: [1] Cassidy, *et al.* (2012); [2] Dementyev, *et al.* PRL (2008); [3] Aptekar, *et al.* ACS Nano (2009); [4] Park *et al.* Nature Materials (2009); [5] Tasciotti *et al.* Nature Nanotechnology (2008).

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