Developing Hyperpolarized Silicon Micro and Nanoparticles for Targeted Molecular Imaging of Ovarian Cancer

Nicholas Whiting[1], Jingzhe Hu[1,2], Niki Zacharias Millward[1], Rajesha Rupaimoole[3], David Gorenstein[4], Anil Sood[3], and Pratip Bhattacharya[1]

[1]*Cancer Systems Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX, United States,* [2]*Department of Bioengineering, Rice University, Houston, Texas, United States,* [3]*Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States,* [4]*Nanomedicine and Biomedical Engineering, The University of Texas Health Science Center at Houston, Houston, TX, United States*

Target Audience: Basic and translational scientists interested in research concerning targeted molecular imaging of different cancer systems using hyperpolarized nuclei.

Purpose: Silicon-based micro- and nanoparticles are well-suited to serve as targeted molecular imaging agents, due to their biocompatibility, biodegradability, and simple surface chemistry that is amenable to drug loading and targeting [1,2]. A method of hyperpolarizing (HP) silicon particles [3], which increases magnetic resonance imaging (MRI) signals by 4-5 orders of magnitude through enhanced nuclear spin alignment, has recently been demonstrated using solid-state dynamic nuclear polarization (DNP). Naturally occurring electronic defects on the particle surface obviate the need for exogenous radicals [4], and the enhanced spin polarization lasts for significantly longer than other hyperpolarized agents (tens of minutes *in vivo*, instead of <1 minute for other hyperpolarized species). Here, we report our recent advances in developing silicon particles as targeted molecular imaging agents for the early diagnosis of ovarian cancer. Early-stage ovarian cancer often goes unnoticed due to the ambiguity of preliminary symptoms and the lack of an effective diagnostic modality; indeed, only about 25% of ovarian cancer cases are detected at a contained stage whereby treatment is most effective [5]. Preliminary *in vivo* studies of orthotopic ovarian cancer murine models examined a variety of particle administration routes in mice, including intraperitoneal, tail vein, and intratumoral injections. Successful demonstration of targeted, long-lived ^{29}Si MR signals *in vivo* will be key to the development of these silicon particles for future clinical use as MRI contrast agents.

^{29}Si Hyperpolarization Decay Times		
SiNP size	**HP T_1**	**DNP time**
20 nm	**~10 min**	**~80 min**
30 nm	**~17 min**	**~120 min**
70 nm	**~16 min**	**~60 min**
2000 nm	**~62 min**	**~300 min**
2000 nm *PEGylated*	**~55 min**	**~330 min**
2000 nm *ESTA-1*	**~56 min**	**~300 min**

Table 1: ^{29}Si polarization decay times for different particle sizes and surface chemistries.

Methods: A range of commercially available silicon particles with varying average mean diameters (~20-2,000 nm) have been investigated. The particles are surface functionalized with aminopropyltriethoxysilane (APTES) and polyethylene glycol (PEG) to improve biodistribution. The reactive amine group on the APTES molecule allows for further functionalization steps for targeting; we are currently pursuing studies that coat the silicon particles with an E-selectin thioaptamer (ESTA-1) functionality that actively seeks out the E-selectin glycoprotein that is overexpressed in the vasculatures surrounding many types of ovarian cancer. For these studies, an orthotopic *HeyA8* ovarian cancer mouse model is used. The home-built ^{29}Si solid-state DNP device is located adjacent to a 7 T small animal MRI system. Co-registered [^{1}H:^{29}Si] imaging is performed using a dual-tuned ^{29}Si/^{1}H Litz coil: *in vivo* ^{29}Si imaging is performed with a RARE sequence (TR/TE: 60 ms/1.8 ms; 6.4 cm FOV; 2 mm resolution), while ^{1}H imaging is performed with a coronal RARE scan (α = 90°), TR/TE: 1800 ms/9.6 ms with a RARE factor of 8; 6.4 cm FOV (0.25 mm resolution).

Results: A variety of particle sizes (20 nm-2 μm) were found to have hyperpolarized relaxation times ranging from ~10-60 minutes. The addition of various functional groups to the particle surface, including PEG and ESTA-1, had no effect on the HP dynamics or relaxation times (Table 1), which appear to be a function of the particle size and purity. Different nanoparticle injection routes have been attempted, including intraperitoneal, tail vein, and intratumoral injection (Fig. 1) for ovarian cancer mouse models.

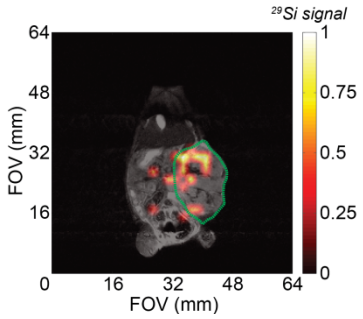

Fig. 1. Co-registered ^{1}H (greyscale) and ^{29}Si (color) MRI 20 minutes after intratumoral injection of ~100 mg of HP ESTA-1 Si particles (dissolved in ~300 μL buffer) into a *HeyA8* orthotopic ovarian cancer mouse model. Green line outlines periphery of tumor mass.

Discussion: The ability to hyperpolarize a variety of sizes of silicon particles with varying surface chemistries increases their viability for targeted molecular imaging. Early proof-of-concept studies used large (2 μm) particles; while these particles provided *in vivo* signals for tens of minutes, their mobility was hampered by their size (and they often settled near the injection site). Indeed, tail-vein injections of large particles were shown to be unviable due to vein obstruction. Recently, we have implemented and characterized smaller (<100 nm) particles that should prove to have greater mobility for *in vivo* studies. The primary barrier to using smaller particles has been a lack of surface defects to provide the free electrons necessary for DNP; we are actively working to remedy this through a collection of chemical and physical treatments.

Conclusion: We present our most recent work developing different sizes of silicon particles for targeted molecular imaging. When fully developed, these particles are engineered to be a platform system, where different targeting agents and therapeutic drugs can be attached for advanced molecular imaging and therapeutic interventions in the clinic.

References: [1] Park, *et al.* Nat. Mat. (2009); [2] Tasciotti, *et al.* Nat. Nano. (2008); [3] Cassidy, *et al.* Nat. Nano. (2013); [4] Dementyev, *et al.* Phys. Rev. Lett. (2008); [5] Han, *et al.* Cancer Res. (2006).

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