

# The Effects of Morphology on Mesoporous Silica Nanoparticles as a Targeted Theranostic for Breast Cancer

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**Statement of Purpose:** Breast cancer is the second leading cause of cancer-related death in the United States; over 230,000 new cases were diagnosed and nearly 40,000 women died of the disease last year [1]. Early detection by mammography has been shown to decrease mortality rates 15–25%, and is recommended for women over 40 [2]. However, mammography uses ionizing radiation, a well-known risk factor for cancer, and is not sensitive for patients with dense breast tissue such as younger women [3]. While ultrasound (US) is widely used as a follow-up to mammography, it has low specificity and often requires the use of an ultrasound contrast agent (UCA) [4]. For lesions that remain ambiguous after mammography and standard US screening, contrast enhanced US using UCAs has been posed a solution. Current FDA-approved UCAs have short half-lives *in vivo* (tens of minutes) and are unstable during insonation, precluding longer-term use in the body [4]. Development of a tumor-targeting UCA with a prolonged half-life *in vivo* may enable the use of US as a standalone diagnostic and real-time imaging modality for long-term tracking of tumor response to therapy. Because mesoporous silica nanoparticles (MSNs) are inorganic, solid, and highly porous, they have been the subject of recent studies for use as a long-lasting *in situ* UCA [5–10]. Here, the ability of MSNs to serve both as a tumor-targeted UCA and therapeutic agent (“theranostic”) is explored. Specifically, MSNs of different morphology are investigated for their ability to provide US contrast using a clinical US machine. Next, MSNs are conjugated to the HER2-overexpressing tumor-specific antibody Herceptin® to confirm tumor-targeting therapeutic effects. **Methods:** Agar ultrasound phantoms were used to investigate the US contrast generated by different types [MCM-41 (flake morphology) and spherical] of MSNs. MSNs were gently aspirated into cooling agar. Phantoms were imaged using clinical US, and the mean pixel intensity (MPI) of images was analyzed using ImageJ software. The MSN type giving the greatest MPI (greatest US contrast) was selected for conjugation to Herceptin® (MSN-Herceptin) and incubated with HER2-overexpressing (HER2+) and HER2-nonoverexpressing (HER2-) breast cancer cells; confocal fluorescence microscopy was performed to show specific binding and internalization of MSN-Herceptin to HER2+ cells; ethidium homodimer (EthD) assay determined cytotoxicity. *Spherical MSNs are the kind gift*

*of Dr. Brian Trewyn, Colorado School of Mines. Results:* Clinical US techniques showed MSNs provide increasing MPI with increasing concentration (Fig. 1); MSN morphology appears to have a significant effect on MPI (Fig. 2). In preliminary studies with MCM-41 MSNs, confocal fluorescence microscopy demonstrated significantly increased specific localization and binding of MSN-Herceptin to HER2+ versus HER2- cells; EthD assay indicated cytotoxicity of MSN-Herceptin to HER2+ cells (data not shown). **Conclusions:** Flake morphology MSNs are demonstrated as a stable, biocompatible and effective theranostic agent for US-based breast cancer imaging, diagnosis and treatment. **References:** [1] American Cancer Society. Breast cancer facts & figures 2013-2014. Atlanta, GA, 2013. [2] Weinberg RA. The biology of cancer. Garland Science, Taylor and Francis Group, LLC, 2007. [3] National Cancer Institute. PDQ® breast cancer treatment. Bethesda, MD, 2013. [4] Hahn MA. Anal Bioanal Chem. 2011;399:3-27 [5] Liu J. Phys Med Biol. 2006;51:2179-2189 [6] Liu J. Phys Med Biol. 2007;52:4739-4747 [7] Liong M. ACS Nano. 2008;2:889-896 [8] Casciaro S. Invest Radiol. 2010;45:715-724 [9] Liu YT. Int. J Pharm. 2011;421:370-378 [10] Liberman A. Biomaterials. 2012;33:5124-5129

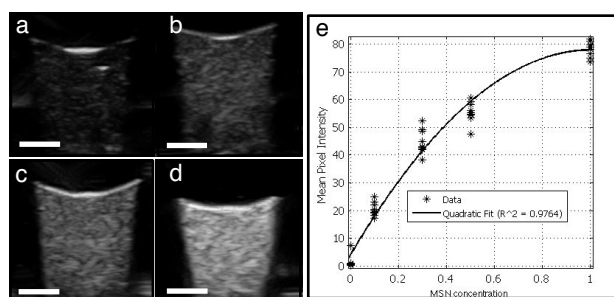


Fig. 1. Phantoms with MCM-41 MSNs at (a) 0.1, (b) 0.3, (c) 0.5, and (d) 1.0 mg/ml. (e) A quadratic polynomial fits MPI-concentration relationship ( $R^2 = 0.9764$ ). Images acquired at 7.5MHz at a depth of 3.5cm. Scale bar: 5mm.

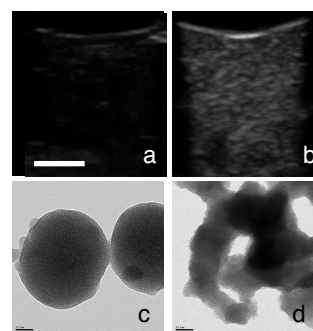


Fig. 2. Phantoms with (a) spherical and (b) MCM-41 MSNs at 0.5 mg/ml, scale bar 5 mm. TEM of (c) spherical and (d) MCM-41 MSNs, scale bar 50 nm.