Optimization of the morphology of multifunctional mesoporous silica nanoparticles to increase therapeutic and diagnostic effects in breast cancer

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Statement of Purpose: Breast cancer is one of the most prevalent carcinomas in the United States affecting over one million women each year [1]. Current chemotherapy treatments can be especially harsh on the body due to the immense cytotoxicity of the chemo-agents and the lack of a targeting modality. Over the past decade, researchers have been utilizing mesoporous silica nanoparticles (MSN) to serve as a drug delivery vehicle in an effort to increase therapeutic effects. Human epidermal growth factor receptor 2 (HER2) is a transmembrane receptor tyrosine kinase which is overexpressed in about 25-30 percent of all human breast cancers [2]. Here, we propose the use of Herceptin (anti-HER2 monoclonal antibody, Genentech) as a targeting moiety, in combination with MSN, to develop a targeted drug delivery vehicle for HER2+ breast cancer. MSN have been successfully utilized as a platform for multifunctional drug delivery/imaging systems. It has previously been shown that MSN-Herceptin produces high-quality ultrasound images; MSN was also shown to aggregate at the site of a tumor tissue and have a longer duration within the body, unlike gas microbubbles [3]. By comparing MSN (e.g. spherical, Sigma-Aldrich MCM-41) and with the conjugation of a fluorocarbon, we hope to optimize both the drug delivery efficiency and ultrasound contrast, maximizing the therapeutic and diagnostic effects.

Methods: Mesoporous silica nanoparticles **(**MSN) are synthesized through a series of condensation reactions. CTAB serves as the surfactant molecule and thus forms a template, around which the TEOS forms a siliceous shell. Surfactant removal results in a porous structure. Surfactant removed MSN were then hydroxylated and further modified with pentaflourophenylpropyl-trimethoxysilane. The remainder of the hydroxyl groups will then be functionalized using aminopropyl triethoxysilane (APTS) in order to successfully conjugate Trastuzumab (Herceptin) to the outer shell of the particles. This step will be performed utilizing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)/ N-hydroxysuccinimide (NHS) chemistry. The structural characterization will then be confirmed with transmission and scanning electron microscopy (TEM/SEM). The functionalization of the particles will then be confirmed by using fourier transform infrared spectroscopy (FTIR). The MSN of different morphologies and MSN conjugated with the fluorocarbon were then compared using ultrasound imaging at varying concentrations of 0 mg/mL, 0.5 mg/mL, 1.0 mg/mL, 2.0 mg/mL, 5.0 mg/mL (in process of optimizing assay). Analysis of mean pixel intensity for each image will be performed using Image J.

Results:

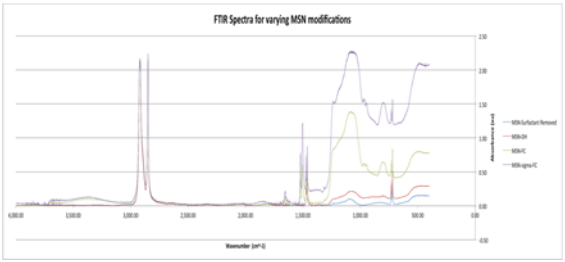

Figure 1. *FTIR Spectra for varied MSN modifications.* FTIR data reveals MSN spherical and Sigma-Aldrich were conjugated to the fluorocarbon.

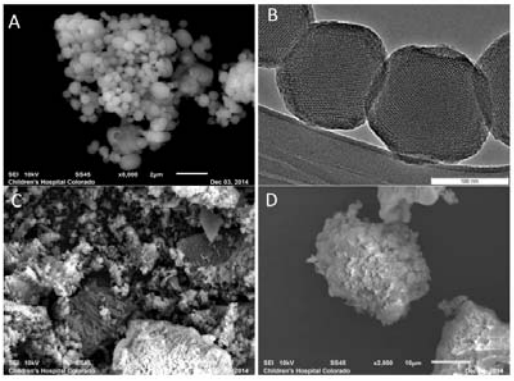

Figure 2. *Scanning and transmission electron microscopy of MSN.* SEM imaging was taken of both spherical MSN (A) and Sigma-Aldrich MCM-41 (C, D). These SEM images reveal a much larger diameter for Sigma-Aldrich MCM-41. TEM imaging of spherical MSN (B) reveals a porous structure with a diameter of ~150-200 nm.

Conclusion: We observed varied differences in morphology and size of spherical MSN and Sigma-Aldrich MCM-41. We are currently optimizing the assay to measure the pixel intensities of both MSN.

References: 1. Nahta, R. Breast Cancer Res, 2006; 8: 215.
2. Colombo, M. Pharm Res, 2010; 62:150-165.
3. Milgroom, A. Colloids and Surf B: Biointerfac, 2014: 116: 652-657.