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Investigating Core-Shell Magnetic Nanoparticles for Hyperthermia Treatment and Imaging of Malignant Neoplastic Tissue

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A. SPECIFIC AIMS

In recent years, the application of magnetic nanoparticles (MNPs) in magnetic fluid hyperthermia (MFH) has emerged as a viable alternative to radiotherapy, chemotherapy, and surgery for the treatment of a wide variety of cancerous tumors. The MFH procedure, which requires raising the temperature of the tumor to 42 – 45^{o} C, has become more prevalent in Europe and Asia as compared to the rest of the world. Current treatments typically use superparamagnetic iron oxide nanoparticles (SPIONs) as the magnetic mediator; however, in today's day and age where efficiency is always a matter of concern, there is a push for multi-purposed materials. It has been found that a core-shell nanoparticle system has the capability to generate a larger specific absorption rate (SAR) than standard nanoparticles [1]. We proposed to develop core-shell magnetic nanoparticles consisting of a gadolinium-doped iron-oxide core surrounded by an iron-oxide shell which will have properties not only suited for use as agents in MFH, but also as contrast agents for magnetic resonance imaging (MRI)

The concept of MFH is based on the high heat-sensitivity of malignant neoplastic tissue when compared to that of normal human cells. For local magnetic fluid hyperthermia, MNPs in a carrier fluid are delivered to the tumor site via direct injection or targeted to the site through the use of tumor specific antibodies. Once inside the tumor, the nanoparticles are exposed to an alternating magnetic field which causes heating of the MNPs due to magnetic relaxation (both Néel and Brownian mechanisms) as well as hysteretic losses. Such a rise in temperature is enough to kill cancer cells while leaving healthy tissue unharmed.

Specific Aim #1: Development of a method to synthesize $Fe_{3-x}Gd_xO_4/Fe_3O_4$ core/shell nanoparticles (CSNPs). Our plan is to develop a method by which $Fe_{3-x}Gd_xO_4$ magnetic nanoparticles synthesized through a standard coprecipitation method can be coated with an Fe_3O_4 shell. The purpose of this is to develop a core/shell system which has increased magnetic susceptibility due to the presence of gadolinium but preserves the biocompatibility of Fe_3O_4-based systems.

Specific Aim #2: Investigation of the structural characteristics of the synthesized $Fe_{3-x}Gd_xO_4/Fe_3O_4$ samples. The $Fe_{3-x}Gd_xO_4/Fe_3O_4$ CSNPs will be characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) for phase identification as well as the determination of particle morphology.

Specific Aim #3: Investigation of the magnetic properties of the proposed nanoparticles through the use of dc- and ac-magnetometry. In order to determine the magnetic properties of the $Fe_{3-x}Gd_xO_4/Fe_3O_4$ CSNPs we will perform temperature-dependent magnetic experiments using the magnetometers of our collaborators at South Dakota State University and Wayne State University

Specific Aim #4: Investigation of the magnetic heating of an aqueous suspension of the nanoparticles under an alternating magnetic field. These studies must be performed for a number of reasons which include the determination of the temperature dependent specific absorption rate (SAR) of the aqueous $Fe_{3-x}Gd_xO_4/Fe_3O_4$ CSNP solution.

Specific Aim #5: Specific Aim # 5: To investigate image contrast properties in magnetic resonance imaging. Using the Magnetic Resonance Imaging capabilities of our collaborators (Insight Institute for Neurosurgery and Neuroscience) we plan to perform *in vitro* investigations of how aqueous solutions of $Fe_{3-x}Gd_xO_4/Fe_3O_4$ CSNP may provide contrast enhancement in functional magnetic resonance imaging.

B. BACKGROUND AND SIGNIFICANCE

Magnetic hyperthermia has been widely considered as a possible non-invasive treatment for cancerous solid tumors since its introduction in 1957 when Gilchrist *et al* [2] used 20—100 nm particles of γ-Fe_2O_3 in conjunction with an alternating magnetic field in the MHz range to heat various tissue samples. In broad terms, MFH involves the dispersion of magnetic nanoparticles throughout a tumor site and the exposure of these nanoparticles to a small (~10^{-3} T) time-varying magnetic field in the RF range. The relaxation of the magnetic nanoparticles into the field causes dispersion of heat due to various methods of energy loss (Néel relaxation, Brownian relaxation, hysteretic losses, etc.). This heat is conducted to the nearby cancerous tissue whereby, if the temperature can be maintained above a threshold of 42˚C – 46˚C for a time of not less than 30 minutes, the cancer will be destroyed via necrosis, coagulation and carbonization. The most commonly used materials for this treatment are mono-metallic oxides such as γ-Fe_2O_3 and Fe_3O_4 (because of their abundance and biocompatibility.

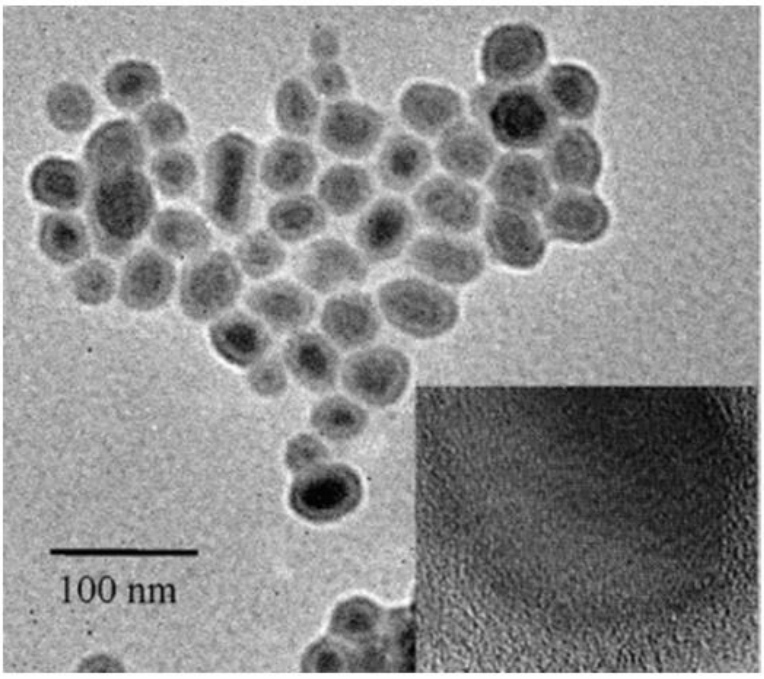

Figure 1. A TEM micrograph of α-MnAs/β-MnAs core/sehll nanoparticles synthesized by the reaction of triphenylarsine oxide and dimanganesedecacarbonyl in the presence of trioctylphosphine oxide. *Taken from K Senevirathne, R. Tackett, PR Kharel, G Lawes, K Somaskandan and SL Brock, ACS Nano 3(5), 1129 (2009).*

In general, heat production via magnetic materials in alternating magnetic fields arises due to two general classes of materials: multi-domain ferro(ferri-)magnetic systems and single-domain superparamagnetic systems. In the former, heat production originates primarily through hysteretic power losses. For superparamagnetic nanoparticles, heating is accomplished through losses as the particles' superspins align with the external field through the Néel mechanism (rotation of the magnetic moment within a fixed particle) and Brownian motion (physical rotation of the particle with a fixed moment), the latter of which can contribute to the dissipation of energy by means of friction [2]. Typically, MFH is accomplished using superparamagnetic iron oxide nanoparticles or SPIONs (Fe_3O_4 and γ-Fe_2O_3) due to their relative biocompatibility [4 – 8]; however, the specific absorption rate (SAR) of magnetic liquids based on these materials is limited by their saturation

magnetization. It is our hope that through doping the core with gadolinium we can increase the saturation magnetization of the particles while preserving their biocompatibility and also provide a material that can be used not only for MFH but for MRI contrast enhancement as well (many MRI contrast agents are based on gadolinium chelates [9]).

C. SUMMARY OF EXPERIMENTAL DESIGN AND METHODS

Synthesis of multicore nanoparticles. The synthesis of $Fe_{3-x}Gd_xO_4$ magnetic nanoparticles nanoparticles will be accomplished via the wet-chemical coprecipitation of iron and gadolinium salts. The resulting powders will then be coated with Fe_3O_4 through various methods outlined in the literature to determine the best suited method for our purpose [10 – 13].

Structural and morphological characterization. Samples synthesized via the method above will be analyzed through x-ray diffraction in order to confirm the structural nature and average size of the nanoparticles. In addition, scanning and transmission electron microscopy will be used to further investigate the phase and morphology of the samples.

Magnetic characterization. Using a Quantum Design Model 6000 Physical Properties Measurement system (at Wayne State University) and a Quantum Design Versalab magnetometer (South Dakota State University), we will investigate the ac- and dc- magnetic properties of the synthesized samples. We will specifically look at the temperature-dependent properties in order to determine the Curie temperature of the samples.

Analysis of the heating characteristics. The heating characteristics of each sample will be measured using Kettering University's Ambrell EASYHEAT system. Specifically, we are interested in determining two main points: The specific absorption rate (SAR) of the sample as it heats from room temperature, and the samples ability to hold a constant temperature in the range of 42—46˚C while constantly being driven by the ac magnetic field. The SAR is defined to be the power dissipated by a magnetic material subjected to an alternating magnetic field. For MFH, the SAR is related to the specific heat of the solvent in which the magnetic nanoparticles are suspended, the weight fraction of the magnetic element, and the slope of the temperature vs. time curve.

D. POTENTIAL SOURCES OF EXTERNAL FUNDING

The preliminary data obtained from this project presents itself well to solicitation of funds from both the National Institutes of Health (NIH) and the National Science Foundation (NSF). For example, the Biomaterials program (BMAT) within the NSF's Division of Materials Research (DMR) which supports fundamental research related to (1) biological materials, (2) biometric, bioinspired, and bioenabled materials, (3) synthetic materials intended for applications in contact with biological systems, and (4) the processes through which nature produces biological materials (taken from www.nsf.gov) would be ideal sources of future external funding for this research.

E. BUDGET

We anticipate the following expenses for this project

Budgeted Item	Amount
Undergraduate Research Assistantships	$4,000.00
Materials and Lab Supplies	$1,500.00
Publication Charges	$500.00
TOTAL	$6,000.00

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