Title: Full Project B: *In Vivo* Assessment of Localized Magnetic Fluid Hyperthermia For Ovarian Cancer Treatment

Co-Leaders: Madeline Torres, Ph.D., Professor, Department of Chemical Engineering, UPR-Mayaguez Campus
Anil Sood, Ph.D., Professor, Gynecologic Oncology and Reproductive Medicine, MDACC

ABSTRACT

Hyperthermia induced by magnetic nanoparticles in high frequency alternating magnetic fields (AMF), or **Magnetic Fluid Hyperthermia (MFH)**, is based on the delivery of thermal energy at the nano-scale to tumors using iron oxide based magnetic nanoparticles (MNP) and an externally applied AMF. This phenomenon is the result of particle rotation or movement of the magnetic dipole. The fact that energy is only dissipated under high-frequency and moderate amplitude fields that can be constrained to the tumor region make *MFH a highly promising form of non-invasive, externally activated cancer treatment.* To this date, the prevailing paradigm in the field is that delivery of nanoscale particles to tumors can be achieved by passive targeting due to the enhanced permeation and retention (EPR) effect. However, *in vivo* experiments tumors suggest otherwise,1-3 thus, posing potential limitations on the successful translation of such systems to the clinic. The aforementioned discrepancy reveals a need to understand the *in vivo* spatial and temporal behavior of nanoparticles as a result of their surface physicochemical properties. To our knowledge, the relationship between surface properties and the resulting temporal and spatial behavior has not been investigated in orthotopic mouse models of cancer.
The long-term goal of this project is to develop MNPs as a clinically feasible tool by providing a comprehensive understanding from fundamental particle design to clinical application. The main objective of this proposal is to pursue the optimization of the spatial and temporal behavior of Magnetic Nanoparticle Heaters (MNH) and perform an *in vivo* efficacy assessment of targeted or "intelligent" (iMNHs) developed in our laboratories for cancer treatment applications. *Our working hypothesis is that long circulating magnetic nanoparticles with specific targeting ligands, iMNH, will improve nanoparticle delivery to ovarian orthotopic tumors, which will result in improved therapeutic outcome.* This hypothesis was based on preliminary data derived during the "pilot project" phase, which demonstrated: (i) *in vivo* nanoparticle's temporal behavior is governed by surface properties, (ii) passive targeting due to the EPR effect may not be sufficient to deliver sufficient particles to the tumor site, and (iii) intelligent targeted nanoparticles have demonstrated significant improvements in treatment efficacy *in vitro*. The rationale for the proposed research is that once the pharmacokinetics, biodistribution, therapeutic efficacy, and, safety of the proposed systems is assessed and understood, future steps can be taken to optimize system's properties thus improving its clinical potential.

SPECIFIC AIMS

Aim 1: To optimize magnetic nanoparticles for the targeted selective destruction of ovarian cancer cells through magnetic fluid hyperthermia.

Hypothesis: Iron oxide MNPs with high energy dissipation rates (>500 W/g), coated with covalently grafted poly(ethylene glycol) of various molecular weights and functionalized with reporter molecules (e.g. fluorophores and radiolabels) and targeting peptides (e.g., RGD, thioaptamers) will be obtained.

Aim 2: To determine the *in vivo* safety, pharmacokinetics and biodistribution of targeted and non-targeted MNHs in orthotopic ovarian cancer models.

Hypothesis: Long-term circulating functionalized particles, specifically employing targeting ligands such as peptides or thioaptamers will result in enhanced delivery to tumors with minimal or no systemic toxicity.

Aim 3: Determine the *in vitro and in vivo* efficacy of targeted and non-targeted MNHs using ovarian orthotopic cancer models.

Hypothesis: MNHs will produce a therapeutically relevant temperature increase in the presence of an AMF in the tumor region that will result in an acceptable therapeutic response. This effect will be enhanced by targeting ligands such as thioaptamers.