A. Personal Statement

As a translational scientist, I have dedicated my life and career to the search for a cure of breast cancer. My research on breast cancer started with the production of human monoclonal antibodies for targeted therapy of breast cancer in 1986. For over seventeen years, I have been working on gene therapy of breast cancer, transcriptional control of anti-apoptosis genes in breast cancer cells, identification of molecular targets that confer apoptosis resistance and aggressive behavior in breast cancer cells for the development of novel molecular targeted therapy, and the development of multifunctional nanoparticles for targeted imaging and therapy of breast cancer. Since the complex biology of breast cancer makes it extremely challenging to treat effectively using a single approach, I believe that comprehensive approaches for early detection and effective treatment are required to reach our ultimate goal of a cure for breast cancer. Currently, my work is focused on the following areas: 1) Early detection of breast cancer using receptor-targeted nanoparticles and novel optical and MR imaging methods. We have developed a novel class of magnetic iron oxide nanoparticles (IONPs) that target EGFR, Her-2/Neu and urokinase plasminogen activator receptor (uPAR), which are receptors highly expressed in breast cancer tissues. We demonstrated that systemic delivery of the targeted IONPs enables specific MRI detection of primary and metastatic breast cancer lesions. We are developing a new MRI method to convert the dark contrast of IONPs to bright signals to enhance the sensitivity and specificity of cancer detection. Preclinical toxicity, biodistribution, and pharmacokinetics studies are underway to bring this targeted breast MRI into a clinical trial in the near future. This research is supported by the Emory University and Georgia Institute of Technology Nanotechnology Center for Personalized Oncology (U54 NIH CCNE) and the Emory Translational Molecular Imaging Center (P50, NIH ICMIC); 2) Prevention of local and distant tumor recurrence by intraoperative optical imaging of breast tumor margin using targeted imaging probes and novel optical instrumentations. Clearly defined tumor margins and complete surgical removal of tumors are critical for preventing local and distant recurrence and, therefore, for increasing disease-free survival. Using receptor targeted optical imaging probes that are produced by conjugating our newly synthesized near-infrared dye (NIR-830) labeled, EGFR, uPAR or Her-2 targeting ligands to biodegradable nanoparticles, we have shown that those imaging probes specifically target to primary and metastatic tumor lesions in orthotopic breast cancer animal models and are detectable by optical and MR imaging. In collaboration with Dr. Shuming Nie at Emory University and Dr. Huabei Jiang at the University of Florida, we are developing two new types of optical imaging systems, including a hand-held Pen-like spectral probe (SpectroPen) and a three-dimensional diffuse fluorescence tomography system (DFT), for intraoperative imaging of tumor margin. This research is supported by NIH R01 (PI. Yang) and GO (PI. Nie) grants; 3) Development of theranostic nanoparticles for targeted therapy and imaging of breast cancer. Tumor recurrence and metastasis are the leading causes of mortality from breast cancer. Novel targeted therapy offers a great opportunity to treat recurrent and metastatic breast cancer and improve prognosis for the patients. Based on the receptor-targeted IONPs, we have further developed theranostic nanoparticles that combine receptor-targeted drug delivery and MRI/optical imaging. Those theranostic nanoparticles target orthotopically implanted breast tumors as well as lung metastases, kill tumor cells and tumor endothelial cells, and significantly inhibit the growth of primary and metastatic tumors.
Importantly, intratumoral drug delivery and changes in the tumor size can be monitored by MRI. In the current R01 research proposal, we will produce new types of theranostic nanoparticles with single or combined therapeutic agents that are highly relevant for the treatment of TNBC and then conduct preclinical studies in TNBC animal models for the development of a clinical protocol for pre-operative targeted adjuvant therapy and MRI monitoring, followed by intraoperative imaging-guided surgery using these nanoparticles. We believe that such an integrated approach will enable effective treatment of drug resistant TNBC and complete removal of small residual tumors to prevent local and distant recurrence. This study does not overlap with current funded research projects that aim at developing receptor-targeted optical and MRI imaging probes (without therapeutic agents) and novel imaging instrumentation and imaging methods.

4) Determination of the role of breast cancer stem cells in developing invasive TNBC and identification of molecular targets and signal pathways that confer aggressive behavior, invasiveness and resistance to apoptosis in TNBCs. We have examined key molecular events in the progression of ductal carcinoma in situ (DCIS) to invasive breast cancer for the identification of prognostic biomarkers and therapeutic targets for TNBC. We are developing therapeutic approaches to modulate those key signal molecules. This project was supported by a NIH R01 grant for which I served as the PI.

As a woman scientist, finding a cure for breast cancer and improving the quality of life of breast cancer survivors and patients not only have special meaning, but also are the very reason why I chose my career in the beginning. Over the years, I have been searching for novel technologies and applying them to breast cancer research. Our invention and research led to three patent applications and twelve NIH and DOD grants on nanoimaging of breast cancer (NCI CCNE), targeted breast MRI (NIH ICMIC), optical imaging guided breast surgery (NIH R01 and NIH GO), quantum dots for multiplexed biomarker detection for breast cancer, magnetic separation and detection of circulating breast cancer cells (four NIH SBIR grants). Our work has been published in nanotechnology as well as clinical journals, such as Nature Biotechnology, Nature Nanotechnology, Small, Biomaterials, Cancer Research, Gastroenterology, and Clinical Cancer Research. Our finding was featured on the cover of the July 2009 issue of Clinical Cancer Research and highlighted in the January, June, and July issues of the NIH/NCI Nanotech News Release, Nanotech Wire News, and BreastCancer.Net News in 2009.

B. Positions and Honors.

Positions
Sep 1986 – Aug 1988 Research Associate, Department of Tumor Immunology, Beijing Institute for Cancer Research, Beijing, China
Jan 1997 - Jul 1998 Assistant Professor, Department of Surgery, Emory University School of Medicine, Atlanta, GA
Aug 1998 - Jul 1999 Research Fellow, Group leader for the preclinical study group on antiangiogenesis, Aventis Pharma, Gencell, Hayward, CA
Aug 1999 - Aug 2007 Assistant Professor, Department of Surgery, Emory University School of Medicine
2007 - Present Associate Professor with tenure, Nancy Panoz Chair of Surgery in Cancer Research Departments of Surgery and Radiology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA

Awards and Honors
2000 - 2009 Scientific Peer Review Panel Member, Breast Cancer Research Program, Department of Defense (DOD)
2005 - Present Editorial Board Member for Apoptosis journal
2006 –present NIH Study Sections, Adhoc, Drug Development and Molecular Pharmacology (DMP), ZRG1ONC-U92, Challenge grant review panels, SBIR review panel Development of Therapeutics (DT, Charter Member), ZCA1 SRLB-9 (ICMIC)
2007-present Scientist Reviewer, California Breast Cancer Research Program
2008 Scientist Reviewer, Susan Komen Foundation
2008-present Editorial Board of Breast Cancer-Targets and Therapy
2008 Best Post Award of 2008 NCI Nanotechnology Alliance Investigators Meeting

C. Peer-reviewed publications or manuscripts in press (selected most relevant publications).


**Patent Applications**


**D. Research Support**

**Targeted Nanoparticles for Intraoperative Optical Imaging of Breast Cancer Margins**

NIH, NCI, R01##CA133722-01 (PI: Yang) 2008 – 2013

The objective of this research project is to develop uPAR targeted NIR optical imaging nanoparticle probes and three-dimensional diffuse optical fluorescence tomography (3D-DFT) for intra-operative imaging of breast cancer margins. This funded research project doesn’t overlap with the new R01 proposal since the current proposed study is to combine preoperative adjuvant therapy using NIR-830-dye-labeled IONPs-drug nanoparticles with intraoperative imaging guided removal of drug resistant tumor lesions using a 2-D SpectroPen video-imaging system.

Role: PI

Theranostic Nanoparticles for targeted treatment of pancreatic cancer
This pending proposal aims at the development of a magnetic iron oxide nanoparticle platform for carrying different types of therapeutic agents, including hydrophilic and hydrophobic drugs or small molecules, and siRNA expressing DNA cassette for targeted therapy of pancreatic cancer.

**Emory-GA Tech Nanotechnology Center for Personalized and Predictive Oncology**

NCI Center of Cancer Nanotechnology Excellence (CCNE)

U54 CA119338-01  (PI: Nie S)  2006-2011

**Project 1. Quantum Dots and Targeted Nanoparticles Probes for Tumor Imaging** The objective of this research is to develop novel tumor targeted quantum dots and other nanoparticles for non-invasive tumor imaging. Research activities in this project involve in the development of targeted optical and MR imaging probes, which have built a strong foundation for the proposed study on theranostic nanoparticles but there is no research overlap with the current proposal.

Role: Project Co-PI.

**Emory SPORE in Head and Neck Cancer**

NIH, NCI  P50CA128613  (PI: D. Shin)  2007-2012

**Project 4: Biodegradable Nanoparticle-Formulated Taxol for Targeted Therapy of Head and Neck Cancer**

The objective of this study is to develop folate receptor targeted biodegradable polymer-based taxol delivery nanoparticles for the treatment of head and neck cancer.

Role: (Co-Project Leader)

**Emory Molecular and Translational Imaging Center grant (EMTIC, P50 ICMIC)**

NIH, NCI  1P50CA128613-01  (PI: C. Meltzer)  2008-2013

**Project 3: uPAR Targeted in vivo Molecular Magnetic Resonance Imaging of Breast Cancer**

The goal of this research project is to develop a novel uPAR-targeted MRI nanoprobe that contains the ATF of uPA conjugated to a magnetic iron oxide nanoparticle and novel MR imaging methods for early detection of breast cancer by MRI. The ICMIC funded research focuses on the development of targeted IONP based MRI probes and novel MR imaging methods. The results from this research project should benefit greatly the current proposed studies. However, there are no research and budget overlaps with the new R01 proposal.

Role: (Multi-PI, Co-PI)

**Nanotechnology for Multiplexed and Intraoperative Cancer Detection**

NIH/NCI (Go Grant) 1RC2CA148265-01  (PI: Nie)  09/30/2009-08/31/2011

This study is to develop a multiplexed SpectroPen-based optical imaging system for intraoperative detection of lung, breast and pancreatic cancer lesions using targeted surface-enhanced Raman scattering (SERS) nanoparticles. The objective of this grant is to develop the SpectroPen optical imaging system and Raman nanoparticle probes that are based on gold-nanoparticles, which doesn't overlap with the research proposed in the current proposal.

Role: Co-investigator

**Multifunctional Nanotubes for in vivo detecting/purging Circulating Cancer Cells**

NIH/NIBIB (R01) 5R01EB009230-02  (PI: ZHAROV, VP, University of Arkansas)  07/15/2009-04/30/2013

The objective of this study is to detect and destroy circulating breast cancer cells in blood vessels non-invasively using targeted nanotubes and photothermal therapy.

Role: Consultant

**Completed research projects during last three years**

**Target Specific and Drug Loaded Iron Oxide Nanoparticles for Cancer Imaging and Therapy**

NIH SBIR Contact No. HHSN261200900078C  (PI. AY Wang, Ocean nanotech, LLC)  2009-2010

**Nanoparticle Based Magnetic Microfluidic Enrichment System (MMES)**

NIH, STTR, CO-PI  (PI, YA Wang, Ocean Nanotech)  2008-2009

**Magnetic nanoparticles for imaging enhancer**

NIH SBIR  R41CA130986-01(Co-PI)  (Pl. Wang, YA, Ocean Nanotech, LLC)  2008-2009

**IAPS As Novel Targets for Cancer Therapy**


**Early detection of breast cancer using molecular beacons.** (Principal Investigator)


**Death signaling in HSV-TK Gene modified tumor cells (Principal Investigator)**

NIH/NCI R29 CA80017-01 (Yang)  8/1/1999 - 7/31/2005