NCI Alliance for

Nanotechnology in Cancer

Principal Investigator’s

Meeting

September 24-26, 2019

Rockville, MD

# Introduction and Welcome

Dear Colleagues:

The National Cancer Institute (NCI) welcomes you to the 2019 Annual Investigators Meeting of the NCI Alliance for Nanotechnology in Cancer being held at the NCI Shady Grove campus, September 24-26, 2019.

The Nanotechnology Alliance started as a quest to incorporate nanotechnology-based materials, devices, and tools into cancer research, but has grown into a strong, biologically and clinically driven program relying on novel use of nanotechnologies to improve effectiveness of cancer interventions. Several of technologies developed under this program have entered clinical trials and are expected to benefit the patient community.

CCNE centers, which many of you represent will sun set in 2020 after 15 years of highly successful operation. CCNEs played a pivotal role in expanding interest of cancer biologists and oncologists in nanotechnology. While CCNE funding was gradually lowered over the years, overall interest in grant submissions related to nanotechnology has grown rapidly. As a result, the total budget of nanotechnology-associated cancer grant awards increased from $100M in 2008 to $216M in 2018 – you all should take credit for growing this grant portfolio so substantially. To capitalize on this continued growth, we will continue other existing nanotechnology funding programs and will thrive to establish new ones.

We would like to extend sincere thanks to those who contributed to making this meeting a reality: all of the participating investigators, committed program officers and staff at NCI.

We look forward to a productive meeting and your active participation in it!

The Nanodelivery Systems and Devices Branch

Cancer Imaging Program, NCI

Piotr Grodzinski  
Christopher Hartshorn  
Christina Liu  
Luisa Russell

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# Agenda

## Day 1, Tuesday, September 24th

8:30 a.m. - 9:00 a.m. Welcome and Introduction

*Douglas Lowy, M.D., Acting Director, National Cancer Institute (NCI)*

*Janet Eary, M.D.*, *Associate Director, Cancer Imaging Program (CIP), DCTD, NCI*

*Piotr Grodzinski, Ph.D., Branch Chief, NSDB/CIP/DCTD, NCI*

**Session I**

Moderator: *Piotr Grodzinski, Ph.D., National Cancer Institute*

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9:00 a.m. – 9:35 a.m. ISB/UCLA/Caltech Center Highlights and Takeaways, U54

*James Heath, Ph.D., Institute for Systems Biology*

9:35 a.m. – 10:10 a.m.  MSKCC-Cornell Center Highlights and Takeaways, U54

*Michelle Bradbury, Ph.D., M.D., Memorial Sloan Kettering Cancer Center*

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10:10 a.m. - 10:30 a.m.  Break (20 minutes)

10:30 a.m. – 11:15 a.m.  Keynote Presentation: Nanomedicine: Past, Present, and Future

*Omid Farokhzad, M.D., M.B.A., Brigham and Women’s Hospital*

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11:15 a.m. – 12:00 p.m.  Keynote Presentation: Most Pressing Needs in Cancer Research and Oncology in Context of New Technology Development

*Phuoc Tran, M.D., Ph.D., Johns Hopkins University*

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12:00 p.m. - 1:15 p.m.  Lunch

**Session II**

Moderator: *Christopher Hartshorn, Ph.D., National Cancer Institute*

1:15 p.m. – 1:35 p.m.  Effective Delivery of a Therapeutic Monoclonal Antibody to Metastases in the Central Nervous System of Mice via Polymer Encapsulation and Receptor Targeting, R01

*Masakazu Kamata, Ph.D., UCLA*  
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1:35 p.m. – 1:55 p.m.  Novel Approach to Attenuate Small Lung Cancer Growth and Metastasis, R01

*Wasim Nasser, Ph.D., University of Nebraska Medical Center*

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1:55 p.m. – 2:15 p.m.  Wireless Nano-optogenetic Immunotherapy, R01

*Gang Han, Ph.D., University of Massachusetts Worchester*

2:15 p.m. – 2:45 p.m.  Imaging the Delivery and Action of Nanomaterials In Vivo: an Update of MGH IRCN Progress, U01

*Miles Miller, Ph.D., Massachusetts General Hospital*

2:45 p.m. – 3:15 p.m.  Break and Cake Alliance Celebration (30 minutes)

3:15 p.m. – 4:55 p.m.  T32 Training Program Overviews

*Jianghong Rao, Ph.D., Stanford University CNTC*

*Konstantin Sokolov, Ph.D., The University of Texas MD Anderson CNTC*

*Alexander Stegh, Ph.D., Northwestern University CNTC*

*Andrew Kummel, Ph.D., University of California, San Diego CNTC*

*Alexander Kabanov, Ph.D., The University of North Carolina at Chapel Hill CNTC*

5:15 p.m. – 6:15 p.m.  **Coordination and Governance Committee Meeting (by invitation only), Rm. 2W910**

## Day 2, Wednesday, September 25th

**Session III**

Moderator: *Christopher Hartshorn, Ph.D., National Cancer Institute*

9:00 a.m. – 9:35 a.m.  UNC Chapel Hill Center Highlights and Takeaways, U54

*Leaf Huang, Ph.D., University of North Carolina at Chapel Hill*

9:35 a.m. – 10:10 a.m.  Washington University Center Highlights and Takeaways, U54

*Samuel Achilefu, Ph.D., Washington University in St. Louis*

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10:10 a.m. – 10:30 a.m.  Break (20 minutes)

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10:30 a.m. – 11:05 a.m.  Northwestern University Center Highlights and Takeaways, U54

*Chad Mirkin, Ph.D., Northwestern University*

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11:05 a.m. – 11:35 a.m.  Use of a Silicasome Nanoparticle Platform for Treatment of Pancreatic Ductal Adenocarcinoma, U01

*Huan Meng, Ph.D., UCLA*

11:35 a.m. - 11:55 a.m.   Whitlockite Nanoparticle-based Immunotherapy for Bone Metastasis, R01

*Shiladitya Sengupta, Ph.D., Brigham and Women’s Hospital*

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11:55 a.m. - 1:10 p.m.  Lunch

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**Session IV**

Moderator: *Luisa Russell, Ph.D., National Cancer Institute*

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1:10 p.m. - 1:30 p.m.  UNC CCNE Clinical/Scientific Highlight

*Andrew Wang, M.D., University of North Carolina at Chapel Hill*

1:30 p.m. – 1:50 p.m.  Northwestern CCNE Clinical/Scientific Highlight

*Andrew Lee, Ph.D., Northwestern University*

1:50 p.m. - 2:10 p.m.  WUSTL CCNE Clinical/Scientific Highlight

*Gregory Lanza, M.D., Ph.D., Washington University in St. Louis*

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2:10 p.m. – 2:30 p.m.  Stanford CCNE Clinical/Scientific Highlight

*Alice Fan, M.D., Stanford University*

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2:30 p.m. – 2:50 p.m.  MSKCC-Cornell CCNE Clinical/Scientific Highlight

*Michelle Bradbury, Ph.D., M.D., Memorial Sloan Kettering Cancer Center*

​

2:50 p.m. - 3:10 p.m.  ISB/UCLA/Caltech CCNE Clinical/Scientific Highlight

*Wei Wei, Ph.D., Institute for Systems Biology*

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3:10 p.m. – 3:30 p.m.  Break (20 minutes)

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3:30 p.m. – 3:50 p.m.  Nanoparticles for the Treatment of Intraperitoneal Mesothelioma: Enhancing Tumor Localization and Increasing Drug-Loading for Improved Efficacy, R01

*Mark Grinstaff, Ph.D., Boston University*

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3:50 p.m. – 4:20 p.m.  The Rodent Eye as a Non-invasive Window for Understanding Cancer Nanotherapeutics, U01

*Kit Lam, M.D., Ph.D., UC Davis*

4:20 p.m. – 4:40 p.m.  Folate-displaying Exosome Mediated Cytosolic Delivery of siRNA Avoiding Endosome Trapping, U01

*Peixuan Guo, Ph.D., Ohio State*

4:40 p.m. – 5:00 p.m.  Alliance Achievements by the Numbers

*Piotr Grodzinski, Ph.D., National Cancer Institute*

5:00 p.m. – 6:00 p.m.  **Poster Session, 2nd Floor Atrium**

## Day 3, Thursday, September 26th

**Session V**

Moderator: *Christina Liu, Ph.D. P.E., National Cancer Institute*

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9:00 a.m. – 9:35 a.m.  Stanford Center Highlights and Takeaways, U54

*Shan Wang, Ph.D., Stanford University*

9:35 a.m.  ̶ 10:05 a.m.  Nanostructure-Embedded Microchips for Liquid Biopsy in Cancer, U01

*Hsian-Rong Tseng, Ph.D., UCLA, and Edwin Posadas, M.D., Cedars-Sinai Medical Center*

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10:05 a.m. ̶ 10:25 a.m.  Break (20 minutes)

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10:25 a.m. – 10:55 a.m.  Targeted Core Shell Nanogels for Triple Negative Breast Cancer, U01

*Alexander Kabanov, Ph.D., University of North Carolina at Chapel Hill*

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10:55 a.m. – 11:25 a.m.  Co-delivery of Targeted Stroma-breaking Theranostic Nanoparticle and Immune Checkpoint Nano-PD-L1 Inhibitor for the Treatment of Pancreatic Cancer, U01

*Lily Yang, M.D., Ph.D., Emory University*

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11:25 a.m. – 11:55 a.m.  Nanoscale Metal-organic Frameworks for Light Triggered and X-ray Induced Photodynamic Therapy of Head and Neck Cancers, U01

*Wenbin Lin, Ph.D., University of Chicago*

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11:55 a.m. - 12:25 p.m.  Delivery of Drugs to Brain Tumors using Multicomponent Nanoparticles, U01

*Efstathios Karathanasis, Ph.D., Case Western Reserve University*

12:25 p.m. - 12:55 p.m. Poster Prizes and Closing Comments

*Piotr Grodzinski, Ph.D., National Cancer Institute* ​

1:00 p.m. Adjournment

# Abstracts

### [Effective delivery of a therapeutic monoclonal antibody to metastases in the central nervous system of mice via polymer encapsulation and receptor targeting](https://apply.cancer.gov/submissions/13870885?page=1&i=1)

*Masakazu Kamata, Ph.D.*

*UCLA*

Central nervous system (CNS) metastases are a major cause of cancer deaths with few therapeutic options. Monoclonal antibody-based therapy for cancer is one of the most successful therapeutic strategies; however, its efficacy is limited against CNS metastases due to insufficient CNS delivery. Here, we show significantly improved antibody delivery to the CNS using novel polymer-based nanocapsules that encapsulate individual antibodies within a thin layer of crosslinked phosphorylcholine polymer, and gradually release cargo over time through hydrolyzable crosslinkers. A single course of rituximab nanocapsule treatment elevates rituximab levels in the CNS by nearly 10-fold compared to native rituximab. We improved control of CNS metastases in a murine xenograft model of non-Hodgkin lymphoma. Moreover, using a xenograft humanized BLT mouse model, lymphomas were eliminated with a single course of rituximab nanocapsule treatment. This approach could be considered for the treatment of cancers with CNS metastases and is generalizable for any antibody delivery to the CNS.

### Novel approach to attenuate small lung cancer growth and metastasis

*Wasim Nasser, Ph.D.*

*University of Nebraska Medical Center*

Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer with limited therapeutic options and poor prognosis. Late diagnosis, drug resistance, and lack of potential drug targets limit the therapeutic options of SCLC. In the quest of novel therapeutic targets for anticancer therapies, we have evaluated miR-1 as a tumor suppressor gene. We have found low expression of miR-1 in the panel of SCLC cell lines compared to normal lung epithelial cells. To demonstrate the functional role of miR-1 in SCLC, we overexpressed miR-1 in the highly metastatic SBC5 cell line. The overexpression of miR-1 inhibits cell migration, and EMT markers in SCLC cells suggested that miR-1 regulates the growth and metastatic properties of SCLC. Furthermore, knockdown of miR-1 increases cell migration, EMT, and colonogenic properties of non-metastatic SBC3 cells. It was observed that miR-1 regulates SCLC tumorigenesis through modulating CXCR4 expression. To evaluate the therapeutic potential of miR-1, we have synthesized PCX-miR-1 nanoparticles (miR-1 containing polymeric CXCR4 antagonist). The treatment of PCX-miR-1 increases the miR-1 expression and inhibits CXCR4 that further enhance apoptosis in SBC5 cells as compared to control. Overall, these results demonstrate the role of the miR-1/CXCR4 axis in SCLC and provide a preclinical rationale for the implication of PCX-miR-1 NPs as a novel therapeutic strategy for the treatment of SCLC.

### Wireless nano-optogenetic immunotherapy

*Gang Han, Ph.D.*

*University of Massachusetts Worchester*

Functional luminescent nanoparticles are promising materials for in vitro and in vivo optical imaging and therapy due to their unique optical and chemical properties. In this talk, we will present new developments regarding engineering Upconversion nanoparticles towards optogenetic applications in immunotherapy.

### Imaging the delivery and action of nanomaterials in vivo: an update of MGH IRCN progress.

*Miles Miller, Ph.D.*

*Massachusetts General Hospital*

The Massachusetts General Hospital Innovative Research in Cancer Nanotechnology (IRCN) program focuses on using advanced imaging approaches to understand mechanisms of nanotherapeutic delivery and action in solid cancers, particularly at a single-cell level. This talk will summarize IRCN progress across three key aims of the program: (1) examining the single-cell distribution of model therapeutic nanoparticles (TNPs) in vivo, primarily focusing on those based on cross-linked dextran, liposomes, and PLGA-PEG polymeric formulations; (2) determining the relative importance of molecular targeting in treating solid tumors, particularly in comparison to strategies that enhance passive routes of TNP delivery; and (3) developing translational imaging strategies to understand and predict the action of TNPs, using MRI and PET/CT of companion imaging nanoparticles. This talk will highlight recent progress in understanding how TNPs can re-polarize tumor associated macrophages for mounting an effective anti-tumor immune response [Rodell et al., 2018, Nat Biomed Eng, 2, 578-588], and how such an approach may combine with tumor priming strategies and companion imaging to achieve amplified delivery and efficacy [Kim et al., 2018, ACS Nano, 12, 12015-12029].

[UCSD T32 CRIN (Cancer Researchers in Nanotechnology)](https://apply.cancer.gov/submissions/13899349?page=1&i=1) *​*

*Andrew Kummel, Ph.D.*

*University of California, San Diego CNTC*

*​*

The UCSD T32 (Cancer Researchers in Nanotechnology) had an initial cohort of 5 PhD students. The focus of the students has changed to mostly nanoparticles for imaging and immunotherapy. All have first author publications and are on track to complete their degrees (1) Jeanne Lemaster: Lemaster and coworkers developed a bimodal synthetic melanin nanoparticle doped with gadolinium (Gd-SMNP) to label cells and image mice in vivo using real-time photoacoustic imaging to monitor delivery and deep tissue MRI to provide longer-term follow-up of immune cell location and quantities. (2) Jiarong Zhou - Zhou and coworkers developed a biocompatible nanoparticle coated in a layer-by-layer fashion with a highly immunostimulatory adjuvant and purified cancer cell membranes to generate a personalized and potent cancer vaccine. (3) Yaou Duan – Duan and coworkers are developing a novel uveal melanoma treatment by combining immune checkpoint blockade with CRISPR/Cas9 based gene editing. The aim to develop tumor exosome coated poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) nanoparticles as drug carriers for intracellular delivery of CRISPR/Cas9 ribonucleoprotein (RNP).. (4) James Wang: Wang and coworkers showed that microshell enhanced mechanical high intensity focused ultrasound ablation of the tumor results in an immune stimulated local environment favorable for dendritic cell activation and T cell priming. When combined with PD-1, a 75% remission rate was observed in a mouse model. (5) Joanna Wang: Wang and coworkers have encapsulated biomarker nanoparticles within porous silicon microparticles for urinary biomarkers for cancer diagnosis.

### Use of a Silicasome Nanoparticle platform for Treatment of Pancreatic Ductal Adenocarcinoma

*Huan Meng, Ph.D.*

*UCLA*

We developed a nano-enabled platform to circumvent PDAC-specific treatment challenges by addressing the stromal barrier, abnormal tumor vasculature, drug resistance, and immune evasion through the introduction of silicasomes, which are comprised of mesoporous silica nanoparticles (MSNP) coated with a lipid bilayer (LB). The platform leverages the large interior packaging space and high stability of the LB, which can be used for single and dual drug loading, including use of remote loading techniques into the porous interior and the LB. One example is irinotecan remote loading, which allowed improved pharmacokinetics and intratumoral drug delivery to the orthotopic Kras-derived PDAC tumor site. This provides improved efficacy, survival outcome and toxicity reduction compared to the free drug or a liposomal irinotecan carrier (Onivyde). The results could be duplicated in an orthotopic colon cancer model. Treatment efficacy in PDAC was further enhanced by using the NRP1-mediated transcytosis pathway that provides vascular access to the tumor site in response to iRGD peptide, providing an avenue for personalized PDAC chemotherapy. The silicasome carrier was also custom-designed for ratiometric delivery of paclitaxel and gemcitabine, which leads to a synergistic treatment outcome that outperforms a gemcitabine/Abraxane combination. Recently, we have expanded the scope of PDAC chemotherapy by using our platform for introducing immunogenic cell death stimuli, such as oxaliplatin and irinotecan. Our preliminary data show synergy between irinotecan delivery and anti-PD1 in an orthotopic KPC model. In light of the considerable promise of the silicasome platform, we have developed innovative techniques for upscale manufacturing, allowing us to consider translation of the platform for clinical use.

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### Nanoparticles for the Treatment of Intraperitoneal Mesothelioma: Enhancing Tumor Localization and Increasing Drug-Loading for Improved Efficacy

*Mark Grinstaff, Ph.D.*

*Boston University*

The treatment outcomes for malignant peritoneal mesothelioma are poor and associated with high co-morbidities due to suboptimal drug delivery. Thus, there is an unmet need for new approaches that concentrate drug at the tumor for a prolonged period of time yielding improved antitumor efficacy and improved metrics of treatment success. Two functional paclitaxel-loaded nanoparticle (NP) systems for the delivery of paclitaxel (PTX) are described to address this unique challenge. The first is a functional expansile NPs that is pH-responsive (PTX-eNP) and the second is a high-dose formulation (PTX-PGC NPs) that delivers unprecedented quantities. The syntheses of the PTX-eNP and PTX-PGC NPs are described followed by several particle characterization techniques, including qNano, DLS, SEM, and TEM that measure particle size. The rate of tumoral uptake of eNPs is rapid and, subsequent disruption of autophagosomal trafficking leads to prolonged intracellular retention. Following intraperitoneal administration, eNPs rapidly and specifically localize to tumors within 4 hr of injection with persistent intratumoral retention for >14 days. The high tumor-specificity of PTX-eNPs leads to delivery of >100 times higher concentrations of drug in tumors compared to PTX alone while the delivery of PTX-PGC NPs further increases the dose delivered. As a result, overall survival of animals with established mesothelioma increases when animals were treated with multiple doses of PTX-eNPs or with a single dose of PTX-PGC NPs compared to an equivalent dose of PTX (standard of care).

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### Folate-displaying exosome mediated cytosolic delivery of siRNA avoiding endosome trapping

*Peixuan Guo, Ph.D.*

*Ohio State*

Folate (FA) receptor is a cell surface glycoprotein overexpressed on many cancer cells. It is a high affinity ligand for cancer cell targeting. However, delivery of siRNA for cancer treatment directly through folate receptor has not, if any, been successful in clinical application. Here we report the application of RNA nanotechnology to construct FA-displaying exosomes for efficient cell targeting, siRNA delivery and cancer regression. It was demonstrated that the efficient cancer suppression with the FA-displaying exosome was due to the receptor-mediated cytosol delivery of the siRNA payload without endosome trapping, as attested by fluorescence colocalization analysis, gene knockdown assay and animal tumor regression. It is expected that the high potency of FA-displaying exosome in cytosolic siRNA delivery will renew the concept and interest in using FA as cancer targeting ligand in human cancer therapy.

Nanostructure-Embedded Microchips for Liquid Biopsy in Cancer  
*Hsian-Rong Tseng, Ph.D. and Edwin Posadas, M.D.  
UCLA and Cedars-Sinai Medical Center*

The current gold standard for cancer diagnosis is the characterization of tumor tissues acquired via invasive procedures, e.g., surgical excision or needle biopsy. As an alternative to solid tumor biopsy, many have proposed the use of a “liquid biopsy” based on blood components like circulating tumor cells (CTCs) and extracellular vesicles (EVs). By detecting, enriching, and analyzing CTCs and EVs, we can noninvasively and dynamically monitor disease progression in individual cancer patients and obtain insightful information for assessing disease status. With NCI’s support over the past 14 years, our joint research team at UCLA and Cedars Sinai Medical Center pioneered the unique concepts of “NanoVelcro” CTC Chips, “NanoVilli” EV Chips, and the newly developed “Click” Chips.  In these devices, nanostructured substrates and immunoaffinity agents were uniquely integrated to achieve highly efficient enrichment and purification of CTCs and EVs. Multiple generations of technologies have been demonstrated for a variety of clinical utilities, e.g., noninvasive molecular analysis for monitoring disease progression and treatment intervention.  In this presentation, Dr. Tseng and Dr. Posadas will review the developmental history of their nanostructure-embedded microchips, and the emerging clinical applications of these new in vitro diagnostic devices for cancer.

### Co-delivery of Targeted Stroma-breaking Theranostic Nanoparticle and Immune Checkpoint Nano-PD-L1 Inhibitor for the Treatment of Pancreatic Cancer

*Lily Yang, M.D., Ph.D.*

*Emory University*

Despite recent successes in cancer immunotherapy, pancreatic cancer showed a poor response to immunotherapeutic approaches. The dense stroma in pancreatic cancer not only forms physical barriers to block delivery of therapeutic agents, but also creates immunosuppressive biological barriers that limit the function of infiltrating cytotoxic T cells. The majority of pancreatic cancers are immunoscore “cold” tumors with a low level of effector T cells. To improve the therapeutic response, we have developed a new combination therapy by co-delivering a stroma breaking theranostic nanoparticle with the 2nd nanoparticle carrying an immune checkpoint PD-L1 inhibitor (Nano-iPD-L1). Our uPAR-targeted and matrix metalloproteinase-14 active ligand conjugated theranostic nanoparticles (ATFmmp14-IONP/drug) bind to cancer and stromal cells and enable nanoparticle-drugs migrating through stromal cell and extracellular matrix barriers to reach tumor cells. Targeted delivery and strong therapeutic effects of ATFmmp14-IONP/drug were demonstrated in pancreatic cancer patient derived xenograft (PDX) and mouse pancreatic tumor models. We further demonstrated that Nano-iPD-L1 selectively accumulated in tumors following systemic delivery and its delivery efficiency was enhanced by co-delivery with ATFmmp-IONP/drug in mouse pancreatic tumor models. Notably, targeted delivery of those nanoparticle-drugs into tumors promoted infiltration of immune cells, especially CD8+ T cells, and activated an immune “cold” pancreatic cancer into a pro-immune “hot” tumor. Improved nanoparticle-drug delivery and immune cell infiltration led to significant inhibition of tumor growth when Nano-iPD-L1 was combined with ATFmmp14-IONP/doxorubicin in a mouse pancreatic cancer model. Therefore, the combination therapy of ATFmmp14-IONP/drug with Nano-iPD-L1 has the potential for the development of a new immunotherapy for pancreatic cancer.

# Poster Abstracts

### Cobalt-based Nanoconstructs for the Treatment of Basal Cell Carcinoma

*Yaolin Xu, Jing Huang, Weiping Qian, Bing Ji, Yuancheng Li, Yongqiang Wang, Lily Yang, Hui Mao*

*Department of Radiology and Imaging Sciences, Emory University School of Medicine*

“Active targeting” based on the ligand-target affinity is a common strategy to precisely deliver nanoparticle (NP) imaging probes or drug carriers to the diseased tissue. However, such ligand-mediated active targeting inevitably takes place with prerequisite “passive targeting”, driven by the enhanced permeability and retention (EPR) effect. Thus, the efficiency of active targeting in relation to off-targeted unbound NPs is of great importance in quantitative imaging of tumor biomarkers and NP delivery. This work re-examined the NP size effect on “active targeting” of transferrin receptor (TfR) using transferrin (Tf)-conjugated sub-5 nm (3 nm core size) ultrafine iron oxide NPs (uIONPs) and larger IONPs (30 nm core size) with the notion that easy clearance of off-targeted uIONPs may lead to enhanced active targeting and tumor accumulation. After equal amounts of active targeting and non-targeting uIONPs (or IONPs) labeled with different fluorescent dyes were co-injected into the same mice bearing 4T1 mammary tumors, multiphoton imaging and confocal fluorescence imaging were applied to quantitatively track different types of NPs in tumors at 1, 3 and 24 hours after co-injection. Active targeting uIONPs exhibited 6 times higher level of tumor retention with deeper penetration comparing to non-targeting uIONPs at 24 hours after co-injection. However, accumulation of active targeting IONPs with a 30-nm core is only 1.5 times higher than non-targeting IONPs. The results suggest that the size-dependent improvement on ligand-mediated active targeting can be achieved with sub-5 nm NPs, which may serve as promising platforms for development of molecular imaging probes and targeted drug carriers.

Plasmonic nanobubbles: Harnessing Cancer Aggressiveness to Overcome Its Resistance

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After establishing a solid in vitro evidence of the plasmonic nanobubble (PNB) mechanism of the tumor aggressiveness-driven amplification of PNBs in cancer cells, we have focused on the preparation for the in vivo study of this novel mechanism of overcoming the tumor aggressiveness and resistance to standard treatments. We focused on the two key components of PNB generation in vivo: (1) to develop plasmonic (gold) nanoparticles with the maximal efficacy of the PNB generation with normal tissue-safe laser pulses in near-infrared wavelength and a low optical fluence, and (2) in developing the experimental methodology for the laser pulse-activated generation and detection of PNB deep enough in tissue to support the PNB mechanism in future animal models of triple-negative breast cancer. Our current results include: - PNB-specific gold nanoparticles, 200 nm hollow gold nanoshells, and there conjugates to clinical anti-EGFR antibody, were developed and tested for the PNB generation it tissue models at the laser pulse of 1064 nm and the optical fluence PNB threshold around 30 mJ/cm2. - PNBs were successfully generated and detected acoustically in a bench tissue model, to the tissue depth down to 5 mm, sufficient for a mice tumor models to be studied. - Drug liposomes, Doxil, were conjugated to the same antibody and gold nanoparticles, to support concurrent systemic targeting of both in vivo. The ongoing effort is aimed at the animal studies of the PNB mechanisms in triple-negative breast cancer tumors.

### miR-1/CXCR4 axis as a novel therapeutic target in Small Cell Lung Cancer

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Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer with limited therapeutic options and poor prognosis. In the quest of novel therapeutic approaches, we have evaluated the role of miR-1 in the progression and metastasis of SCLC. Bioinformatics analysis showed that miR-1 is downregulated and CXCR4 is upregulated in the majority of SCLC patient samples. The expression analysis of miR-1 and CXCR4 in two different SCLC tissue microarrays showed a basal level of miR-1 with concurrent increase in CXCR4 as compared to matched normal tissues. Similar expression pattern of miR1 and CXCR4 was also observed in the majority of SCLC cell lines. We also used miR-zip technology to downregulate miR-1 in SBC3 cells, and tet-On technology to stably overexpressed miR-1 in SBC5 cells. We observed that miR-1 overexpression reduces migration and proliferation of SBC5 cells, and miR-1 downregulation enhances the migratory properties of SBC3 cells. Importantly, it was observed that miR-1 expression is inversely associated with CXCR4 expression, EMT, and oncogenic signaling. To evaluate the therapeutic potential of miR-1 via targeting CXCR4, miR-1 loaded polymeric CXCR4 antagonist (PCX) nanoparticles (NPs) were synthesized and characterized. The treatment of PCX-miR-1 increases the miR-1 expression and induces apoptosis in SBC5 cells. These bifunctional PCX-miR-1 NPs work as optimal dual warheads in SCLC as they increase the miR-1 expression along with the targeting of CXCR4/CXCL12 axis. Future studies will explore the targeting of CXCR4 through PCX-miR-1 NPs in SCLC preclinical models. Overall, these studies provide a sound rationale for the implication of PCX-miR-1 NPs as an innovative therapeutic strategy for the treatment of SCLC.

### Enhanced brain delivery of rituximab using timed-release polymer nanocapsules in non-human primates

*Presenter: Jing Wen, Co-Authors: Meng Qin, Lan Wang, Di Wu, Christopher K, Williams, Duo Xu, Qi Guo, Jiaoqiong Guan, Emiko Kranz, Harry V. Vinters, Yun Luo, Guibo Sun, Xiaobo Sun, Zhanlong He, Yunfeng Lu, Masakazu Kamata, and Irvin S.Y. Chen*

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Although monoclonal antibody (mAb) therapy has been used to successfully treat various types of cancer, delivery of mAbs to the brain has remained a great challenge in clinical practice. Here, we tested a nanotechnology platform, termed “nanocapsules”, whereby each individual mAb molecule is encapsulated within a thin phosphorylcholine polymer shell, enabling access to the central nervous system (CNS) as well as sustained controlled release of mAbs through hydrolysis of crosslinkers at physiological conditions. To provide proof of concept for the therapeutic use of nanocapsules as antibody delivery vehicles to the CNS in clinical applications, we modeled delivery and efficacy in non-human primates (NHP) with rituximab (RTX), which recognizes CD20 on B-cells to treat B-cell malignancies. Following a single intravenous injection into NHP, nanocapsules maintained RTX in peripheral blood comparably to native RTX. Importantly, delivery by RTX encapsulated in nanocapsules significantly enhanced the RTX levels in the cerebrospinal fluid and the brain tissue without notable adverse effects in treated animals. This nanocapsule technology holds promise for non-invasive mAb therapy of brain-associated diseases.

### Very-Small-Nuclear Circulating Tumor Cells: Nuclear Size Reduction is Associated with Poor Clinical Outcomes in Metastatic Castration-Resistant Prostate Cancer

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Background: Circulating tumor cells (CTCs) have arisen as contemporary noninvasive prognostic biomarkers for prostate cancer (PC). Previously, a subgroup of PC CTCs, with particularly small nuclei (&lt;8.54 μm), were found to be correlated with the presence of visceral metastases (VM). This subgroup was named very-small-nuclear CTCs (vsnCTCs). We proposed vsnCTCs as a putative biomarker of a lethal subtype in metastatic castration resistant PC (mCRPC). We also explored a biological pathway that potentially drives this morphologic phenomenon. Studies have shown that the disruption of the LINC complex proteins (e.g. emerin) leads to nuclear envelope instability in cancer cells. The disposition of emerin was found to drive cancer cells to an amoeboid phenotype increasing their capacity of migration and invasion. Methods: 80 blood samples were obtained from patients with mCRPC. Concurrently, emerin staining was performed and the distribution and expression levels of emerin were analyzed in selected vsnCTC samples. Using NanoVelcro CTC Assay, we captured and enumerated the CTCs from patient samples with high resolution imaging. Survival analysis were performed to exam the correlation between vsnCTC status and prognosis. Results: The presence of vsnCTC(s) strongly correlated with worse overall survival (OS). We also observed lower emerin content in vsnCTCs compared to WBCs, and more prominent emerin dislocalization in vsnCTCs than non-vsnCTCs. Conclusion: Our study strongly demonstrated the importance of morphologic characterization of CTCs and suggested that vsnCTC is a blood-borne biomarker for prediction of shortened OS. Additionally, emerin dislocalization in vsnCTCs is a potential biological relationship between nuclear morphology and aggressive disease.

### Preclinical Development of a Circulating Tumor Cell Based RNA-Classifier to Optimize the Treatment Selection in Patients with Metastatic Castration-Resistant Prostate Cancer

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Rationale: Our objective is to develop a circulating tumor cell (CTC)-RNA Assay for characterizing clinically relevant RNA signatures for the treatment selection of androgen receptor signaling inhibitor (ARSI) in patients with metastatic castration-resistant prostate cancer (mCRPC). Methods: We developed the CTC-RNA Assay by combining the Thermoresponsive (TR)-NanoVelcro system with the NanoString nCounter platform for CTC purification and RNA analysis, respectively. Based on the well-validated, tissue-based Prostate Cancer Classification System (PCS) which categorizes prostate cancer (PC) into 3 subtypes (PCS1-3), a CTC-PCS panel was developed using a rigorous bioinformatic process. We applied the weighted Z-score method and nearest centroid classification method to calculate gene expression and to assign PCS subtype. Results: We retrospectively enrolled 34 patients with mCRPC who were beginning therapy with ARSI (abiraterone, enzalutamide or apalutamide). Pre-treatment blood samples were subjected to the CTC-RNA Assay. Each patient’s PCS subtype was assigned. The median overall survival for PCS1 (n=3), PCS2 (n=20) and PCS3 (n=11) was 49, 149 and 157 weeks, respectively. The p-value (log-rank test) was 0.0132 for PCS1 vs. PCS2, and 0.0847 for PCS1 vs. PCS3. Conclusion: In the original PCS panel, PCS1 correlates with the most clinically aggressive cases and points toward the lowest sensitivity to AR inhibition. Our blood-borne PCS classifier can categorize PC into 3 subtypes, which are related to aggressiveness of PC, including prediction of treatment response. Through early identification of high-risk biology and timely adjustment of therapeutic strategies, physicians could potentially prevent disease progression to lethal PC, thus improving clinical outcomes and reducing mortality.

### Theranostic Nanoparticles for T1-MR Imaging and Phototherapy of Pancreatic Cancer

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Pancreatic ductal adenocarcinoma with an 8% five-year survival rate is the fourth-leading cause of cancer-related death in the United States. The low survival rate is due to poor diagnosis, high metastasis rate, and lack of effective treatment options. Current FDA-approved gadolinium-based Magnetic Resonance Imaging (MRI) contrast agents have the potential to detect such disease due to their high longitudinal relaxivity (e.g., Magnevist, 2.8 mM-1 s-1 at 4.7 T). However, there are newly raised safety concerns with these contrast agents due to Gd deposition in the brain and bone. Here, we present a compact near-infrared (NIR) plasmonic nanoparticle of Au@SiO2@Au nanomatryoshkas (NM) with Gd-DOTA and fluorescent dyes doped in the inner SiO2 layer as a solution for a better in vivo imaging capability and minimum toxicity. Our NM design emphasizes the “see and treat” approach in which it provides dual imaging modalities and strong NIR photothermal treatment capability. With this NM structure, the MRI signal of Gd-DOTA and the photostability of Cy7 dye are enhanced ~8-fold and ~23-fold, respectively. Furthermore, to reduce the overall nanostructure bio-toxicity, the Gd ions have been replaced with Fe ions. The encapsulation of Fe-DOTA in the silica layer of the NM structure has improved MRI signal by ~15-fold in comparison to Fe-DOTA alone and twice that of Gd-DOTA. This enhancement opens the possibility of using Fe-NM plasmonic nanostructure as a better alternative for T1-MRI contrast agents with a better in vivo visualization, minimum Gd-related toxicity, and efficient imaging-guided photothermal therapy of pancreatic cancer.

### Atomistic molecular dynamics simulations of self-assembling amphiphilic tetrapeptide with alkylated residues

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Self-assembling peptides have received more attention in recent years due to their biocompatibility and multifunctionality. The hydrophobic‐to-hydrophilic ratio of the amino acids in the particular peptide sequence control the overall self-assembly pathway. A bottom-up approach of designing a peptide sequence from an amino acid library allows us to focus on the specific needs of the particular application. We are proposing a new template for self-assembling amphiphilic tetrapeptide with two distinct sides, having alkylated hydrophobic residues on one side and the hydrophilic residues on the other side. Self-assembly of tetrapeptides YXKX (Y = tyrosine, X = alkylated tyrosine, K = lysine) were modelled with the help of all atom molecular dynamics simulations using the GROMACS 2018.3 package. Within the first 100 ns simulation time, tetrapeptides self-assembled into densely packed nanospheres. Alkylated hydrophobic residues initialize the aggregation process and to reduce the solvent exposure, they formed a hydrophobic core. Hydrophilic amino acids occupied at the surface shows significant effect on the ordered arrangement of peptides through the secondary structure formation. By forming a hydrogen bonding network with the adjacent beta strands, the tetrapeptides stabilized themselves in a beta sheet structure. The number of hydrogen bonds between the backbone atoms consistently increased during the simulations. The proposed template was primarily designed for nanoparticle surface coating. Coating self-assembling peptides on nanoparticle surface increases its colloidal stability and makes them physiologically compatible; this opens up potential applications in the biomedical field.

### Upconversion X: Designing next generation organic photon upconversion nanoparticles

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Upconversion nanoparticles have stood out as an important emerging tool in numerous biological and material applications. We will present the development of a new generation of brighter and safer organic upconversion nanoparticles as well as their anticancer and optogenetic applications.

### Photoacoustic Monitoring of Drug Release from PLGA Nanocarriers for Tumor Treatment

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Nanodrug delivery systems have the potential to revolutionize cancer therapy by site-specific delivery with increased efficacy and reduced side effects. However, one of the current challenges in nanomedicine is monitoring the amount and distribution of drugs released in vivo. In order to address this challenge, we used photoacoustics to monitor drug delivery over time. We developed a nanoparticle which covalently linked the FDA-approved drugs methylene blue and paclitaxel and synthesized a photoacoustic-responsive paclitaxel-methylene blue conjugate, PTX-MB. A redox switch of the methylene blue between the leuco (LMB) and oxidized forms (MB) caused a change from photoacoustically silent to photoacoustically active states. We then encapsulated the leuco form of PTX-LMB into biocompatible poly(lactic-co-glycolic acid) (PLGA) nanoparticles to create a biocompatible, time-released nanodrug. Initially, the PTX-LMB was photoacoustically silent in the PLGA nanoparticles; as it was released, the PTX-LMB combined with oxygen and was spontaneously oxidized to yield the PTX-MB photoacoustically active form. The photoacoustic intensity of the PTX-LMB switch to PTX-MB changed increased 669.9 times in 120 hours in a phantom. Next, we imaged the drug release activity in a murine model and found an increase of activity of 3.86-fold from baseline over 24 hours when injected subcutaneously. We then used a bioluminescent CT-26 engraftment in a murine model and found that the radiance of the tumor decreased 21.6% in mice treated with the PLGA encapsulated PTX-LMB compared to the free drug.

### siRNA Therapy to Manipulate Immune Cell Gene Regulation

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Immunotherapy is an emerging field for treating cancer by way of stimulating T cells to recognize and eradicate cancer cells. Targeted antibody therapies [e.g. programmed death-ligand 1 (PD-L1), programmed death receptor-1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)] have been developed to promote T cell stimulation and promote tumor cell killing and clearance. However, these therapies neglect to address innate immune cells of the myeloid lineage that can suppress T cell antitumor immune responses. Scavenger receptor type B-1 (SR-B1) is a cell surface receptor responsible for the uptake of cholesterol via binding cholesterol-rich, spherical high-density lipoproteins (HDL), and is a receptor shared by adaptive and innate immune cells. Native HDLs specifically target and bind SR-B1 to deliver nucleic acid cargo. We hypothesized that SR-B1 may enable targeted delivery of siRNAs to regulate gene expression in adaptive and innate immune cells to enhance T cell antitumor immunity while simultaneously dampening the innate immune response. Accordingly, we have designed a HDL-inspired nanoparticle, called a templated lipoprotein particle (TLP), that closely mimics the size, shape, and surface composition of native HDL, and targets SR-B1. Our data demonstrate that cells of the myeloid lineage and proliferating T cells highly express SR-B1, and may be targeted using the TLP platform. We have optimized TLPs for siRNAs targeted to PD-1, PD-L1, and CTLA-4. Our delivery platform may be ideal for exploring new methods of immunotherapy.

### Neoantigen nanovaccine improves personalized cancer immunotherapy

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Neoantigens are attractive targets for personalized anti-tumor vaccination given they are unique to the tumor and bypass immune tolerance. Recently, the feasibility of neoantigen vaccine has been demonstrated in patients. However, the response rate of neoantigen vaccines is unsatisfied because of their low immunogenicity, undesired degradation, limited cross-presentation, and acquired resistance. Here, we developed a nanoparticle-based neoantigen vaccine system to overcome these challenges. Using a bioinformatics pipeline, we predicted both MHC Class I and Class II neoantigen peptides for B16-F10 melanoma model with high IFN-γ immune response. We then screened an optimal incorporation strategy to formulate nanovaccines by either directly absorbing neoantigen peptides on PLGA nanoparticle (NP) or conjugating them to PEG-PLGA through a pH-responsive strategy or a redox-responsive strategy. By formulating nanovaccine with redox-responsive neoantigen-polymer conjugates and a STING agonist, we demonstrated that our nanovaccine combined with αPD1 was significantly more effective in tumor inhibition than non-formulated neoantigen peptides, with a 50% survival rate on day 38, compared to 0% for PBS-treated group and 20% for non-formulated neoantigen peptides-treated group. To understand the mechanism, we evaluated the immune related cytokines in mouse blood on day 15 after treatment and found that our neoantigen nanovaccine achieved the highest expression of immune related cytokines among all arms, indicating that our nanovaccine induced higher immune response than non-formulated neoantigen peptides or other NP strategies. Our work develops a novel nanoparticle-based neoantigen vaccine that will improve current personalized cancer immunotherapy.

### Nano-based delivery of Cas9-guide RNA complex for tumor immunotherapy

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Uveal melanoma (UM) is one of the most common intraocular tumors with a high chance of liver metastasis. Currently, there is no effective treatment available for UM once it become metastatic. Immunotherapies through checkpoint inhibition, such as the blockade of programmed death-1 (PD-1), and PD-1 ligand (PD-L1), have opened a new avenue in the field of cancer treatment. The current standard of care for PD-1/PD-L1 inhibition is systematic administration of antibodies such Nivolumab, which however, is always accompanied by the risk of breaking peripheral immunological tolerance. In addition, local delivery of the inhibitors through suprachoroidal space injection is challenging due to the need for frequent administration, which can lead to retinal detachment, hyphema, and cataract development. A potential solution is to permanently downregulate PD-L1 on tumor cells through a single administration. This can be achieved by the application of highly precise genome editing ability of CRISPR-Cas9. However, current viral based delivery system for Cas9 possesses significant limitations in clinical application, including low packing efficiency, potential off-target effects, and immune to AAV capsid. The recent development cell membrane coated nanoparticles, typically ones using exosomes, as drug carrier provide a promising alternative method for in vivo genome editing due to their immunomodulatory and high cellular uptake nature. Here, we developed tumor exosome-coated poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) nanoparticles as drug carrier for Cas9/PD-L1 ribonucleoprotein (RNP). We have demonstrated that, exosome-coated PDMAEMA nanoparticles could efficiently load with Cas9/PD-L1 RNP, promote the penetration into melanoma cell-lines, and accelerate the endosomal escape, thus enabling targeted PD-L1 downregulation.

### Plant virus-like particle in situ vaccine immunotherapy: Insights into the unique potency of CPMV

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Cancer immunotherapies are designed to modulate the local tumor microenvironment (TME) by eliminating the blockade of immune-suppression and favor an anti-tumor immune response. We have established that plant- based Cowpea mosaic virus like particles (CPMV-VLPs) are highly potent immune-modulator of TME when applied as an in situ vaccine. The efficacy of CPMV in situ vaccine has been demonstrated in several mouse cancer models and canine patients. Our data has indicated that the systemic anti-tumor immunity and immune memory prevents metastasis and recurrence. While we continue to evaluate and expand the potency of CPMV immunotherapy in more challenging cancer models, this U01 program focuses on understanding the underlying mechanism for the unique potential of CPMV VLPs. In this meeting, we will provide updates on our efforts in these directions: 1) Our data has revealed that the uniqueness of CPMV as an in situ vaccine is not merely a manifestation of particle morphology. As compared to several other icosahedral plant viruses, the CPMV capsid is a significantly stronger immune-stimulator. Our experimental results are supported by the in silico analysis on capsid protein immunogenicity. 2) Our studies have also indicated that cell surface vimentin expressed on immune cells could play a critical role in driving the CPMV-immune cell interactions. Using a library of VLPs with engineered vimentin affinity we are investigating whether or not vimentin plays a role in the CPMV-mediated anti-tumor efficacy. 3) We have also investigated the role of pre-existing immunity against the CPMV virus in determining the outcome of in situ vaccine. Interestingly, our results suggest that pre-existing anti-CPMV antibodies could further potentiate the efficacy of the in situ vaccine immunotherapy.

### Development of CS1-targeted nanoparticles for the treatment of multiple myeloma

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Multiple myeloma (MM) is the second most common hematological malignancy and accounts for approximately 20% of the deaths annually from hematological malignancies. Signaling lymphocytic activation molecule F7 (SLAMF7, also called CS1) is a glycoprotein expressed on myeloma and natural killer cells but not on normal tissues and hematopoietic stem cells. The overarching objective of this project is to develop, characterize, and demonstrate a CS1-targeted nanotherapy approach that would improve the efficacy of chemotherapy against MM. Our studies with wild type and CS1 knockout cells showed efficient (>95%) and CS1-specific targeting of wild type MM cells in mice with a CS1-targeted monoclonal antibody (mAb). Subsequently, we have developed CS1-mAb-conjugated polysorbate/phospholipid-based nanomicelles that are similar in size to an antibody and rapidly penetrate into bone marrow, spleen, and other extravascular MM metastatic depots and deliver payloads in a contact-facilitated manner. CS1-targeted nanomicelles loaded with a chemotherapeutic agent target and kill myeloma cells in vitro. We next examined if melphalan (an alkylating chemotherapy drug) and/or a VLA4 inhibitor could enhance the efficacy of MM killing by CS1-targeted nanomicelles loaded with camptothecin (CPT; a DNA topoisomerase inhibitor). Addition of melphalan to the CS1-CPT nanomicelles significantly prolonged the median survival time of mice from approximately 50 days to 73 days (P&lt;0.01). The addition of a VLA4i did not enhance the efficacy of the CS1-CPT nanomicelles alone or in combination with melphalan. A smaller single-chain variable fragment to CS1 is being developed to conjugate to nanomicelles and test in mice.

### Nanovaccine platform to combat pancreatic cancer

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Pancreatic cancer (PC) is one of the most lethal malignancies and represents an increasingly challenging threat. Our U01 synergistically integrates tumor upregulated antigen(s), nano-delivery systems, combination vaccine design, and new antigen-specific murine PC models. The overall goal is to develop novel mucin-containing nanovaccine platforms and combine them with checkpoint blockade agents that can induce both long-lived cytotoxic T lymphocyte responses and maintain the T cell response, overcoming the immunosuppressive tumor microenvironment. We purified the differentially expressed transmembrane tumor antigen MUC4β and encapsulated it within polyanhydride, polyester, and diaminosulfide nanoparticles. We showed that the protein retained its structural conformation during polyanhydride and polyester nanoparticle synthesis and its antigenicity upon release, leading to the emergence of polyanhydride nanoparticles as a lead candidate nanovaccine. Next, we showed that the MUC4β-nanovaccine activated bone marrow-derived dendritic cells, as indicated by upregulation of CD80 and CD40, pro-inflammatory cytokine secretion, and induction of MUC4β-specific antibodies. Current work is focused on predicting immunodominant T and B cell epitopes of the MUC4β domain and identifying multiple peptides with high binding affinity for tetramer synthesis. We generated and characterized a panel of syngeneic PC cell lines from tumors developed from a genetically engineered KPC model and transfected them with human MUC4 minigene. Upon implantation in mice, MUC4 transfected cells produced larger tumors compared to the vector control. To analyze the MUC4-specific immune response, ongoing work is focused on the generation of hu-MUC4 transgenic mice. Altogether, these results have laid the foundation for development of a PC immunotherapy nanovaccine platform.

### Simultaneous Treatment of Cancer and Atherosclerosis with a Targeted Multifunctional Immunotherapy Nanoparticle for Cancer Patients with Comorbid Atherosclerosis

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Given the high percentage of cancer patients with co-existing cardiovascular diseases, there is an unmet need to develop targeted therapeutics for cancer and comorbid atherosclerosis. We have developed an immunomodulatory nanoparticle by conjugating PD1 mimetic peptides (PD1Y) to hyaluronic acid nanoparticles (HANPs) encapsulated with Avasimibe (PD1Y-HANP/Avasimibe), which is an inhibitor of acyl-coenzyme A: cholesterol acyltransferase that reduces intracellular cholesterol, activates cytotoxic T cells, and inhibits tumor growth. To accurately evaluate the effects of such multifunctional therapeutic agents, we developed a mouse model carrying both diseases by implanting mouse cancer cells in Apoe -/- mice, resulting in tumor bearing mice developing atherosclerosis. We found that systemic administration of PD1Y-HANP/Avasimibe led to targeted delivery into both tumors and atherosclerotic plaques in Apoe -/- mice bearing colon tumors. Intratumoral accumulation of PD1Y-HANP/Avasimibe promoted infiltrating the antigen presenting dendritic cells and effector T cells as well as activating tumor specific CD8+ T cells in tumors. Importantly, PD1Y-HANP/Avasimibe treatment had the strongest tumor growth inhibition compared with Avasimibe and HANP/Avasimibe. PD1Y-HANP/Avasimibe treated mice had significantly reduced tumor recurrence, prolonged survival and protected from tumor cell re-challenging. Furthermore, histological analysis of the major arteries revealed that the amount of atherosclerotic plaques was significantly decreased in the PD1-HANP/Avasimibe treated mice. The treatment also resulted in markedly lower levels of CD8+ T cells and CD68+ macrophages in the plaques compared to the control. Therefore, this immunomodulating and tumor-inhibiting nanoparticle demonstrated the potential for the development of a novel targeted therapy for cancer patients with atherosclerosis.

### Image-guided systems pharmacology of nanoparticulate prodrug activation

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Despite successful translation of therapeutic nanoparticles (TNPs) into the clinic, the field continues facing challenges in predictably and selectively delivering nanomaterials for the treatment of solid cancers. Here, we apply a combination of intravital microscopy, computational systems-level modeling, and multiscale confocal imaging of optically-cleared tissues to study the delivery and activity of nanotherapies in mouse models of solid cancers. In particular, we apply this image-guided systems-pharmacology approach to understand how a recently described prodrug activation strategy, based on dual administration of two co-activating nanoparticles, is able to more selectively act in the tumor compared to elsewhere in the body [Miller et al., 2018, ACS Nano, 12, 12814-12826]. We employ a new bio-orthogonal chemistry based on palladium-catalyzed prodrug uncaging, such that nanoparticle-delivered palladium activates the cytotoxic action of a co-administered, nanoparticle-delivered prodrug. A combination of imaging and computational modeling reveals that the two-nanoparticle strategy mitigates exposure outside of the tumor compared to a traditional single-nanoparticle approach, in part due to a compounding of physiological factors underpinning the enhanced permeability and retention effect, combined with the potential for saturable mononuclear phagocyte system (MPS) clearance. To support these conclusions, we leverage published experimental data based on traditional single-nanoparticle treatments, Kupffer cell depletion studies, and MPS saturation experiments using “loading doses” of pre-administered empty nanoparticles. Overall, we demonstrate how in vivo imaging combined with quantitative reaction/transport modeling can guide the interpretation and optimization of combination drug delivery strategies.

### Amphipathic Secondary Structure of Melanoma Antigens Drives Stable Encapsulation in STING-Activating Ultra-pH-Sensitive Nanoparticles

*Jonathan Wilhelm (Presenter), Manuel Quinones Perez, Min Luo, Zhaohui Wang, Zhida Liu, and Jinming Gao\**

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Due to its high mutational burden and immunogenicity, melanoma has been a prominent responder to immunotherapeutic treatments like checkpoint inhibitor therapy. However, significant autoimmune disorders and lack of response in immune-desert patients have limited the overall efficacy of these therapeutics. We have developed an ultra-pH-sensitive nanoparticle, PC7A, capable of efficient spatio-temporal orchestration of innate immune activation through the STING pathway and cytosolic delivery of antigens for cross presentation in antigen presenting cells. Through robust innate immune activation and antigen presentation, vaccination by PC7A generates tumor specific cytotoxic T lymphocytes, potentiating anti-tumor efficacy without the dangerous systemic cytokine expression associated with current clinically available adjuvants. We have expanded the nanovaccine platform with multiple melanoma antigens and found specific peptide properties that enhance antigen encapsulation efficiency and stability. Alignment of hydrophilic and hydrophobic amino acids along an alpha helical structure in an amphipathic arrangement induces helical formation within the nanoparticles, facilitating antigen stability for robust delivery to lymph nodes for downstream immune activation.

### mRNA Analysis in Circulating Tumor Cells Purified by Click Chips

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Recent research focus in the field of circulating tumor cells (CTCs) has moved beyond the simple capture or enumeration of CTCs and gravitated towards approaches that allow for mRNA profiling. CTCs house intact mRNA, providing reliable gene signatures for non-invasive cancer diagnosis and prognosis. For this purpose, we’ve developed a new covalent chemistry-enabled CTC capture/release platform – “Click Chip”. This platform is designed by integrating click chemistry-mediated CTC capture (sensitive and rapid) and disulfide cleavage-driven CTC release (mild, specific, and rapid) on nanostructured substrates to enable efficient purification of CTCs with well-preserved mRNA. The CTC-derived mRNA was subjected to RT-droplet digital PCR (RT-ddPCR) for quantifying single genes or Nanostring nCounter platform for profiling gene panels. In our proof of concept study, ALK/ROS1 rearrangements were quantified using CTC-mRNA recovered by Click Chips and matched with those identified in biopsy specimen in late-stage ALK/ROS1 positive non-small cell lung cancer patients. Furthermore, we’ve optimized the click chips for CTC purification from hepatocellular carcinoma (HCC), where highly prevalent mutations have not been identified. HCC-specific mRNA profiling on CTCs recovered from HCC patients by Click Chips can be used for predicting HCC prognosis. This streamlined workflow is optimum for non-invasive gene expression profiling based on well-preserved CTC-derived mRNA.

### Covalent chemistry enables EV purification on nanosubstrates – toward non-invasive detection of early-stage hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths worldwide. The poor prognosis of HCC is due to the fact that diagnosis is often made at a late stage in disease development. Earlier detection of HCC is critical to reducing the high HCC mortality rates, particularly because numerous potentially curative therapeutic interventions are available to treat early-stage HCC. In this study, we developed a covalent chemistry-based nanostructured silicon substrate (“EV Click Chip”) for the isolation of HCC extracellular vesicles (EVs). The EV Click Chip leverages specific bioorthogonal ligation reactions and sensitive multi-marker cocktail antibody identification of the HCC EVs. The EV Click Chip also allows for the subsequent release of the captured HCC EVs and is optimal for the downstream molecular analysis. A well-validated 10 HCC-specific genes were quantified using reverse transcription droplet digital PCR (RT-ddPCR) in HCC EVs purified by the optimized EV Click Chips for the detection of HCC. Our EV Click Chip-based HCC EV Assay outperformed clinical AFP test for specifically distinguishing early-stage HCC from at-risk cirrhosis patients.

### A First-in-Human Study of a Spherical Nucleic Acid (SNA) Cancer Immunotherapy

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Immunestimulatory spherical nucleic acids (IS-SNAs) have advanced to clinical evaluation for the treatment of solid tumor cancers. IS-SNAs are nanostructures consisting of CpG-oligonucleotides, adsorbed and oriented onto liposomes at high surface density. This structure and formulation of CpG has been developed by Exicure (as AST-008), advanced through pre-clinical studies, and completed a Phase 1 clinical trial; it is currently under evaluation in a Phase 1b/2 clinical trial in cancer patients. AST-008 is designed to enter and activate immune cells to treat solid tumors in combination with immune checkpoint therapeutic agents (e.g., pembrolizumab). Outcomes in a Phase 1 trial with healthy volunteers found no adverse effects and the activation of cellular immunity (% of CD69+ NK and T-cells) in response to subcutaneous injection of AST-008. In an ongoing Phase 1b/2 trial, Exicure plans to administer AST-008 intratumorally into palpable tumors across several cancer types (Merkel cell carcinoma, melanoma, head and neck squamous cell carcinoma). This trial is evaluating escalating doses of AST-008 in combination with pembrolizumab, and no severe adverse effects or dose-limiting toxicities have been observed to date. A subsequent Phase 2 trial, upon completion of the dose-finding and pathology studies of the Phase 1b, is expected to include the treatment of PD1- and PD-L1-refractory patients and generate safety, pharmacokinetics/pharmacodynamics, and efficacy data using IS-SNAs. Outcomes from this trial will support the progression towards clinical use of IS-SNA technology for cancer immunotherapy as an agent for stimulating anti-tumor immune responses with a nanotechnology-based formulation of CpG oligonucleotides.

### Spherical Nucleic Acids targeted to wild-type Isocitrate Dehydrogenase-1 for metabolic reprogramming of Glioblastoma

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Wild-type Isocitrate dehydrogenase-1 (IDH1) is overexpressed in 65% of Glioblastoma (GBM), compared to normal brain tissue, and genetic and pharmacologic inactivation of IDH1 decreases GBM cell growth and prolongs survival of animals bearing patient-derived xenografts. To downregulate GBM-associated IDH1 expression, we developed PLGA-based Spherical Nucleic Acid (SNA) nanostructures, with enhanced endosomal release properties for the co-delivery of siRNA targeted to IDH1 and the endo-porter peptide, an agent capable of disrupting the endosomal membrane. GBM cells treated with siIDH1-conjugated endo-porter encapsulated PLGA-SNAs showed enhanced IDH1 knockdown activity compared to SNAs without endo-porter functionalization. As GBM tumors with elevated levels of IDH1 are characterized by a highly immune-suppressive tumor microenvironment, characterized in particular by robust infiltration of tumor-promoting M2 macrophages, we developed SNAs that target the cGAS-STING DNA sensing pathway, to repolarize M2 tumor-associated macrophages, and to activate a T cell effector response against IDH1 wild-type tumor. SNAs carrying a 45bp IFN-simulating dsDNA oligonucleotide, the most commonly used and widely characterized cGAS activator, potently activated cGAS-STING innate immunity, as evidenced by increased IRF responses, elevated protein marker expression indicative of the activated M1 macrophage state, and enhanced expression of pro-inflammatory cytokines in macrophage cultures in vitro, and in intracranial isogenic GBM explants in vivo. Our use of SNAs establishes cGAS-agonistic SNAs as a novel class of immune-stimulatory modalities for triggering innate immune responses in particular against IDH1 wild-type GBM tumors, and point to combinatorial treatment regimes of gene-regulatory siIDH1- and immunomodulatory STING-agonistic SNAs.

### Elucidating the Design Rules for Cancer Nanomedicine with High-Throughput Experimentation and Machine Learning

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The potential design space for nanotherapeutics is vast, but the extent of characterization of this space is limited, due to the challenges associated with synthesizing, assaying, and analyzing large numbers of nanostructures. In this work, we present an approach for systematically exploring the design space of spherical nucleic acids (SNAs) designed as cancer vaccines. We synthesized more than 3,000 SNAs by varying 11 independent design parameters related to the liposomal core, oligonucleotide shell, and peptide antigen. We developed a high-throughput assay using self-assembled monolayers for MALDI mass spectrometry (SAMDI) to evaluate immune cell activation by SNAs. We used non-linear machine learning models to accurately predict Toll-like receptor (TLR) activation as a function of SNA design. This analysis revealed the relative importance of parameters and combinations of parameters and determined the minimum number of SNAs needed to elucidate the structure-activity relationships in the design space. These insights have guided subsequent parameter exploration and have important implications in the design of SNA-based therapeutics. In addition, the methodology is general and provides a framework for optimizing nanomedicines for a variety of applications.

### Spherical Nucleic Acids as Immunotherapeutic Agents for Prostate Cancer

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Spherical nucleic acids (SNAs) are a novel platform that holds promise in the field of rational immunology. A dense radial arrangement of adjuvant oligonucleotides around a nanoparticle core makes up the immunostimulatory SNA architecture. This structure leads to emergent properties such as rapid cellular uptake, increased nuclease stability, and favorable lymph trafficking, which make these constructs more efficacious than their individual components mixed together. This CCNE effort focuses on developing SNA technology towards the treatment of prostate cancer. Previously, we have shown that SNAs can eradicate tumors in 30% of mice using MHC-I peptides. To further increase tumor clearance, we sought to activate additional immune pathways by incorporating MHC-II antigens. This approach resulted in complete tumor remission for 66% of mice. Importantly, as we have previously demonstrated for MHC-I peptides, the manner in which the peptides are incorporated into the SNA architecture has a profound effect on tumor clearance. In addition, we have found that the conjugation chemistry used to incorporate antigenic peptides into SNAs influences their efficacy, possibly due to the rates at which the linkers liberate the native peptides. We synthesized SNAs using linker chemistries with varied rates of peptide release to investigate their impact on the immunostimulatory potency of SNAs and found that they increase immune activation by up to two orders of magnitude. Taken together, these results highlight the incredible potential of SNAs to impact cancer treatment.

### A first-in-human phase 0 clinical study of RNAi-based Spherical Nucleic Acids in patients with recurrent Glioblastoma

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The lack of precision therapies for Glioblastoma (GBM) combined with insufficient delivery of drugs to intracranial tumor sites, have contributed to making GBM one of the most difficult cancers to treat. We have developed a novel precision medicine approach for treating GBM through inhibiting the expression of oncogenes using brain-penetrant RNA interference (RNAi)-based Spherical Nucleic Acids (SNAs). SNAs consist of gold nanoparticle cores covalently conjugated with densely packed, highly oriented siRNA oligonucleotides. Based upon preclinical evaluation in patient-derived cells and xenograft models, here we assessed SNA toxicology in non-human primates, and conducted a single-arm, open-label phase 0 first-in-human trial (NCT03020017) to determine safety, pharmacokinetics and bioavailability of intravenously administered SNAs carrying siRNA specific for the GBM oncogene Bcl2Like12 (Bcl2L12). Recurrent GBM patients were treated with systemically administered siBcl2L12-SNAs (NU-0129) at a dose of 0.04 mg/kg, corresponding to 1/50th of the No Observed Adverse Event Levels (NOAEL), followed by tumor resection 20-28 hours later. Safety assessment revealed no significant treatment related toxicities. Inductively Coupled Plasma Mass Spectrometry, X-ray fluorescence microscopy (XFM), and silver staining on resected GBM tissue demonstrated that intravenously administered SNAs crossed blood-brain/blood-tumor barriers and robustly accumulated in patient tumor, with gold enrichment observed in the tumor-associated endothelium, macrophages and tumor cells. In conclusion, this first in-human clinical trial in recurrent GBM identified NU0129 as a safe, brain-penetrant precision medicine approach for the systemic delivery of siRNA oligonucleotides to intracranial tumor sites, and point to advanced dose escalation studies to assess efficacy as the next step in clinical development.

### Target-Activated in Situ Nano-Aggregation of a Small-Molecule Probes for Cancer Therapy

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Nanoparticles have often been considered as novel choices of delivering drugs selectively to tumors by taking advantage of the well-known EPR (Enhanced Permeability and Retention) effect at tumors. However, it is also widely accepted that nanoparticles have poor penetration into the solid tumor mass because of their large size, high intratumoral pressure and also tumor hypoxic condition; this significantly compromises the delivery efficiency and thus treatment efficacy. Recently, we reported a novel target-activated in vivo self-assembly nanoplatform for bioorthogonal reaction between aromatic nitriles and cysteine. In this project, we applied this strategy to overcoming the low efficiency in delivering nanoparticles to tumors and amplify radiotherapeutic effect. Instead of direct use of nanoparticles, we used small molecules to assemble nanoparticles in situ at tumor sites. A caspase/ROS-sensitive prodrug was designed to enhance radio-therapeutic effects. The prodrug took advantage of radiation-induced apoptosis and reduction environment to trigger intracellular nano-aggregation and release paclitaxel to enhance cell death during the radiotherapy. The results have demonstrated the tumor suppression effect of prodrugs combined with low-dose of radiation (2 Gy) in both prostate tumor PC-3 model in NSG mice and breast cancer 4T1 model in BALB/c mice. In combination even with low treatment radiation dose, the median survival time of NSG mice with PC-3 human prostate cancer xenografts has been increased to 87 days from 44-52 days for controls.

### Lu-177 Labeled α-Melanocyte Stimulating Hormone Functionalized Ultrasmall Core-Shell Silica Nanoparticles for Melanoma Radiotherapy.

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Lutetium-177 (177Lu) radiolabeled ultrasmall (~6 nm dia.) fluorescent core-shell silica nanoparticles (Cornell prime dots or C’ dots) were examined for targeted melanoma radiotherapy. It was hypothesized that the unique and tunable surface chemistries of the C’ dots could be optimized to improve in vivo pharmacokinetics resulting in a reduction of dose limiting off-target toxicities coupled with enhanced treatment efficacy and survival in the B16F10 murine melanoma mouse model. Polyethylene glycol (PEG) encompassed C’ dots were engineered to display 10-15 alpha melanocyte stimulating hormone (αMSH) peptide analogs, which bind the melanocortin-1 receptor (MC1-R) expressed on melanoma. The 177Lu-DOTA-αMSH-PEG-C’ dots were radiochemically stable and exhibited high MC1-R mediated melanoma cellular affinity and internalization. In vivo, selective tumor uptake and favorable biodistribution properties were demonstrated in the syngeneic B16F10 mouse tumor model. Correlative histopathology revealed expected tumor tissue necrosis, while no acute pathologies were observed in the liver or kidneys. Moreover, a limited survey of immune cell populations in tumor tissue suggested that both radiolabeled and non-radiolabeled MC1-R targeted C’ dots may prime cytotoxic T cells in the tumor microenvironment. These results demonstrated that 177Lu-DOTA-αMSH-PEG-C’ dot treatment of B16F10 melanoma tumor bearing mice resulted in clear survival benefits with no observable acute toxicities, with the potential to augment the tumor microenvironment and synergize with immunotherapy.

### Stiffness of Paclitaxel-Loaded Nanoparticles Dictates Cellular Uptake

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The incorporation of chemotherapeutic agents, such as paclitaxel, into polymeric nanoparticles (NPs) enhances their safety and efficacy, but the conundrum remains as to the optimal composition and properties of the carrier material. Specifically, the effect of NP stiffness on cellular uptake is of keen interest. Herein we report that stiffness modulates cellular internalization and nanocarrier efficacy, with softer structures generally exhibiting more rapid cellular internalization and enhanced potency. We have previously demonstrated sustained and efficient high dose delivery of the common chemotherapeutic paclitaxel (PTX) using poly(1,2-glycerol carbonate)-graft-succinic acid-paclitaxel (PGC-PTX) conjugate NPs. Incorporation of a more hydrophilic polymer, such as poly(lactide-co-glycolide) (PLGA) or polypropylene glycol (PPG), disrupts compact aggregation in the hydrophobic polymer core and reduces particle stiffness. Conversely, addition of cholesterol increases compact aggregation in the core and increases stiffness. We evaluated the modulation of nanocarrier mechanical properties as well as efficacy through atomic force microscopy and various in vitro methods such as flow cytometry.

### Ultrasmall silica nanoparticle platforms for improved small molecular inhibitor delivery and efficacy

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Objective: To demonstrate that ultrasmall (sub 8-nm), multimodal (PET/optical), renal-clearable silica nanoparticles (Cornell prime dots or C’ dots) are an ideal drug delivery vehicle for enhanced delivery, efficacy, and improved therapeutic index of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in murine xenograft models of non-small cell lung cancer. Method: Ultrasmall C’ dot nanoparticles (&lt;8 nm diameter) functionalized with a gefitinib analog (APdMG) bound to an enzymatically-cleavable dipeptide (Phe-Lys) linker were synthesized in aqueous environments using previously established methods and resulted in the generation of a gefitinib-nanoparticle drug conjugate (i.e., Gef-NDC). Varied drug-per-particle ratios (DPR = 11-56) were compared in vivo via PET imaging (89Zr-Gef-NDC) to ensure primary renal clearance. Uptake and potency of released gefitinib analog was validated in vitro using flow cytometry (optical; Cy5) and target inhibition studies (Western blot), respectively. Efficacy of the optimized Gef-NDC construct was compared to free gefitinib in both in vitro and in vivo models to evaluate LD50 values, tumor growth inhibition, and overall survival. Results: Highly stable Gef-NDCs with varying DPRs (DPR = 11-56), demonstrated predominant renal clearance (DPR ≤ 40) in naive mice and a dose-dependent decrease in the levels of phosphorylated EGFR in ECLC26 non-small cell lung cancer cells. Gef-NDC constructs, optimized to demonstrate primary renal clearance (DPR = 40), were then further evaluated both in vitro and in vivo. Dose-dependent cellular uptake was observed for Gef-NDCs when incubated with ECLC26 cells. Evaluation of cytotoxicity demonstrated significantly enhanced killing of the Gef-NDC over free gefitinib, resulting in LD50 vales of 9.6 nM and 3 uM, respectively. ECLC26 tumor-bearing mice were treated with either intravenous saline control (Days 0, 3, 6), oral gavage gefitinib (150 mg/kg/day), or intravenous Gef-NDC (3 nmoles; Days 0, 3, 6) while tumor volumes were monitored daily. Although tumor growth inhibition and overall survival were found to be fairly equivalent between treated groups, the amount of total gefitinib dose administered to mice in the NDC group was orders of magnitude less (360 nmoles) than the cohort receiving the native drug (78 umoles), equating to a 216-fold dose reduction. Additionally, evaluation of off-target (ear) tissue phosphorylated EFGR levels revealed reduced inhibition for Gef-NDC treated mice. Conclusion: To improve the delivery and efficacy of the small molecular inhibitor gefitinib, we engineered C’ dots to display varying densities (n= 11-56) of an enzymatically-cleavable gefitinib linker construct. It was demonstrated that particle DPRs can be accurately tuned over a wide range, allowing for the selection of optimal drug loading while maintaining dominant renal clearance. Optimized Gef-NDCs demonstrated enhanced delivery and therapeutic efficacy over that of the free drug for both in vitro and first-time in vivo studies. Overall, these results demonstrate that ultrasmall C’ dots function as an ideal drug delivery vehicle exhibiting favorable pharmacokinetics, high drug loading, low off-target toxicity, and antitumor efficacy at a fraction of the administered free drug dose.

### Ultra Small Renal-clearable Silica Nanoparticle Targets Prostate Cancer

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Prostate cancer (PCa) is the second leading cause of cancer-related diseases among men in the United States with estimated 174,650 new cases and 31,620 deaths in year 2019. Non-invasive, highly sensitive and quantitative positron emission tomography (PET) imaging plays vital roles in primary staging, treatment planning and response evaluation of PCa. Although great advance has been achieved during the last decade in developing radiolabeled PSMA-targeting ligands (such as monoclonal antibody, antibody fragments and urea-based small molecule inhibitors) for PCa-targeted imaging and therapy, challenges still exist. Building upon the successful clinical translation of a serials of ultrasmall renal clearable dye-encapsulated Cornell Dots (C dots) and Cornell Prime Dots (C’ dots) (NCT01266096, NCT03465618 and NCT02106598) for metastatic melanoma and malignant brain tumor patients, in this study, we aim to develop a C’ dot-based PET/optical dual modality ultrasmall silica nanoparticle that can specifically target PCa while evading undesired accumulation in kidneys and salivary glands. As-developed nanoparticle also holds the potential as a theranostic (dual-modality imaging & therapy) platform by providing not only bright near-infrared (NIR) optical signal during the surgery, but also further labeling with therapeutic radionuclides (e.g., Lutetium-177 [177Lu, t1/2=6.6 d], Actinium-225 [t1/2=10 d], etc.) for targeted PCa radiotherapy.

### Phenotyping animal models of multiple myeloma in vivo

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In vivo phenotyping of animal models of MM can provide invaluable insight about the pathogenesis of MM as well as aid in the identification of both therapeutic and imaging strategies. The Imaging Biomarker Quantification and Standardization (IBSQ) Core has developed and implemented methodologies to enable high-throughput phenotyping and characterization of animal models of MM. Through ongoing informatics efforts on a co-clinical imaging program, we leveraged activities to develop a mouse hotel segmentation pipeline. The pipeline is further being developed as a web-based pipeline to facilitate PET image analysis. In addition, we developed pipelines to enable automated (or semi-automated) segmentation of disseminated tumors of MM. These technologies are expected to significantly enhance throughput and standardization of research activities involving animal models of MM. Finally, we characterized VLA-4 expression and glucose metabolism in animal models of MM and assessed response therapy. U266 cell-lines are reported to exhibit higher expression of VLA-4 compared to MM.1S. We hypothesized that these cell lines can be used to develop a theranostic strategy for VLA-4 targeted imaging/therapy. In collaboration with Project 3, we transfected reporter genes to enable BLI imaging of tumor burden in U266 cell lines. Both U266 and MM.1.S cell lines were used to generate sub-cutaneous and disseminated animal models of MM. We characterized VLA-4 expression (via 64Cu-LLP2A/PET) and glucose metabolism (via 18FDG/PET) longitudinally in animal models of MM, characterized the association between VLA-4 expression versus glucose metabolism, and assessed response to Bortezomib therapy as a benchmark for VLA-4 targeted therapies.

### MT1-MMP Activatable Provector for Targeting of Pancreatic Cancer

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As of 2015, pancreatic ductal carcinoma (PDAC) has an overall 5-year survival rate of 8.5% which is attributed to most cases being diagnosed after the cancer has metastasized. In epithelial cancers, such as PDAC, metastasis results in an increase in expression of certain membrane bound proteins including MT1-MMP (MMP-14). MMP-14 is a member of the matrix metalloproteinase (MMP) family of enzymes that have been directly correlated with tumor progression. Therefore, our lab is developing protease responsive adeno-associated virus (AAV) virus nanoparticles (VNPs), known as provectors, to target sites of MMP overexpression. In this work, we have developed an AAV9 based VNP capable of sensing the presence of upregulated MMP-14, referred to as IPES. Protease-switchability is accomplished by blocking the receptor binding site on the virus capsid with a negatively charged aspartic acid motif flanked by protease cleavage sequences. At sites of high protease concentration, the negative motif is cleaved from the virus capsid by active proteases, “un-locking” the binding site for transduction. Silver stain of VNP proteins confirms MMP-14 cleavage of IPES mutant. Transduction experiments indicate that the IPES mutant has a 13.8-fold activatability as compared to the previously developed particles’ 3.5-fold activation. Animal work in a xenograft KPC tumor C57BL/6 mouse model is ongoing and will quantify VNP targeting of tumor cells from retro-orbital injection. A viral vector optimized to target metastatic sites through their upregulation of MMP-14 is a promising non-invasive treatment that could be used in conjunction with surgery to treat PDAC and other highly metastatic cancers.

### PEDF-derived peptides for targeted delivery of anti-cancer agents.

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67 kDa laminin receptor (67LR) is located on the surface of different cells at low levels. When 67LR is overexpressed, in cancer cell lines it is associated with increased aggressiveness and malignancy, in cancers such as ovarian, breast, gastric, colorectal, lung thyroid, pancreatic, prostate, uterine, glioma and leukemia. High levels of 67LR are signs of aggressive tumor cells and there is a correlation between the amount of 67LR with an adhesive and invasive effect of tumor cells, and their ability to resist chemotherapy. We have focused on Pigment epithelium-derived factor (PEDF). PEDF is a growth factor which on its surface displays an alpha-helical 34-mer therein that binds to 67LR. From the 34-mer we have located the specific region of the sequence, comprising just 8-9 amino acids which binds to 67LR and leads to 67LR internalization via endocytosis. Liposomes are vesicles composed of a lipid bilayer that are used as drug carrier to increase targeting ability and reduce toxicological side effects due to poor pharmacokinetics of anti-cancer drugs. Arsenic-Platinum liposome (nanobin) is a therapeutic agent which has shown attenuated cellular toxicity and high efficacy against tumor cell lines of lymphoma, breast cancer and ovarian cancer. Modifying the liposome surface with similar peptides to co-internalize with 67LR will increase specificity of this drug delivery system the cellular uptake will enhance and thus anti-cancer efficacy. A PEDF-mimetic peptide is being conjugated to the surface of As-Pt nanobins to improve drug delivery and specificity against aggressive tumors witch express 67LR on the surface.

### Icaritin Exacerbates Mitophagy and Synergizes with Doxorubicin to Induce Immunogenic Cell Death in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) resistant to both chemotherapy and immunotherapy is among the deadliest malignancies. Doxorubicin widely used in transarterial chemotherapy in HCC can induce immunogenic cell death (ICD), but the resulting immunogenicity is still weak. We aim to seek a new strategy which can improve the efficacy of ICD in HCC based on a novel immune regulation drug called icaritin. Icaritin induced mitophagy and apoptosis to provoke ICD both in mouse Hepa1-6 and human Huh7 HCC cells. Combination of icaritin and doxorubicin with molar ratio of 1:2 played a synergistic role in ICD induction. Poly lactic-co-glycolic acid (PLGA)-polyethylene glycol (PEG)-aminoethyl anisamide (AEAA) nanoparticle (NP) target co-delivery of icaritin and doxorubicin remodels immune-suppressive microenvironment and triggered a robust immune memory response, which exerts satisfactory anti-HCC effect in early stage mouse HCC model. For the advanced stage, combination PLGA-PEG-AEAA NP together with lenvatinib prolonged survival time significantly. Collectively, our findings reveal a new anti-HCC mechanism of icaritin and provide a novel immune-based therapeutic strategy for HCC.

### Turning cell adhesion-mediated drug resistance against multiple myeloma: proof of principle for the use of VLA4-CPT-PD nanoparticles in combination with chemotherapy

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In Multiple Myeloma (MM), Very Late Antigen 4 (VLA-4) is a key contributor of cell-adhesion mediated drug resistance (CAM-DR), the process whereby myeloma cells (MMC) survive chemotherapy thanks to protective interactions with the bone microenvironment. We hypothesized that combining VLA4-targeted nanoparticles loaded with a camptothecin (CPT) pro-drug (VLA4-CPT-PD) would enhance the effects of chemotherapeutics and delay recurrence. RNAsq in patient samples showed that the target of CPT, TOP1, is highly expressed in MMC of patients. In vitro, CPT or VLA4-CPT-PD reduced proliferation, induced cell death, and improved response to lenalidomide, melphalan, and rapamycin in a panel of MMC lines. Both in human and murine models of co-culture of MMC and stromal cells, VLA4-CPT-PD, alone and/or in combination with melphalan, effectively and selectively depleted MMC. In 5TGM1/KaLwRij MM-bearing mice, co-treatment with VLA4-CPT-PD and low-dose melphalan reduced tumor burden at multiple skeletal sites (p&lt;0.01) and in the spleen (p&lt;0.05) by ex-vivo optical imaging. Serum protein electrophoresis (SPEP) showed a 66% reduction of the M-component relative to VLA4 particles with no drug (VLA4-ND p&lt;0.001) and a 60% reduction relative to VLA4-ND plus melphalan (p&lt;0.05) 28 days post tumor inoculation. Accordingly, histology and immunohistochemistry demonstrated a reduction in bone marrow and spleen invasion by tumor cells. Finally, co-treatment with VLA4-CPT-PD and high dose melphalan (10mg/kg/week) in 5TGM1/KaLwRikj MM mice prolonged survival even after drug withdrawal (p&lt;0.001), without added toxicity to the kidneys, liver, or gut. In conclusion, VLA4-CPT-PD nanoparticles could represent a promising novel therapeutic tool for multiple myeloma combination regimens.

### High Co-loading Capacity and Stimuli-Responsive Release Based on Cascade Reaction of Self-Destructive Polymer for Improved Chemo-Photodynamic Therapy

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Photodynamic therapy (PDT) shows a promising synergy with chemotherapy in the therapeutic outcome of malignant cancers. The minimal invasiveness and nonsystemic toxicity are appealing advantages of PDT, but combination with chemotherapy brings in the nonselective toxicity. We designed a polymeric nanoparticle system that contains both a chemotherapeutic agent and a photosensitizer to seek improvement for chemo-photodynamic therapy. First, to address the challenge of efficient co-delivery, polymer-conjugated doxorubicin (PEG-PBC-TKDOX) was synthesized to load photosensitizer chlorin e6 (Ce6). Ce6 is retained with DOX by a π–π stacking interaction, with high loading (41.9 wt %) and the optimal nanoparticle size (50 nm). Second, light given in PDT treatment not only excites Ce6 to produce cytotoxic reactive oxygen species (ROS) but also spatiotemporally activates a cascade reaction to release the loaded drugs. Finally, we report a self-destructive polymeric carrier (PEG-PBC-TKDOX) that depolymerizes its backbone to facilitate drug release upon ROS stimulus. This is achieved by grafting the ROS-sensitive pendant thioketal to aliphatic polycarbonate. When DOX is covalently modified to this polymer via thioketal, target specificity is controlled by light, and off-target delivery toxicity is mostly avoided. An oral squamous cell carcinoma that is clinically relevant to PDT was used as the cancer model. We put forward a polymeric system with improved efficiency for chemo-photodynamic therapy and reduced off-target toxicity.

### Multimodal Theranostics using Composite Nanoshells

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Silica nanoparticles are attractive materials in biomedicine due to their high biocompatibility, stability, and chemical and mechanical tunability. Hollow silica nanoshells have been demonstrated with unique acoustic properties when filled with perfluoropentante (PFP) gas, making them attractive ultrasound contrast agents. These nanoshells not only demonstrate high intratumoral retention but their mechanical properties can be tuned to optimize mechanical index threshold, signal brightness, and continuous imaging longevity. These qualities make silica nanoshells appealing for image-guided surgical procedures, such as ultrasound-guided tumor resection. Silica nanoshells are also attractive nanomaterials for therapeutic applications. When conjugated to 1V209, a toll-like receptor (TLR) agonist, silica nanoshells demonstrated enhanced proinflammatory immune response via interleukin 1β (IL-1β) release and increased adjuvant efficacy by activating T helper cell-based immunity, making this conjugated system an appealing immunotherapeutic agent. To build upon this existing platform, research into novel composite nanoshells capable of multimodal cancer imaging and therapy would be the next step. When integrating the silica nanoshells with other materials, the resulting composite nanoshells are hypothesized to demonstrate additional properties of the embedded materials while retaining its acoustic properties. Gadolinium oxide nanoparticles (GON) are MRI contrast agents capable of lower toxicity and brighter MRI signals when compared to clinical chelated-gadolinium agents. Embedding GON into surface-modified hollow silica nanoshells can impart MRI-contrast functionality to the particles without sacrificing their optical, acoustic, or therapeutic properties. The initiative to develop hierarchical silica/GON composite nanoshells opens the opportunity for achieving a theranostic nanoplatform capable of supporting diagnostic imaging, image-guided procedures, and immunotherapy.

### Nano-optogenetic immunoengineering: Photo-tunable Remote Control of CAR T-cells

*Nhung Thi Nguyen, Kai Huang, Yun Huang, Gang Han, Yubin Zhou*

*Center for Translational Cancer Research, Institute of Biosciences and Technology, Texas A&M University*

Chimeric antigen receptor (CAR) T-cell immunotherapy has demonstrated high potential for the elimination of tumors, particularly in patients with CD19-positive lymphoma and leukemia. CARs are synthetic receptors engineered onto the surface of T cells, where they can engage specific tumor antigens in a major histocompatibility complex (MHC)-independent manner. The recognition of antigen allows T cells to be activated and subsequently perform their killing/effector activities toward tumor cells. Despite the tremendous success of CAR T-cell therapy in cancer treatment, this type of immunotherapy imposes significant safety challenges, as most notably exemplified by the cytokine release syndrome (CRS) and the “on-target, off-tumor” cytotoxicity due to the lack of precise control over the location and duration of anti-tumor immune response. Herein we present the design of light-switchable CAR T-cell (designated “LiCAR”) that enables photo-tunable activation of therapeutic T cells to induce tumor cell killing both in vitro and in vivo. When coupled with imaging-guided surgically removable upconversion nanoplates that have enhanced near-infrared (NIR)-to-blue upconversion luminescence as miniatured deep tissue transducers, LiCAR enables precise spatiotemporal control over CAR T cell-mediated anti-tumor therapeutic activity. This remotely controllable nano-optogenetic device sets the stage for the future application of optogenetic immunotherapy to attenuate side effects associated with the current therapeutic regimen and to deliver personalized anti-cancer therapy.

### Cobalt-based Nanoconstructs for the Treatment of Basal Cell Carcinoma

*Tyler Whittemore, Meghan B. Ward, Andrew Johnson, Thomas J. Meade*

*Northwestern University Center of Cancer Nanotechnology Excellence*

This research focuses on optimizing the delivery of cobalt(III)-based drugs to cancer cells using nanoplatforms. This relies on the inhibitory effect of a class of inorganic molecule known as cobalt(III) Schiff bases (Co-SB), which are known to inhibitors of a zinc finger structural motifs. One class of zinc finger proteins of the Gli family are known to be crucial in cell growth and development, including differentiation of cells into separate function and patterning in the Hedgehog signaling pathway. As cancers are marked by uncontrolled cell growth and migration, Zn finger Gli proteins have been shown to be overexpressed in the growth and metastasis in a number of cancers, including prostate cancer, basal cell carcinoma, and the pediatric brain cancer medulloblastoma. Zinc finger proteins are targeted by inhibiting their expression in cells through Zn finger transcription factors (Zn-TFs), where many signaling pathways terminate at the Zn-TF step. The Meade lab has developed a number of Co(III)-Schiff base complexes that have recently demonstrated specific inhibition of the Gli family of Zn-TFs with effectiveness in cell lysates and embryos. However, more work is necessary to activate the drug in cancer cells to minimize off-target effects. My research focuses on optimizing the delivery of Co-SB inhibitors to basal cell carcinoma using nanoplatforms such as graphene-oxide (GO) and polymerosomes (with collab. Evan Scott). Current work involves synthesis of stable nanoplatforms and the measurement of their delivery via cell uptake studies, cell localization via confocal microscopy, and efficacy using cell migration and invasion assays.

### Intratumoral Generation of Photothermal Gold Nanoparticles through a Vectorized Application of Ionic Gold

*Aaron S. Schwartz-Duval*

*University of Texas MD Anderson Cancer Center*

Various cancer cells have been demonstrated to have the capacity to form plasmonic gold nanoparticles when chloroauric acid (HAuCl4) is introduced to their cellular microenvironment. The exact mechanism for this biomineralization process is not fully understood and it is not clear whether this is a property exclusively found in cancer. This process, wherein cells are able to reduce ionic gold to form nanoparticles in millimolar concentrations in 24-hour periods, is known to cause shock and stress to the cells. Generating gold nanoparticles that capitalize on their plasmonic properties without inducing shock and stress would better enable this process for biomedical applications. Here we describe a simplistic method for intracellular biomineralization of plasmonic gold nanoparticles (in full cell media) at nanomolar concentrations. These plasmonic formations are observable as early as 30 minutes after application. This simplistic approach utilizes polyethylene glycol, which forms nano-scaled clusters that collect cations in acidic conditions, as a delivery vector for ionic gold. We have characterized this process for intracellular gold nanoparticle formation, which progressively accumulates proteins as the ionic gold polyethylene glycol clusters migrate to the nucleus. We demonstrate potential biomedical applications for cancer treatment with our ionic gold vectors wherein fluorescent and photothermally active nanoparticles are generated on-site, utilizing biomolecules from the pathological tissue. By utilizing cellular machinery reliant on cellular pathology and not profoundly on benchtop synthesis we further ourselves toward a personalized medicine approach. We anticipate future applications, which utilize the strategies similar to this technique, to propel the next major advancement in nanomedicine.

### RNA Nanotechnology for specific cancer targeting, siRNA delivery, endosome escape and tumor regression

***Zhefeng Li****1****,***  *Fengmei Pi1, Zhen Zheng1, Daniel Binzel**1**,**Peixuan Guo1, 2, \**

*1College of Pharmacy, Center for RNA Nanobiotechnology and Nanomedicine; 2Comprehensive Cancer Center, Dorothy M. Davis Heart and Lung Research Institute, Department of Cancer Biology and Genetics, College of Medicine; The Ohio State University, Columbus, OH 43210, USA.*

We design membrane-anchoring arrowtail 3WJ RNA nanoparticles to display tumor targeting ligand (PSMA RNA aptamer, EGFR RNA aptamer or folate) on *BIRC5* siRNAs loaded exosomes. We found the orientation of arrow-shaped RNA can be used to control ligand display on exosomes membranes for specific cell targeting. By placing membrane-anchoring cholesterol at the tail of the arrow results in display of RNA aptamer or folate on the outer surface of the exosomes and enhance cancer cell binding and uptake. By using fluorescence colocalization analysis, we also reveal the potent tumor suppression were due to cytosolic delivery without endosome trapping. Taking advantage of the RNA ligand for specific targeting and exosomes for efficient cytosolic delivery, the resulting ligand-displaying exosomes or plant derived exosomes-like nanovesicles were capable of specific delivery of siRNA to cells, and efficiently blocked tumor growth in different cancer model.

# Speaker Biographies

[](https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&ved=2ahUKEwjg1OvH-dzkAhWDTd8KHXWFD5IQjRx6BAgBEAQ&url=http%3A%2F%2Ffarokhzad.bwh.harvard.edu%2Fwp%2Fmembers%2Fprincipal-investigator%2F&psig=AOvVaw3MJYAzO2J7X9rreU_GBy6p&ust=1568984680782018)

## Omid Farokhzad, M.D.

*Brigham & Women’s Hospital*

Omid Farokhzad is an Iranian- American physician, scientist, and entrepreneur in the development of nanomedicines. Farokhzad is a Professor of Anesthesiology at Harvard Medical School. The Boston Globe selected him among the top innovators in Massachusetts and the Boston Business Journal selected him among the Health Care Champions for his innovations.

He is an associate editor for ACS Nano, an international forum for the communication of comprehensive articles on nanoscience and nanotechnology research at the interfaces of chemistry, biology, materials science, physics, and engineering. He is widely recognized as leader in the field of nanomedicine and drug delivery. In 2016, he was the recipient of the Ellis Island Medal of Honor. He was also elected in the National Academy of Inventors in 2018.

Farokhzad completed his residency in Anesthesiology and fellowship in Pain Medicine at the Brigham and Women Hospital and Harvard Medical School. He completed a post-doctoral research training with Professor Robert Langer at MIT in the Harvard-MIT Program of Health Sciences and Technology. He joined Harvard Medical School in 2004 as a faculty member, after his clinical training, he served as Professor of Anesthesia.

He has popularized the usage of specific targeting agents for the delivery of chemotherapy agents to cancerous cells found within a cancer patient. Beyond cancerous phenotype he has addressed atherosclerosis-related disease, He has demonstrated the usage of targeted biodegradable nano ‘drones’ that delivered a special type of drug that promotes healing. This remodeling of the plaque environment would be predicted in humans to block plaque rupture and thrombosis and prevent heart attacks and strokes.

[](https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&ved=2ahUKEwjh6p3r-dzkAhVMn-AKHdRVDAcQjRx6BAgBEAQ&url=https%3A%2F%2Fwww.hopkinsmedicine.org%2Fprofiles%2Fresults%2Fdirectory%2Fprofile%2F0024208%2Fphuoc-tran&psig=AOvVaw2MywZNK_3fCnFwU0uk8Ytn&ust=1568984756133880)

## Phuoc Tran, M.D., Ph.D.

*Johns Hopkins School of Medicine*

Dr. Phuoc Tran is an Associate Professor for multiple departments at the Johns Hopkins School of Medicine: Radiation Oncology and Molecular Radiation Sciences; Oncology; and Urology. Dr. Tran treats patients with cancers of the genitourinary system and uses stereotactic radiation techniques (such as SRS and SBRT/SABR) for the treatment of patients with oligometastatic disease. His research focuses on the improvement of clinical radiotherapy for the treatment of primarily prostate cancer, but also adrenal, bladder, urethral, testicular and penile cancer as well as patients with oligometastatic disease. Dr. Tran has published more than 100 scholarly works in peer-reviewed journals, has received numerous awards for his research, and is a primary investigator on a number of clinical trials. He is a member of and holds leadership positions in the Radiological Society of North America (RSNA), NRG Oncology and the American Society for Radiology Oncology (ASTRO). He is also Senior Editor/Editorial Board Member of the publications Cancer Research and the Journal of Clinical Oncology. Dr. Tran completed his medical and graduate training at the Oregon Health & Sciences University in Portland, OR.