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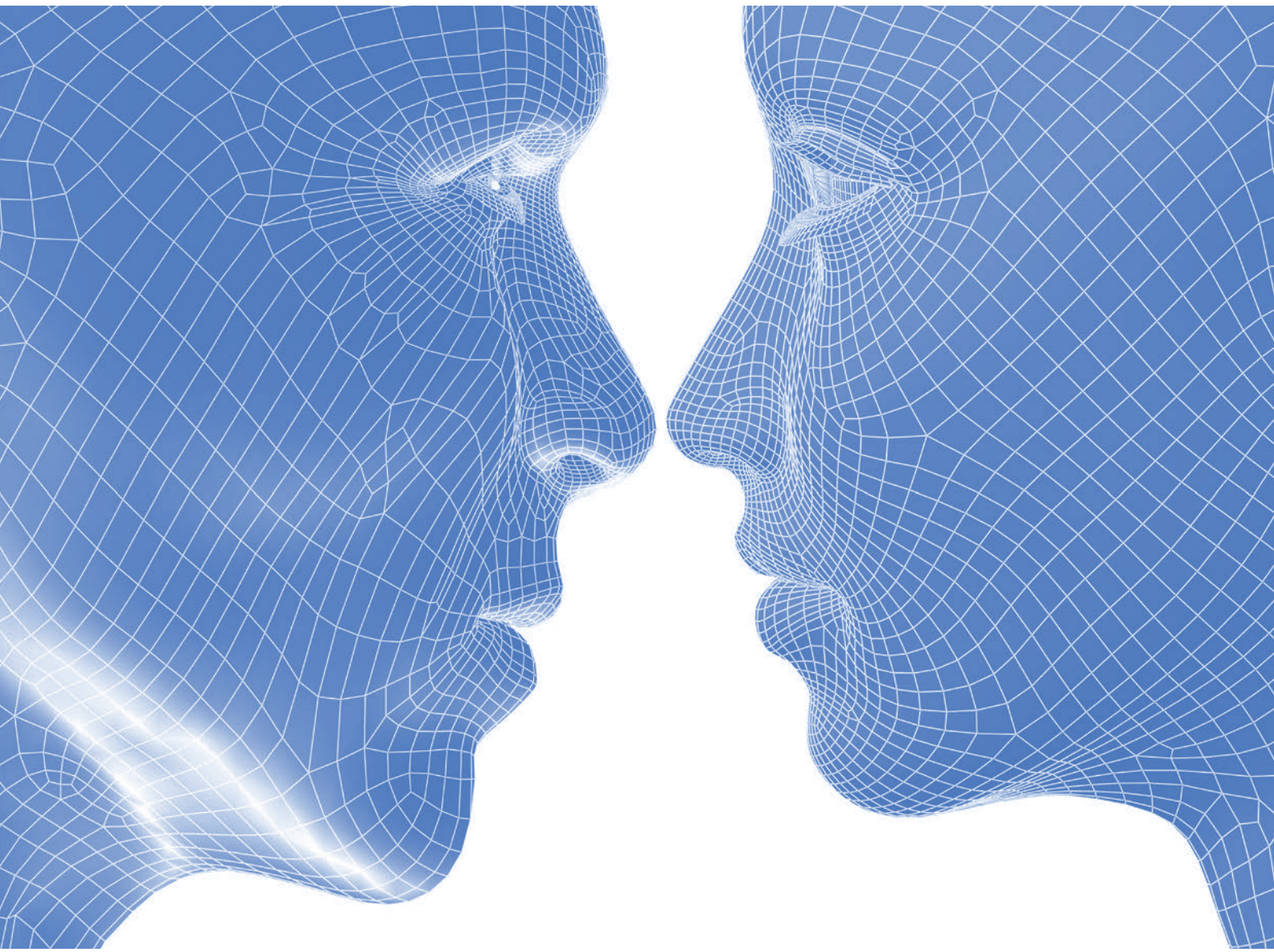
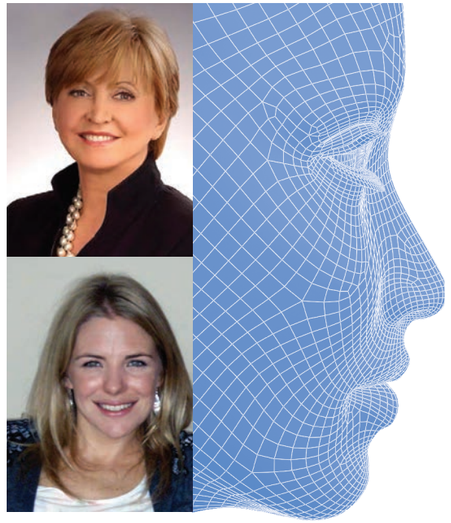
2014 | Research Progress Reports



Memorial Sloan-Kettering Cancer Center

Principal Investigator: **Hedvig Hricak, MD, PhD, DrHC**
Chairman of Department of Radiology
Carroll and Milton Petrie Chair

Peter Michael Postdoctoral Fellow: **Nicola Robertson, MBChB**



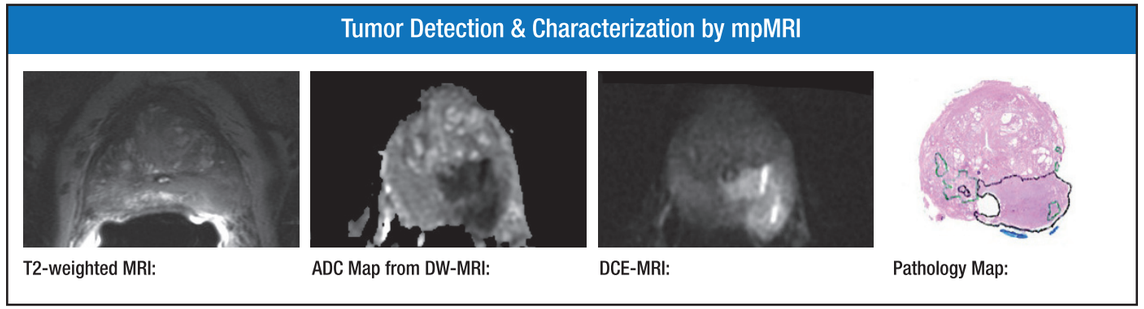
The Future of Magnetic Resonance Imaging (MRI) for Prostate is Multiparametric

Memorial Sloan-Kettering acknowledges that the Peter Michael Foundation has been remarkably forward thinking in its dedication to supporting research on MR imaging (MRI) of the prostate. Well before prostate MRI entered the mainstream of cancer care, the Foundation spotted its potential to serve as a "GPS" for guiding prostate cancer detection and management. The research the Foundation has supported has helped to realize that potential and stimulate interest in the use of prostate MRI among the broader medical community.

At MSKCC, we have been working to develop and optimize multiparametric MRI examinations that combine anatomic with functional imaging sequences. This work has helped increase the accuracy of MRI in prostate cancer localization. In turn, this has facilitated more precise staging and planning of surgery and contributed to wider adoption of prostate MRI for these purposes. Even more importantly, perhaps, our research has helped to demonstrate the potential of MRI for tumor characterization and risk stratification. For example, we have shown that lack of tumor visibility on anatomic MRI is predictive of a lack of clinically significant cancer, and that measures of water diffusion obtained with diffusion-weighted MRI correlate with tumor aggressiveness.

Thanks in part to the support and advocacy of the Peter Michael Foundation, at our center and others the focus of prostate MRI research has been shifting toward better distinguishing patients who require immediate treatment from those who do not. For example, our 2014 PMF-funded fellow Nicola Robertson recently worked on a study examining whether the use of computerized tumor volume measurement—also known as "volumetry"— in combination with quantitative functional metrics derived from multiparametric MRI—could predict upgrading of prostate cancer on so-called "confirmatory" biopsy in patients being considered for active surveillance (the results are now being analyzed).

In a study published in January in the Journal of the American Medical Association, investigators at the National Cancer Institute compared standard ultrasound-guided biopsy to targeted MR/ultrasound (US) fusion biopsy, during which multiparametric MR images are superimposed onto real-time ultrasound images. The study, which was conducted in a large cohort of 1003 men suspected of having prostate cancer, found that in comparison to standard biopsy, targeted biopsy significantly increased the detection of high-risk prostate cancer while decreasing the detection of low-risk disease. In a smaller study, PMF fellow Nicola Robertson and collaborators at MSK recently showed that the combination of tumor volumetry and diffusion-weighted MRI could be highly effective for targeting clinically significant disease with MR-ultrasound fusion biopsy. Specifically, when lesions that were measurable and had a mean apparent diffusion coefficient (ADC) <1 mm^2/s were targeted, the likelihood that they would be found to contain clinically significant cancer was 94%. The study has been accepted for oral presentation at the 2015 meeting of the International Society of Magnetic Resonance in Medicine. Although further studies will be needed to determine the cost-effectiveness of targeted biopsy and its effects on patient outcomes, these highly encouraging results are a testament to the understanding and commitment of the Peter Michael Foundation.



MP-MRI figure: Axial T2-weighted, diffusion-weighted, and dynamic contrast-enhanced images, along with step-section pathology, from a patient who underwent pre-operative multiparametric MRI of the prostate.

The advent of multiparametric prostate MRI has also opened up new possibilities for assessing treatment response. In general, response assessment on anatomic MRI is hampered by treatment-induced changes in the appearance of the prostate. However, adding an additional layer of information about physiology often makes it possible to differentiate between areas with a similar appearance on anatomic MRI. A study led by our 2014 PMF fellow Andreas Hoetker found that in patients treated with hormone therapy, changes in ADC values on diffusion-weighted MRI, as well as the post-therapeutic ADC values themselves, differed significantly between benign and cancerous prostate tissue. As the change in ADC values also correlated with the decrease in PSA, the study suggested that ADC values could help in monitoring the response to hormone therapy. The study has been accepted for publication in European Radiology—one of the world's most respected peer-reviewed imaging journals.

At MSKCC, we are now expanding our MR imaging research into the nascent disciplines of radiomics and radiogenomics. These novel approaches involve high-throughput, computerized extraction of textural and other features from MR images, and correlation of these features with prognostic factors, including genetic signatures. These techniques should allow radiologists not only to better detect prostate cancer, but also to more accurately predict its biological characteristics and even discern specific differences in biology within a single tumor. Moreover, radiomics and radiogenomics could enable automated tumor detection and make accurate interpretation of prostate MRI much easier, so that it could be used reliably even at centers where radiologists have very limited experience with it.

Recently, European Radiology accepted for publication a study led by 2013-2014 PMF fellow Andreas Wibmer, which examined the applicability of automated Haralick texture analysis to prostate MRI. Haralick texture analysis evaluates the spatial distribution of pixels in a gray-scale image to provide quantitative information about the image that cannot be discerned with the naked eye. It has been successfully applied for various purposes, including automated recognition of land use on satellite images and facial recognition software. Dr. Wibmer's study showed that Haralick texture analysis of prostate MRI provides parameters that may help differentiate cancer from normal tissue and assess prostate cancer aggressiveness. These features could ultimately be correlated not only with Gleason scores, but also with other prognostic factors, including genetic signatures.

Crossing yet another frontier, we are also beginning to explore a new MRI-based modality known as hyperpolarized MR spectroscopic imaging (HP-MRSI). This approach permits the safe study of injected, "hyperpolarized" (HP) metabolic substrates and their downstream metabolic products in nearly real time in patients. Studies in cell, tissue and animal models have shown that the conversion of HP pyruvate to HP lactate is a marker of prostate cancer aggressiveness. We are planning a study to assess and establish the reproducibility of HP pyruvate imaging in prostate cancer patients--an essential step for validating HP lactate as a non-invasive biomarker of prostate cancer

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STANFORD
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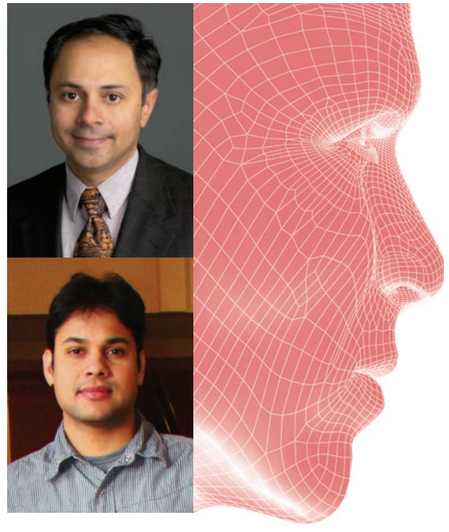
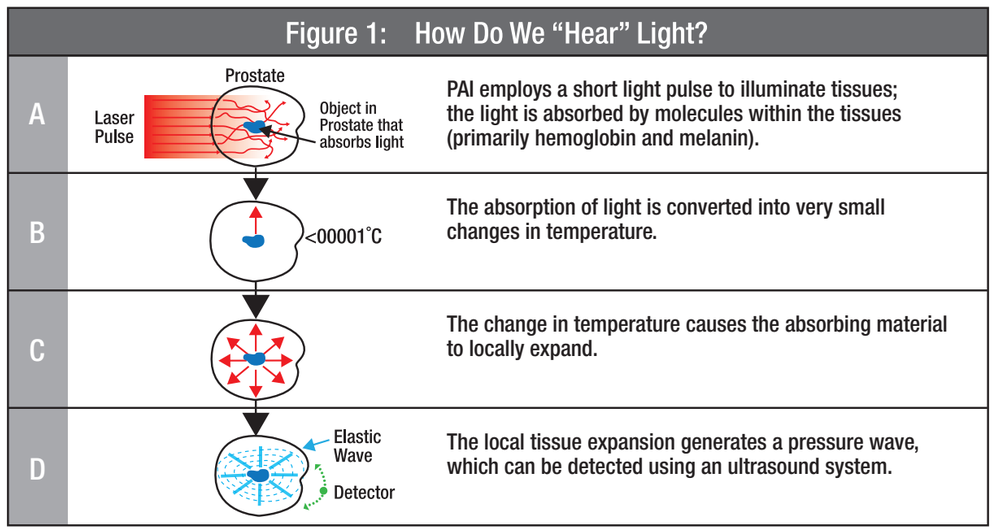
Peter Michael Postdoctoral Fellow: **Sri-Rajasekhar Kothapalli, PhD**



Progress on Dual Modality Transrectal Ultrasound and Photoacoustic Imaging of Prostate

Photoacoustic imaging employs a short light pulse to illuminate tissue. The molecules (such as hemoglobin and melanin) within the tissue absorb the light photons and cause small changes in temperature. This temperature change causes the surrounding tissue to expand. This expansion further generates a pressure wave (ultrasound/photoacoustic wave) which can be detected using an ultrasound system. This photoacoustic imaging principle can be exploited to detect and eventually kill tumors by administering theranostic agents into the patient. In the first step these agents are designed to specifically attach to tumors and send a readout signal to the imaging system. The imaging system in turn, in the next step, will increase the activity of these agents such that tumors are destroyed.

Figure 1: How Do We "Hear" Light?



In the last 5 years we have optimized the design and developed a novel dual modality transrectal ultrasound and photoacoustic (TRUSPA) imaging device using one dimensional (1D) Capacitive Micromachined Ultrasound Transducer (CMUT) array. The TRUSPA device was coupled with the new portable photoacoustic laser and supported by data acquisition hardware and image reconstruction software. The complete TRUSPA imaging system was assembled into two portable carts to facilitate our clinical investigations. The imaging system was repeatedly tested in standard phantoms to monitor stability and reproducibility of the imaging system. We also imaged in-tact whole prostate glands of several patients under-going prostatectomy as a routine standard of care. In the last one year, we translated the TRUSPA imaging system to Urology clinic at Stanford University and have conducted pilot clinical studies on several patients. Our results demonstrate that TRUSPA device was able to visualize prostate anatomy in ultrasound mode and optical contrast of the prostate, presumably from vasculature surrounding several prostatic structures, in photoacoustic mode. In this on-going clinical trial, we are currently recruiting more patients to systematically investigate photoacoustic signatures of prostate cancer in relation to histopathology studies on prostate biopsy specimens through the current standard of care: transrectal ultrasound guided biopsy.

Molecular Imaging Studies in Mice Prostate Cancer Models

Besides building a TRUSPA imaging device, we are currently investigating photoacoustic molecular imaging approaches that can reliably improve the sensitivity and specificity of the prostate cancer. We developed some mice prostate cancer models and identified a contrast agent that is highly promising for clinical translation and also molecular targets such as PSMA, an antigen highly expressed in prostate cancer cells, to enable molecular imaging of prostate cancer. In the first step, we tested a non-targeted contrast agent in mice models of prostate cancer. We are currently working on functionalizing these agents for molecular targeting.

Our end goal is to integrate clinically translatable photoacoustic molecular imaging approaches with our novel TRUSPA imaging system, to improve the current transrectal ultrasound based screening in the clinic.

Future Directions in Clinical TRUSPA

1. To recruit different types of patients (including patients with well-defined cancer) in the next one-year in our study and systematically investigate photoacoustic signatures of prostate cancer.
2. Further develop photoacoustic molecular imaging approaches in mice models
3. Integrate these molecular imaging approaches to TRUSPA imaging system and apply them in the clinic.

Conference Presentations of Drs. Raj Kothapalli and Sam Gambhir in 2014

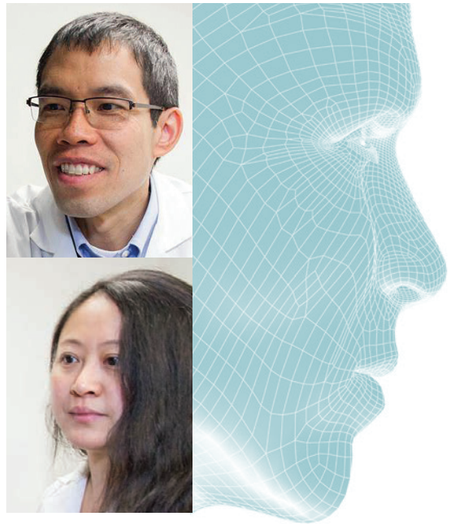
Kothapalli S.R., Nikoozadeh A., Choe J.W., Moini A., Jouannot E., Khuri-Yakub B.T., and Gambhir S.S., *Real time intraoperative ultrasound and photoacoustic molecular imaging system using a micro linear CMUT catheter,* WMIC, Seoul, Korea, September 2014

Dr. Raj Kothapalli completed his Ph.D. in Biomedical Engineering from Washington University in Saint Louis under the supervision of Dr. Lihong Wang in 2009. He moved to Stanford University for his postdoctoral work in the lab of Dr. Sam Gambhir in the Department of Radiology. His post-doctoral work was focused on the development and translation of transrectal ultrasound and photoacoustic imaging technology for prostate cancer screening under the guidance of Dr. Khuri-Yakub and Dr. Gambhir in Electrical Engineering and Radiology Departments respectively. Currently he is an instructor in the Department of Radiology. His research interests include developing novel medical technologies and integrating them with relevant molecular imaging strategies to improve the current standards of cancer/disease diagnosis and management. The postdoctoral fellowship from the Peter Michael Foundation supported his postdoctoral research efforts. Recently he received the K99/R00 Pathway to Independence Award from NIH.

UCSF Helen Diller Family Comprehensive Cancer Center

Principal Investigator: **Lawrence Fong, MD**
Department of Medicine, Hematology & Oncology

Peter Michael Postdoctoral Fellow: **Serena S. Kwek, PhD**



Developing biomarkers to guide cancer Immunotherapy

Cancer immunotherapy has now become a pillar of cancer treatment. With the FDA approval of immunotherapies including sipuleucel-T (Provenge), anti-CTLA-4 antibody (ipilimumab) and anti-PD-1 antibodies (pembrolizumab, nivolumab), immunotherapies will become critical components of treatment for many different cancers. In contrast to other cancer therapies, the clinical responses to immunotherapy can also be very durable. Despite these significant advances, only a fraction of patients benefit from these therapies. We have focused on identifying biomarkers that may help to identify which patients may or may not respond to these treatments. One study published this year used next generation sequencing to track individual T cell clones at an unprecedented level of detail in patients receiving immunotherapies (Cha et al. 2014). We show that prostate cancer patients who have improved survival with anti-CTLA-4 antibody treatment possess pre-existing T cells that are enhanced with treatment. We have also found that another protein, lactate dehydrogenase (LDH), a protein that can be expressed by cancer cells, can also suppress the immune system (Crane et al. 2014). Because this protein can be measured in clinical labs, this could represent another potential biomarker in selecting patients. Moreover, high levels of LDH have long been known to be associated with worse cancer prognosis. These results provide an additional explanation as to why this is the case. Nevertheless, these two publications show that immunologic biomarkers can be developed that associate with clinical outcomes.

Developing combinations of immunotherapy treatments

Sipuleucel-T (Provenge) represents the only immunotherapy currently approved for prostate cancer. To understand how immunotherapies work in people, we performed a clinical study giving sipuleucel-T prior to surgery to remove the prostates of men with localized disease. This allows us an unprecedented opportunity to determine what this treatment does to the immune system in the actual tumor. We found that this treatment recruits T cells to the actual prostate tumors, but these immune cells are localized to the rim of the tumors (Fong et al. 2014). These results provide the rationale for combining sipuleucel-T with ipilimumab. The latter is an immune checkpoint inhibitor that releases the brakes on the immune system. The goal of this study is to see whether combining these treatments will lead to more robust immune and clinical responses. This study is currently underway at UCSF.

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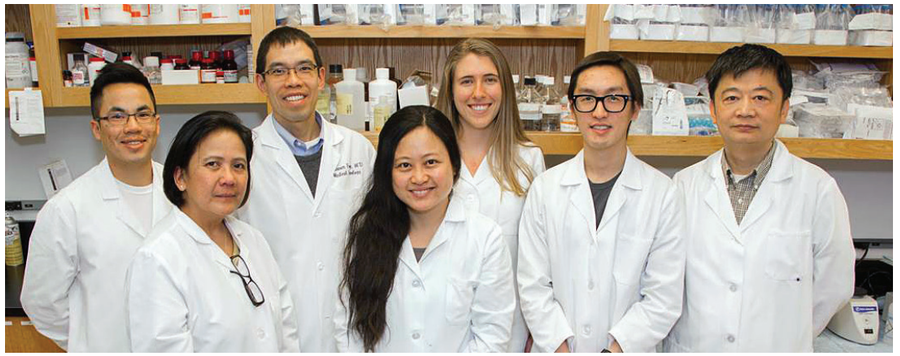
Dr. Serena Kwek received her Ph.D. from the University of Illinois, Chicago in 2001. She subsequently completed her postdoctoral research in cancer genetics under the supervision of Dr. Donna Albertson at the University of California San Francisco. Grant funding from the Department of Defense fellowship program was awarded to Dr. Kwek for her postdoctoral research. Currently she is a specialist in the laboratory of Dr. Lawrence Fong (Professor in Residence, Division of Hematology/Oncology, and Department of Medicine) at the University of California San Francisco. Her current research program is the discovery and validation of immunological biomarkers which may be predictive or prognostic for patients undergoing cancer immunotherapy, and investigating the mechanisms underlying these immunological biomarkers which are also differentially expressed in cancer patients compared to cancer-free controls. During this time, Dr. Kwek has identified several candidate biomarkers for a clinical trial in prostate cancer patients with immunotherapy treatment (ipilimumab), which may help to identify the patients most likely to benefit before treatment. She has mentored several pre-doctoral and pre-medical students in research and published several articles in highly regarded peer-reviewed journals.



Lawrence Fong, MD and Serena S. Kwek, PhD with staff

UCSF Helen Diller Family Comprehensive Cancer Center | Entrance

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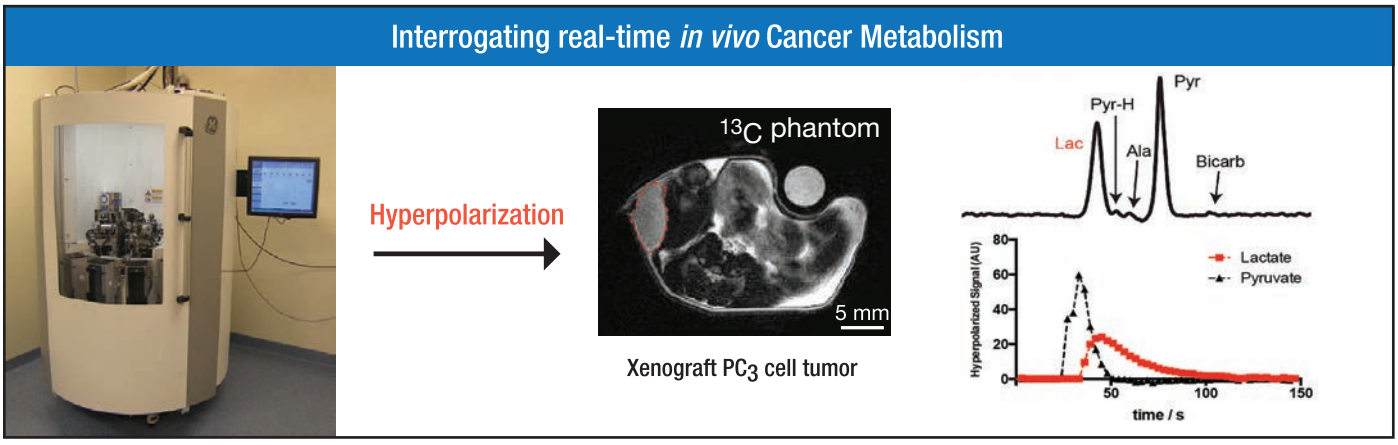
aggressiveness in patients. Once validated, this biomarker could allow non-invasive assessment of variations in tumor aggressiveness throughout the entire prostate and could therefore have tremendous implications for prostate cancer care. Ultimately, we expect that HP-MRSI will become a vital component of initial treatment selection as well as clinical trials of new therapies, with imaging of HP lactate guiding the discovery of novel drugs, providing early detection of aggressive cancer and allowing early assessment of treatment response.



HP-MRSI figure: Interrogating real-time in vivo cancer metabolism: To characterize metabolism in cancer, we take novel hyperpolarized biomolecules created in a GE Spin Lab (left) and infuse them in living systems. In a murine pre-clinical model of prostate cancer (Pc-3 prostate cancer cells, center) we utilize anatomic MRI to define the tumor (dotted red line). We can then infuse hyperpolarized pyruvate, an intermediate in our metabolism, and observe its dynamic metabolism (right). The conversion of pyruvate to lactate is indicative of high rates of glycolysis, a significant metabolic change we observe non-invasively in cancer. We are now translating this method from preclinical models into the clinic at MSKCC. Specifically, we will aim to determine if imaging of the conversion of pyruvate to lactate can be used to non-invasively characterize cancer aggressiveness and differentiate indolent from clinically significant disease in patients.

Dr. Nicola Robertson received her medical degree from the University of Bristol, England in 2006. She subsequently completed residency training in surgery, with a special focus on urologic surgery. From 2011 to 2012, she worked as a Clinical Research Fellow at University College London and University College Hospital London under the supervision of Professor Mark Emberton (Professor of Interventional Oncology, Divisional Director), a leading investigator of the value of MRI for improving prostate cancer diagnosis and treatment. During this time, Dr. Robertson coordinated two clinical trials in prostate cancer patients, including one that evaluated MR imaging of primary prostate cancer after exposure to dutasteride, a drug used to treat benign prostatic hyperplasia. She further specialized in MRI-targeted biopsy of the prostate gland in men at risk of prostate cancer. She presented her research at national as well as international conferences and published several articles in highly regarded peer-reviewed journals. She is currently completing a 5-year Registrar training program in the London Clinical Radiology Training Scheme, based at The Royal Free Hospital.

Memorial-Sloan Kettering, Manhattan

Memorial-Sloan Kettering, Basking Ridge, New Jersey