Memorial Sloan-Kettering Cancer Center

2009 Progress Report

Both clinical and basic research in advancing the imaging methods of prostate cancer continue to advance in a multidisciplinary approach at Memorial Sloan-Kettering Cancer Center (MSKCC). The group involved in prostate imaging is large and includes, physicists, chemists, pathologists, biologists, radiologists and nuclear medicine physicians, urologists, radiation oncologists and medical oncologists. Dr. Jan Grim was a Pelican funded fellow and is a member of the group. Last year, Dr. Jan Grimm finished his additional medical training in Nuclear Medicine and fellowship in Body Imaging at MSKCC. Furthermore, he obtained board certification in Nuclear Medicine and joined the faculty of MSKCC. He has a dual appointment in the Radiology Department and an appointment in Molecular Pharmacology and Chemistry at Sloan-Kettering Institute (SKI). Through his appointment at the SKI, Dr Grimm is heading his own laboratory focusing on molecular imaging in oncology. In this laboratory, he is continuing research he began as a Pelican Fellow, developing molecular imaging approaches for cancer, focusing on innovative imaging methods for early detection and better characterization of prostate cancer. As the primary target of his molecular imaging studies he has chosen prostate-specific membrane antigen (PSMA), an antigen highly expressed in prostate cancer cells and neovasculature. PSMA was originally cloned at MSKCC, and there is a long history of research on this transmembrane protein. Its expression correlates with the grade and prognosis of prostate cancer. It also has an enzymatic function that can be exploited for imaging purposes.

Hedvig Hricak. MD, PhD
Chairman, Department of Radiology

Jan Grimm, MD, PhD
Pelican Fellow

Three ongoing studies in Dr. Grimm's lab are related to prostate cancer:

1) A novel magneto-fluorescent nanoparticle, developed by Dr. Grimm, binds to PSMA and can be detected with both MRI and optical imaging. The lab has since shown the specificity of the agent for PSMA and is currently exploring its utilization as a tool for monitoring the effects of prostate cancer therapy.

2) In collaboration with the organic chemistry core facility at MSKCC, Dr. Grimm also developed a unique agent that senses the enzymatic activity of PSMA. This agent is being studied intensively and used to image prostate cancer in mouse models. The lab is in this case also exploring the expression of PSMA on tumor vessels, which might open a wide field of applications for this agent, leading to other assays on the basis of this agent, which may have the potential for clinical applications.
3) Finally, a novel approach is being pursued to monitor therapies for prostate cancer with PET imaging. Here we are using a clinically approved agent (but for another indication) to detect cells that are killed by either radiation or chemotherapy. This approach allows detection of apoptotic (i.e., dying) prostate cancer cells following therapy such as radiation. Because the agents employed are already in clinical use, the approach could be applied directly in the clinic. An expansion of this project in the near future is planned after publication of these first data, to bring the approach into the clinical arena.
All three of Dr. Grimm's prostate cancer imaging projects are in advanced stages and promise to result in translation into clinic within the next few years.

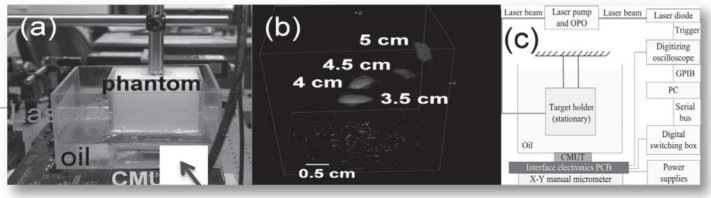
Stanford University Cancer Center
2009 Progress Report

BACKGROUND

Standard screening methods for prostate cancer - such as blood screening for prostate specific antigen (PSA), digital rectal examination (DRE), and transrectal ultrasound (TRUS) guided prostate biopsy – have limited ability (sensitivity and specificity) in the early diagnosis of prostate cancer. Physicians employ a combination of these methods to improve diagnosis. Unfortunately, even a combination of all the above three methods of evaluation lack overall diagnostic accuracy. Other emerging imaging modalities for prostate diagnosis, such as MRI (magnetic resonance imaging), CT (computed tomography), PET (positron emission tomography) suffer from problems that include employing ionizing radiation (CT and PET), limited soft tissue contrast (CT), limited sensitivity (CT and MRI), limited spatial resolution (PET) and high cost (MRI, PET, and CT). However, TRUS employs non-ionizing radiation and is relatively cheap and continues (despite some pitfalls) to be the most successful imaging technique in the screening stage.

To improve the diagnostic accuracy of TRUS, we propose transrectal photoacoustic (TRPA) imaging of the prostate with sub-millimeter spatial resolution and high soft tissue contrast based on both endogenous (blood vasculature) and exogenous molecular imaging agents. Since TRPA and TRUS share a common platform-ultrasound detection, TRPA can be easily built on the strengths of TRUS. This facilitates multimodality (ultrasound and photoacoustic) imaging of prostate using one common device, where structural information of prostate can be obtained using TRUS and functional and targeted imaging can be obtained using TRPA. As physicians are familiar with TRUS, this combined device will likely enable easy physician acceptance and clinical translation. The literature on photoacoustic imaging suggests that TRPA would have enough sensitivity to detect early cancer, at extremely small concentrations and yet highly targeted (specificity due to photoacoustic molecular imaging agents).

PRELIMINARY RESULTS

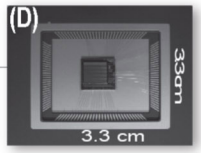


The key challenge of photoacoustic (PA) imaging has been limited depth penetration compared to conventional ultrasound imaging. Our study on transrectal sonograms of prostate show that average distance of the TRUS probe to the far end of prostate lobe is approximately 5 cm. Our primary aim is to develop a TRPA probe and evaluate the depth penetration in a tissue mimicking phantom. We used state of art 16x16 element array CMUTs with integrated electronics for our photoacoustic experiments. CMUT technology offers advantages such as wide bandwidth, sensitivity, very high level of integration and batch fabrication (low cost) and thus is expected to replace conventional piezoelectric transducers. Figures (a) and (c) show the schematic experimental setup. Tunable (675 nm to 800 nm) laser light illuminates the phantom along the X-axis. A CMUT is placed below the phantom along the Z-axis. The tissue mimicking phantom sample (XYZ dimensions of 7 cm x 5 cm x 7 cm) with strong optical scattering ($\mu s'$=10 cm-1) contains horse hair objects at 3.5 cm, 4 cm, 4.5 cm, and 5 cm depths along both the X and Z axes. These objects absorb diffused laser light and generate PA signal. Each element (total 256 elements) of CMUT is then scanned electronically to detect the PA signal. This generates local volumetric data within the field of view of CMUT. Phantom sample (or CMUT) is then scanned to generate desired volumetric data. Figure (b) shows reconstructed volumetric data of all 4 embedded objects at different depths.

Sanjiv Sam Gambhir, *MD, PhD (right) Head, Division of Nuclear Medicine*

Raj Kothapalli, *MD, PhD (left) Pelican Postdoctoral Fellow*

FUTURE DIRECTIONS

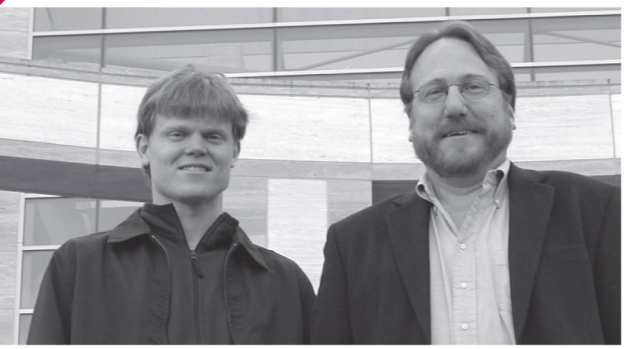


1) As shown in figure (d), current CMUT + associated electronics is 3.3 cm wide. But the rectal opening is only 3.2 cm wide. We will receive a 1 cm x 1cm wide CMUT soon.
2) Once received, we integrate optical fibers (for light delivery) with CMUTS and package it to make TRPA probe which will look like a clinically used TRUS probe.
3) Then the TRPA probe will be tested using PA prostate phantoms (not shown here due to limited space) that we built in our lab. These prostate phantoms simulate both optical and acoustical properties of rectal wall, prostate (both benign and malignant), urethra, and seminal vesicles.
4) Light delivery through urethra will be considered in case of limited penetration depth of TRPA probe.
5) We are simultaneously developing Monte Carlo simulations to simulate TRPA imaging of prostate.
6) Using the above mentioned simulations and experiments we will optimize performance of the probe.
7) Then we plan to test the TRPA probe in a canine prostate model, and later employ functional and molecular imaging strategies that we are developing, with this TRPA probe.

SUPPLEMENTARY POINT

Dr. Raj Kothapalli, Pelican Fellow at Stanford, occasionally visits the VA hospital affiliated to Stanford, to watch and learn (under guidance of Dr. Joe Liao) all clinical procedures related to prostate screening (such as TRUS biopsy of prostate) and surgery (e.g., prostatectomy).

University of California Institute for Quantitative Biomedical Research **2009 Progress Report**



Daniel B. Vigneron, PhD
Professor, Department of Radiology

Peder Larson, PhD
Pelican Postdoctoral Fellow

With the generous support of the Peter Michael Foundation,

prostate cancer imaging research at the University of California, San Francisco advanced greatly in 2009. Highlights include being awarded $1.2M in stimulus funds from the National Institutes of Health (NIH), working with medical device companies to make our multiparametic prostate MRI techniques commercially supported with widespread availability, and the development of new metabolic imaging methods to assess prostate cancer aggressiveness (a critical clinical management problem).

Under the direction of Professor Daniel Vigneron, Ph.D., the research team including the Pelican Fellow, Dr. Peder Larson Ph.D., works on developing and testing improved methods for anatomic and metabolic Magnetic Resonance imaging (MRI) of prostate cancer.

Improved imaging is required for more accurate treatment selection, guidance and evaluating current and emerging therapies. Another research focus of the UCSF prostate cancer imaging research is to better monitor patients who have deferred treatment and are under "active surveillance." In these patients, the goal is to better characterize and changes in the cancers that would indicate the need for treatment. The need for improved prostate cancer imaging was clearly stated in the consensus of participants of the Colloquium on Prostate Cancer, sponsored by the Pelican Cancer Foundation in 2008 in the United Kingdom. This continues to be an under-funded area of research, but a very necessary one that offers great potential benefit to prostate cancer patients.

In 2009, the funding from the Peter Michael Foundation has supported the effort of Dr. Peder Larson as a Pelican Fellow researching new prostate cancer imaging methods. He is an outstanding young imaging scientist who has a very strong background in basic science through his graduate studies in electrical engineering at Stanford University. At UCSF he has gained in-depth knowledge of prostate cancer biology, physiology and clinical management issues. He has applied his strong knowledge of basic physics and engineering to develop new magnetic resonance imaging (MRI) techniques for improved prostate cancer imaging. His efforts have been divided into two areas. One is short term improvements of MRI techniques for current patients studies to provide improved speed, scope, and information content. His improved methods are now used in hundreds of prostate cancer patient studies at UCSF and through our collaboration with GE Healthcare these methods are now been applied in initial evaluations at other major prostate cancer imaging sites including Memorial Sloan-Kettering in New York. GE plans to include this as a clinical product in future commercial releases starting later this year.
Dr. Larson's other research focus is on the development of new metabolic imaging methods which will take a longer time to be clinically available. This project is to develop a new method called hyperpolarized carbon-13 MRI.

This exciting new metabolic imaging technique with General Electric Healthcare will take somewhat longer to develop but provides over 50,000-fold improvement for imaging cellular metabolism. This new method was developed by GE scientists and through a collaboration with UCSF, it is being further refined with the goal of initiating the first prostate cancer patient trial later this year. Initial studies in prostate cancer cell cultures and model systems have shown the ability to detect the abnormal metabolism of prostate cancer and differences with progression and response to therapy. Dr. Larson is specifically working on developing and optimizing new acquisition methods for improved pre-clinical studies and for the first human studies. This extraordinary new technique has the potential to become an important new radiological tool for metabolic imaging by directly observing specific metabolic pathways in prostate cancer that can characterize prostate cancer aggressiveness and response to treatment.