Medical Imaging Research at Dartmouth

Extracted from the June 2010 Radiology Report

The Department of Radiology and its faculty actively support clinical and basic science research in medical imaging and image-guided therapies. Within the department, research is conducted by a full-time, grant-funded research staff, as well as by our DHMC-based clinical faculty. (While many recent studies by the clinical faculty are not described here—as the focus of this section are the larger, externally-funded, and cross-disciplinary research programs underway—their work is an essential component of D-H imaging research, and the reader is directed to the list of publications in the appendix to this report.)

The department’s research is best seen in the context of a robust commitment to medical imaging studies throughout a Dartmouth medical and scientific community that includes various departments at DHMC and Dartmouth Medical School, Norris Cotton Cancer Center (NCCC), Thayer School of Engineering, and the Dartmouth Institute for Health Policy and Clinical Practice (TDI). Cross-disciplinary collaboration is a common characteristic of this work, resulting in synergies which have established us as leaders in multiple areas of medical imaging research.

I. RESEARCH FACILITIES

The principle resource for clinical radiology research consists of the department’s complement of radiographic, MR, CT, and molecular imaging systems. Additional clinical studies, as well as the bulk of the Dartmouth community’s basic-science imaging research, are conducted at a number of specialized facilities as described below.

**The EPR Center**  The Electron Paramagnetic Resonance (EPR) Center for the Study of Viable Systems is home to the world’s first clinical EPR system, has been for over fifteen years a world leader in the development of biological and clinical applications for EPR spectroscopy, and plays a key role in international EPR research education and resource sharing. The center operates several laboratories, including an instrument-development facility at the Hanover campus, a small-animal research area within the NCCC (Rubin 6), and a clinical EPR facility in the Department of Radiation Oncology (Rubin 2). Directed since its inception in 1992 by Dr. Harold Swartz, the EPR Center staff includes Dr. Nadeem Khan, Dr. Huagang Hou, Dr. Benjamin Williams, several adjunct faculty researchers, nine research associates. (See appendix for full listing.) Faculty is assisted by full-time non-faculty researchers, Jean Lariviere, Xiaoming He, and Javier Nicolalde.

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1 For brevity, “Dartmouth” or “Dartmouth community” refers here to the academic and medical research community comprised of Dartmouth Medical School, Mary Hitchcock Memorial Hospital, Dartmouth-Hitchcock Clinic, Dartmouth College, the Thayer School of Engineering (“Thayer”), and affiliated institutions such as the Norris Cotton Cancer Center (NCCC) or The Dartmouth Institute for Health Policy and Clinical Practice (TDI).
The NMR Center  The Biomedical Nuclear Magnetic Resonance (NMR) Research Center conducts basic research aimed at the development of MRI and MR spectroscopy (MRS) imaging techniques. A key focus is the use of MRS to identify and depict concentrations of metabolites which can be associated with specific tumor varieties; the resulting database of metabolic “fingerprints” may ultimately provide significant clinical tools for cancer staging and treatment monitoring. The center also provides support for the neuroscience program at Dartmouth College, with ongoing investigations of fMRI techniques based on hemodynamics and oxygenation to probe brain activation, and of MRI and MRS 'biomarkers' for detection of acute brain injury—capitalizing on the neuroimaging background of Dr. Risto Kauppinen, director of the NMR Center since 2007.

The NMR Center operates a 7T Varian Unity-Inova high-field MRI scanner designed for rodent MRI and Magnetic Resonance Spectroscopy. The capacities provided by the 7T unit are expected to be augmented later this year with the installation of a 9.4T large-bore animal MR scanner. This NIH-funded magnet will accommodate larger subjects (e.g., rabbits and piglets) than the existing 7T scanner, and offers improved sensitivity in both MRI and MRS modes, opening new possibilities for NMR imaging research and for affiliated Dartmouth researchers in neuroscience, cardiology and oncology. Dr. Kauppinen and the Department of Radiology welcome the recent arrival of Dr. Barjor Gimi. Dr. Gimi, from the University of Texas, is a multi-disciplinary specialist in molecular microimaging with extensive background in encapsulation nanotechnology.

The Advanced Imaging Center (AIC)  The Advanced Imaging Center at DHMC provides imaging support for NIH-funded studies, clinical trials and animal research studies, typically involving multi-disciplinary programs in cancer, vascular, and neurologic imaging. Specific projects include hybrid imaging (e.g., NIR-MR and MR elastography), novel contrast agents for early cancer detection, fMRI brain-activation studies, and accurate image-based treatment guidance for heart disease and cancer. AIC facilities include a dedicated Philips whole-body 3T MRI scanner, hybrid MRI-Near Infrared imaging with micro-imaging capabilities, micro-PET, small-animal CT, and a microCT specimen scanner.

The AIC includes the Neuroimaging Research Center, and the Alternative Breast Cancer Imaging Center (ABCIC), which supports research programs for the development of alternative breast-cancer imaging modalities, and serves as an imaging clinic for associated patient trials. With support from the National Institutes of Health, the AIC was opened in 2006 as a joint venture by Mary Hitchcock Memorial Hospital, the Dartmouth Medical School, the Thayer School of Engineering, and a number of clinical departments at DHMC. John Peiffer is AIC Managing Director; Dr. Keith Paulsen is Scientific Director.

Cancer Imaging at NCCC  The goal of the Cancer Imaging and Radiobiology (CIR) Research Program at the Norris Cotton Cancer Center is to foster a collaborative environment that promotes the incorporation of imaging, radiobiology, biophysics, and engineering approaches into the development and evaluation of new cancer diagnostic and treatment strategies. The CIR program
is co-directed by Thayer’s Dr. Keith Paulsen and Dr. Harold Swartz, Radiology’s Scientific Research Director. The program utilizes the research labs at NCCC’s Rubin and Borwell facilities, which include a variety of spectrographic and other imaging equipment, as well as the Brain Imaging Laboratory, where our faculty has participated in fMRI neuroimaging research.

**Thayer School of Engineering** One of the key areas of biomedical engineering research at Dartmouth’s Thayer School is medical imaging, especially in the development of new techniques for cancer detection and staging. The alternative breast-cancer imaging (ABCI) program has been a central element in this work for over a decade. Related projects aim at developing “hybrid” platforms in which established modalities (e.g., MRI, CT and ultrasound) are combined with functional-imaging techniques such as near-infrared or microwave spectroscopy, electrical impedance tomography, or modified MR systems designed to measure tissue elasticity. Additional hybrid imaging studies underway include the use of fluorescence imaging coupled to MR and CT. Drs. Poplack, Weaver, Cheung and others from the Department of Radiology participate in Thayer imaging research as consultants, clinical directors, or co-principal investigators.

**DISCOVERY** The Dartmouth Initiative for SuperComputing Ventures in Education and Research (or “DISCOVERY”) is a supercomputing server cluster available to the Dartmouth research community. It consists (as of January 2010) of an 888-CPU Beowulf/Linux cluster with 3 Tb of memory, more than 35 TB of disk space, and high-speed Infiniband interconnects. Much of the radiology research at Dartmouth—including most of Thayer’s medical imaging work, and the alternative breast-imaging modalities program in particular—involve complex non-linear image reconstruction which would not be possible without DISCOVERY’s computational power.

**II. RESEARCH PROGRAMS AND MAJOR PROJECTS**

In the past five years, medical imaging research in the Dartmouth community has been supported by external grants totaling nearly $40 million (includes roughly $20 million of awards to the Thayer biomedical engineering faculty.) The synergies, flexibility, and culture of teamwork associated with these multi-disciplinary collaborations have energized imaging research and stand as one of this institution’s most distinguishing characteristics. The following summary includes medical imaging research from all faculties and disciplines of the Dartmouth community.

**Alternative Breast-Cancer Imaging Program** Now in its eleventh year, the $15 million, NCI-funded *Alternative Breast Cancer Imaging Modalities* (ABCI) program involves over 40 investigators throughout the Dartmouth community. The program seeks adjunct or alternative techniques to mammography and other existing modalities of breast cancer imaging. Keith D. Paulsen, PhD, Professor of Engineering and of Radiology, is PI for the program overall. Radiology’s Dr. Poplack is PI for the clinical core component, with additional clinical leadership provided by surgical oncologist Richard Barth.

![Drs. Steven Poplack and Keith Paulsen have helped establish Dartmouth as a leader in breast-cancer imaging research](image)
medical oncologist Peter Kaufman, and pathologist Wendy Wells.

The investigational modalities of the ABCI, unlike mammography, differentiate tissue on the basis of metabolic and electromagnetic properties such as oxygenation, hemoglobin concentration, elasticity, and electrical conductivity. In addition to anticipated improvements in diagnostic efficacy, the new techniques do not subject patients to ionizing radiation or compression of the breast. Described below are the four principal modalities under investigation.

1. **Magnetic resonance elastography** (MRE) is based on the association of tissue stiffness and cancer—which is why a clinical breast exam involves physical manipulation to feel for hardness or lumps. MRE uses a modified MRI scanner to create images based on variation in breast-tissue elasticity. Project leader: John Weaver, PhD, Radiology Department physicist.

2. **Electrical impedance spectroscopy** (EIS) uses a painless low-voltage electrode system to create a “tissue map” of the breast based on variations in how cells conduct and store electricity. These characteristics (conductivity and permittivity) are used to reconstruct images differentiating healthy from cancerous tissue. Project leader: Alexander Hartov, PhD, Thayer School of Engineering.

3. **Microwave imaging spectroscopy** (MIS), uses microwave deflection patterns to differentiate cell types on the basis of water content. Resultant high-contrast images can be used for diagnosing cancer and treatment monitoring. Project leader: Paul Meaney, PhD, Thayer.

4. **Near-Infrared Spectral Tomography** (NIRST) utilizes the blood sensitivity and tissue-penetrating properties of near-infrared light to locate and quantify regions of hemoglobin, a key indicator of the microvascularity characteristic of cancerous tissue. The program is using NIRST in two different configurations: as a stand-alone system designed to monitor tumors being shrunk with chemotherapy, and as a hybrid with MRI in which MR provides precise tumor location and NIR categorizes its vascular makeup. Project leader: Brian Pogue, PhD, Thayer.

**Digital Breast Tomosynthesis (DBT)** Recent controversy on the role of mammography screening in younger women highlights the need for further data and for improved screening technologies. *Digital breast tomosynthesis* (“DBT” or “BTS”) is a tomographic application of mammography which may lead to improved cancer-screening sensitivity, and reductions in unnecessary recalls and breast biopsies, particularly in younger women with denser breast tissue. DBT involves multiple low-dose X-ray exposures across an arc of motion, creating 3D views which can reduce the incidence of false positives and false negatives found in conventional mammography.

Dr. Poplack and colleagues have been active in DBT research since its introduction, having conducted a groundbreaking early clinical trial comparing diagnostic tomosynthesis with that of conventional film-screen mammography. Results of the study results strongly supported a clinical role for diagnostic DBT and suggested the likelihood of reduced unnecessary recalls. 

Breast Imaging technician, Joyce Wagner, with the Hologic Silena Dimensions DBT scanner
when used in conjunction with digital screening mammography (AJR, 2007). Subsequently, we participated in a larger study, as one of five institutions in the nation’s first multi-center DBT clinical trial.

With research capabilities enhanced by the 2009 installation of a next-generation DBT scanner, several DBT studies are now underway. The first, a clinical trial sponsored by Hologic, Inc., compares DBT and MRI for diagnostic accuracy in preoperative breast cancer staging. The second is the R01 program, *Optical Imaging Fused with Tomosynthesis for Improved Breast Cancer Detection*. This five-year program seeks to develop a clinical exam platform combining the functional imaging of near-infrared spectral tomography (NIRST) with the detailed spatial resolution of DBT—a hybrid device which may yield improved sensitivity, specificity, and a reduction in unnecessary patient call-backs. The program is led by Drs. Paulsen and Poplack, with the University of Massachusetts, and DBT industry leader, Hologic, Inc.

**Other Breast-cancer Imaging Studies**  Breast-cancer imaging is the clinical focal point of several additional projects involving cross-disciplinary Thayer-DMS teams led by Drs. Paulsen and Weaver. *Frequency Domain Optical Imaging of Breast Cancer* looks to at the diagnostic potential of a single platform combining the functional-imaging advantages of NIR with the spatial resolution of MR. *MR Microwave Absorption and Tomography Imaging*, another NCI-funded project, seeks the development of two hybrid modalities (possibly in a single combined platform): magnetic resonance microwave absorption (MRMA) imaging, and MR-compatible microwave tomography (MRMT).

The routine use of preoperative breast MRI is recognized as a potentially powerful, if still controversial, diagnostic adjunct to breast mammography. In 2009, AJR published the results of significant recent study on the procedure, directed by Dr. Lewis. *The role of breast MRI in the preoperative evaluation of patients with newly diagnosed breast cancer* considered 199 patients with newly diagnosed cancer who underwent breast MRI; for nearly 20 percent of these patients, additional malignant tumors were found by MRI which had not previously been discovered.

**In Vivo EPR Programs**  Electron Paramagnetic Resonance (EPR) spectroscopy is a technique for studying chemical species that have one or more unpaired electrons, such as organic and inorganic free radicals or inorganic complexes possessing a transition metal ion. The basic physical concepts of EPR are analogous to those of nuclear magnetic resonance (NMR) and MRI, but it is electron spins that are excited instead of spins of atomic nuclei. A number of unique capabilities for the measurement of physiologic parameters are available using EPR, including direct measurement of tissue pO2 through a repeatable non-invasive measurement procedure and the measurement of endogenous free-radical species.

*In vivo* EPR oximetry, the central research activity of Dr. Swartz’s EPR lab since inception in 1992, has a number of potentially valuable clinical applications. By means of accurate pO2 detection, EPR can be used to monitor oxygen level in a variety of tissue types. In tumors, hypoxia is associated
with angiogenesis as well as with resistance to radiotherapy and chemotherapy; accurate assessment of changes in tumor pO\textsubscript{2} can be used in cancer detection and staging, and in monitoring of therapeutic efficacy. Other types of vascular pathology are also associated with decreased tissue-oxygen levels, such as the ischemia caused by peripheral vascular disease in diabetic patients and wound healing following radiation damage to normal tissues. EPR oximetry could provide information critical for effective clinical management of these and other oxygen-dependent pathologies and for the assessment of novel therapeutic measures.

Recently, the center has focused on the development of radiation biodosimetry techniques and devices. In a disaster scenario involving the accidental or hostile release of significant levels of ionizing radiation, public health officials remain without effective portable means of determining exposure levels in affected individuals, jeopardizing the ability to carry out appropriate triage strategies. During irradiation, free radicals are created in biologic tissues in proportion to the absorbed dose. In certain tissues, such as tooth enamel, bone, and nails, these radicals remain in a stable state following irradiation and their concentration can be quantitatively measured using EPR to estimate the dose. The center has received major funding from a number of NIH and DoD sources, including the NIH Centers for Medical Countermeasures Against Radiation (CMCR) program and the Defense Advanced Research Projects Agency (DARPA). As this report goes to press, the EPR Center awaits confirmation of an expected new $16.6 million five-year NIH grant for dosimetry research.

**In Vivo Optical Spectroscopy**  
Associated with the EPR Center, Dr. Roger Springett’s Redox Laboratory conducts independent research on the uses of visible light spectroscopy for imaging neural processes in the mammalian neocortex through the measurement of changes to mitochondrial oxygenation. Specifically, the current five-year NIH-funded program, *Imaging the Mitochondrial Response to Neural Activity*, seeks to develop and validate spectral domain imaging technology to collect and reconstruct images of the oxidation state of mitochondrial cytochrome, and of hemoglobin and extrinsic chromophore concentrations. Spectral domain imaging of mitochondrial oxygenation, presently unique to Dr. Springett’s lab, has the potential to add significant understanding of the manner in which the cortex process information, and also offers the possibility of precise, non-invasive location of tumors and other metabolically significant structures during certain types of neurosurgery.

**Neuroimaging Research**  
Dr. Weaver, Dr. Eskey, and the neuroradiology faculty continue collaborations—with the Dartmouth Brain Imaging Laboratory, the Advanced Imaging Center in projects including innovation in advanced 3T imaging in glioblastoma recurrence, fMRI imaging, MRI in pediatric head trauma, CTA in intracerebral hemorrhage and aneurysm evaluation, imaging of pharyngeal carcinoma, vertebroplasty, and synovial cyst rupture. In addition, the Thayer School, independently and in collaboration with DHMC departments such as Radiology and Psychiatry, has been active in a range of neuroimaging research, including: the development of dynamic multimodal imaging; fluorescence signatures for image-guided neurosurgery; and molecular imaging for the detection of glioma brain tumors.

**Department-funded Research**  
The Radiology Research Committee, chaired by Dr. Belden (following several years of capable leadership by Dr. Harris), assists faculty, residents and fellows with clinical research guidance and seed grants made possible by the Radiology Chair. In the past 3 years, the committee (also including Drs. Eskey, Weaver, Swartz, and Black) has funded studies on: hemodialysis access outcomes and complications in the elderly; interventional radiology procedure in
patients with abnormal coagulation parameters; thyroid nodule ultrasound characterization and differentiation of benign vs. malignant nodules (part of a multi-center trial); and interobserver variability of CTA aneurysm perception

III. OUTCOMES RESEARCH

The Dartmouth Institute for Health Policy and Clinical Practice (TDI)—formerly known as the CECS—originated the pivotal Dartmouth Atlas and has taken a leading role in advancing outcomes-based medicine. Nearly 20 years ago the Radiology Department signaled its embrace of the principles of outcomes research by recruiting radiologist William C. Black, MD, to a joint appointment with TDI. Dr. Black has developed and teaches a core curriculum on technology assessment, and is nationally recognized as an authority on the evaluation of screening and diagnostic testing. The department’s association with the institute has strengthened in recent years as five additional faculty members have earned MS or MPH degrees at TDI. In late 2008, we established the Radiology Outcomes Group (DHROG) in order to identify opportunities to apply outcomes-based medical practice to clinical imaging, cost-effectiveness, physician education, and shared decision-making with patients.

The National Lung Screening Trial

The National Lung Screening Trial (NLST) is a randomized, multi-center study designed to compare the efficacy of two different techniques to screen for lung cancer: low-dose helical computerized tomography (LDCT) versus chest radiography (“plain film” X-ray). With a budget of over $200 million and enrollment of over 53,000 current or former smokers with three annual screenings for each, NLST is the largest randomized study of lung cancer screening in a high-risk population ever conducted, and represents a major milestone in the application of outcomes-research principles to a major public health concern. The NLST has generated widespread interest and considerable controversy, and will almost certainly impact future policy-making for lung cancer screening. Publication of study results and analysis is expected in 2011.

Radiology’s William C. Black was instrumental in the design of the study, directs its cost-effectiveness component, is PI for the DHMC site, serves on numerous national committees for the NLST, and is slated to present study results at the 2010 RSNA Annual Meeting. Dr. Black, in addition to clinical duties as a chest imaging specialist, serves on the TDI faculty, and as Chair of the Outcomes and Economics Core Laboratory at the American College of Radiology Imaging Network (ACRIN).

CER Center for Cancer Imaging

In late 2009 a multi-institutional Dartmouth-initiated consortium was awarded a 2-year, $4 million NIH Recovery Act “Grand Opportunities” grant for Comparative Effectiveness of Advanced Imaging in Cancer. Funding is provided for establishing a CER center as a component in a national infrastructure for comparative effectiveness of cancer imaging research. The project, led by NCCC’s Dr. Anna Tosteson and Radiology’s Dr. Black, includes several Dartmouth community disciplines and faculties, as well as the American College of Radiology Imaging Network (ACRIN), Brown University, and Tufts University’s Evidence-Based Practice Center.