



## **Advanced Imaging Pilot Research Grants**

The Harvard Catalyst Innovation and Implementation and Translational Imaging Programs sponsored the Advanced Imaging Pilot Research Grants and Concept Development Prizes. The goal was to encourage the Harvard community to develop innovative research projects and ideas that would use advanced imaging technologies (PET, Optical or Physiological MR) to directly address areas of unmet clinical need.

The Pilot Grant RFA sought proposals for collaborative, innovative research projects that applied Advanced Imaging technologies to pressing medical issues. The intent of the Concept Development Prize was to develop speculative and novel ideas that addressed a potential application or evolution of advanced imaging to solve a key medical question. Participation in an Advanced Imaging Symposium was required to be eligible to apply for these funding opportunities.

Funding decisions for the Advanced Imaging funding opportunities were announced in May 2012. Fourteen Pilot Grants were awarded in amounts of up to \$50,000 for each one-year project. Four Concept Development prizes were awarded of in the amount of \$2,000 each.

For more information about these awards, see the following [news article](#).

## **Advanced Imaging Pilot Grant Awards**

### **MR Elastography for Assessment of Kidney Fibrosis in Chronic Kidney Disease (CKD)**

Principal Investigator: Robert Brown, MD, Beth Israel Deaconess Medical Center

Co-Investigators: Walter Mutter, MD, Beth Israel Deaconess Medical Center  
Isaac Stillman, MD, Beth Israel Deaconess Medical Center  
Maryellen Sun, MD, Beth Israel Deaconess Medical Center  
Jesse Wei, MD, Beth Israel Deaconess Medical Center

The increasing incidence of CKD is leading to a large burden of cardiovascular mortality and renal failure. Kidney fibrosis is considered the final common pathway of renal injury leading to progression of CKD. It is thus useful to know the degree of fibrosis to determine treatment and prognosis, but there is currently no non-invasive way to do so with acceptable sensitivity and specificity. Estimates of glomerular filtration rate are often discordant with tissue damage and subject to hemodynamic fluctuation. Even kidney biopsy has sampling error and its risk precludes frequent repetition.

A novel MRI technique known as MR elastography (MRE) has been developed to assess tissue elasticity. In the liver, elasticity or stiffness has been shown to correlate with hepatic fibrosis. The technique has been applied to the normal kidney, but studies have not yet been performed to correlate tissue stiffness as measured by MRE with pathologic degree of fibrosis, renal function or progression in CKD patients.

We propose applying MRE to detect and quantify kidney fibrosis in patients with CKD. First, we will validate our protocol in normal controls; second we will see if MRE measured stiffness correlates with renal fibrosis in patients with CKD; and third we will correlate stiffness with renal function as measured by glomerular filtration rate.

If effective, this technique could become a useful noninvasive tool for assessing early renal disease when GFR is still normal and evaluate the efficacy of emerging treatments to delay fibrosis and CKD progression.

### **Spectral Domain OCT 3-Dimensional Neuroretinal Rim Analysis of the Optic Nerve Head**

Principal Investigator: Teresa Chen, MD, Massachusetts Eye and Ear Infirmary

Co-Investigators: Anne Coleman, MD, PhD, University of California, Los Angeles  
Johannes de Boer, PhD, VU University and Rotterdam Eye Institute  
Vivek Srinivasan, PhD, Massachusetts General Hospital

*Abstract withheld at request of investigator.*

## **Optical Coherence Tomography: A Revolutionary Noninvasive Diagnostic Tool for Middle Ear Disease**

Principal Investigator: Jeffrey Cheng, PhD, Massachusetts Eye and Ear Infirmary

Co-Investigators: Daniel Lee, MD, Massachusetts Eye and Ear Infirmary  
John Rosowski, PhD, Massachusetts Eye and Ear Infirmary  
Seok-Hyun Yun, PhD, Massachusetts General Hospital

Middle ear disorders constitute a large fraction of patients seen in an otolaryngology practice. Middle ear pathology, such as ossicular chain fixation or interruption, is a common cause of significant conductive hearing loss of up to 60 dB. Current imaging approaches do not have the resolution to detect subtle changes in the middle ear and the most accurate means to diagnosis middle ear disease requires surgery under general anesthesia to elevate the eardrum in order to visualize the middle ear to make proper diagnosis. Optical coherence tomography (OCT) is an exciting new technology that can image cross-sections of soft tissues with a high spatial resolution, thus it can see through the intact eardrum to noninvasively examine the middle ear. Using a recently developed triggered OCT technique, we can simultaneously measure sound-induced vibration of the eardrum and the ossicles without violating the eardrum. The combination of morphological information of the middle ear structures and quantification of acoustically-driven vibration of the middle ear using OCT as a noninvasive diagnostic tool has the great potential to revolutionize the diagnosis and management of middle ear disease. We have performed proof-of-concept structural and ossicular motion measurements using triggered OCT in cadaveric ears with no ear canal. In this project, an otoscope probe that couples both sound and OCT laser beams into the intact cartilaginous and bony ear canals of patients will be developed, along with bench testing on cadaveric human temporal bones. These steps are precursors of translational studies in live subjects and patients.

## **Real-Time Endoscopic Guidance using Near-Infrared Fluorescent Light for Thoracic Surgery**

Principal Investigator: Sylvain Gioux, PhD, Beth Israel Deaconess Medical Center

Co-Investigators: John Frangioni, MD, PhD, Beth Israel Deaconess Medical Center  
Sidharta Gangadharan, MD, Beth Israel Deaconess Medical Center

Lung cancer is the leading cause of cancer death in the United States, accounting for 28% of all cancer deaths. Standard of care for potentially curable lung cancer involves preoperative radiographic or invasive staging, followed by surgical resection. With recent adjuvant chemotherapy and radiation studies showing a survival increase in node-positive patients, it is crucial to accurately surgically stage these patients in order to identify those who may benefit. However, lymphadenectomy in lung cancer is currently performed randomly, mainly due to the lack of tools permitting real-time, intraoperative identification of sentinel lymph nodes (SLNs). Given the implications of inadequate staging underlying the high recurrence rates reported in early stage lung cancer, it is imperative to develop new tools to improve surgical nodal assessment.

Optical near-Infrared (NIR) fluorescence imaging has the potential to solve this clinical problem by providing real-time, intraoperative guidance for lymphadenectomy. Previous studies have shown that injection of a safe, FDA-approved fluorescent tracer such as indocyanine green (ICG) into a tumor permits accurate intraoperative identification of lymphatic drainage and

SLNs. In this project, we propose to design, validate and translate an NIR-compatible endoscopic fluorescence imaging system in combination with a fluorescent tracer for intraoperative guidance. This system will be tested preclinically using Yorkshire pigs in our laboratory and translated to a pilot human study in lung cancer with our clinical collaborator. Together, this study aims to solve an unmet clinical need and has the potential to profoundly impact the management of lung cancer patients.

### **Transforming Brain Tumor Surgery Through Coherent Raman Microscopy**

Principal Investigator: Alexandra Golby, MD, Brigham and Women's Hospital

Co-Investigator: Daniel Orringer, MD, Brigham and Women's Hospital

The central objective in brain tumor surgery is to maximize removal of tumor, while sparing adjacent healthy tissue. Despite clear differences on a histologic level, cancerous tissue is often indistinguishable from healthy tissue in the operating room. Consequently, tumor that would be safe to remove is left behind. The presence of residual tumor may result in premature recurrence, treatment failure and poor outcome. In addition, normal tissues, mistaken as tumor, may be removed, resulting in unnecessary neurologic deficits.

Currently, there is no widely accepted method for delineating tumor from normal brain during surgery. Stimulated Raman scattering (SRS) microscopy, a cutting-edge imaging method, has the potential to enable surgeons to reliably differentiate cancer-infiltrated tissue from healthy tissue during surgery. SRS microscopy enables rapid, high-resolution, label-free, cellular-level imaging of biological tissues based on the intrinsic spectroscopic properties of their macromolecular components such as lipids, proteins and DNA. SRS microscopy is uniquely well suited for intra-operative imaging because it can be performed *in situ* based on back-scattering of the excitation signal.

We have recently demonstrated that cancerous tissue can indeed be detected and differentiated from normal brain, on a cellular level, in primary human glioblastoma xenograft animal models *in vivo* using an SRS microscope. This proposal, designed to carry out the first SRS imaging of human brain tumor specimens, will lay the foundation for the integration of SRS as an intraoperative imaging technique capable of improving the accuracy of brain tumor surgery.

### **Pre-Operative Nodal Staging of Thyroid Cancer Using Ferumoxytol**

Principal Investigator: Mukesh Harisinghani, MD, Massachusetts General Hospital

Co-Investigators: Gilbert Daniels, MD, Massachusetts General Hospital  
Elkan Halpern, PhD, Massachusetts General Hospital  
Peter Sadow, MD, PhD, Massachusetts General Hospital

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer. Metastases to the central and lateral neck compartments occur in 20-50% of patients with PTC. Nodal metastases predict disease recurrence and possibly decreased survival in PTC. Unfortunately central nodes cannot be reliably assessed using preoperative ultrasound or intra operative examination. Therefore, central compartment lymph nodal dissection (CLND) is the current gold standard for nodal staging. However, the role of prophylactic CLND is controversial because of the significantly increased morbidity of CLND plus total thyroidectomy, compared to total thyroidectomy alone.

Lymphotropic nanoparticle enhanced magnetic resonance imaging (LNMRI) was developed at the MGH to detect metastatic nodal disease in prostate cancer, independent of size and morphology of the lymph nodes, after intravenous administration of ultras-small superparamagnetic iron oxide nanoparticle (ferumoxytol). We propose a pilot trial of LNMRI to detect metastatic lymph nodes in patients who are scheduled for resection of a primary thyroid cancer or resection of lymph node metastases from thyroid cancer. Our goal is determine the sensitivity and specificity of high resolution LNMRI to identify small and otherwise undetectable lymph node metastases in patients who are scheduled for surgical resection of papillary thyroid carcinoma, and to determine whether LNMRI will identify metastatic lymph nodes that would not have been noted during surgery.

The hypothesis is that LNMRI will provide enhanced accuracy of nodal staging in patients with thyroid cancer. The technique will identify small and otherwise undetectable lymph node metastases in patients with papillary thyroid carcinoma.

### **Assessing Activation of Brain Microglia in Chronic Pain with Simultaneous MR-PET**

Principal Investigator: Jacob Hooker, PhD, Massachusetts General Hospital

Co-Investigators: Randy Buckner, PhD, Harvard FAS  
Ciprian Catana, MD, PhD, Massachusetts General Hospital  
Ru-Rong Ji, PhD, Harvard Medical School  
Marco Loggia, PhD, Brigham and Women's Hospital  
Bruce Rosen, MD, PhD, Massachusetts General Hospital  
Ajay Wasan, MD, MMSc, Brigham and Women's Hospital

Chronic pain is an enormous public health issue, with a prevalence of ~105 million individuals in the US. Until recently, pain disorders have been thought to arise primarily from the dysfunction of nociceptive neurons. This view, however, has been lately challenged by the demonstration that animal models of chronic pain present evidence of microglia activation (MA) in the central nervous system, i.e., an immune response traditionally known to occur in response to other pathological conditions (e.g., neuroinflammation). Importantly, increasing evidence indicates that MA is not simply an epiphenomenon co-occurring with pathological nociception, but is likely to have a causal role. Nonetheless, it is currently unknown whether microglia contribute to the pathophysiology of chronic pain in humans. In this project we will test the hypothesis that chronic pain patients present evidence of brain MA. We will use combined Magnetic Resonance/Positron Emission Tomography, a novel technology synergizing two leading imaging methodologies, and [<sup>11</sup>C]PBR28, a recently developed marker of MA with binding specificity far superior to that of other ligands targeting MA. The concomitant acquisition of PET and MR data will provide the unique opportunity to perform MR-based motion- and attenuation-correction of the PET images, and to assess the co-localization of MA and structural/functional/perfusion abnormalities during a single imaging visit. Recognizing the role of microglia in chronic pain would have tremendous clinical implications, including the development of much needed novel pharmacological approaches to pain. The data collected with the support of this Grant will represent an important foundation for future NIH grant proposals.

## **Electrophysiological Basis of Cortical Abnormality in Children with Encephalopathy of Prematurity**

Principal Investigator: Stephanie Jones, PhD, Boston Children's Hospital

Co-Investigators: Banu Ahtam, DPhil, Boston Children's Hospital  
Ellen Grant, MD, Boston Children's Hospital  
Yoshio Okada, PhD, Boston Children's Hospital  
Christos Papadalis, PhD, Boston Children's Hospital

The incidence of premature birth is high and growing. The ability to save the lives of babies born prematurely is improving each year. However, diagnosis of resulting brain injury is lacking and large numbers of premature children have serious neurodevelopmental disabilities. Brain injury from premature birth consists primarily of periventricular leukomalacia (PVL), exhibiting cerebral white matter injury often accompanied by neuronal/axonal disease. We propose to integrate three cutting-edge neuroimaging technologies to develop a novel method to identify the electrophysiological basis of cortical abnormalities in children with PVL. We will focus on children who have developed cerebral palsy (CP) with sensorimotor deficits due to PVL. Magnetic resonance (MR) based high-angular resolution diffusion imaging (HARDI) of axonal structural connectivity will be used to quantify differences in thalamocortical and cortico-cortical fiber tracts to somatosensory cortex between CP patients and age-matched controls. Quantified differences in fiber tract number and conductance velocities will then be implemented into a biophysically principled mathematical neural modeling that simulates magnetoencephalography (MEG) measured somatosensory evoked fields (SEFs), which depend explicitly on thalamocortical and cortico-cortical connectivities. Predictions on resulting abnormalities in SEFs will be made and then tested with a custom designed pediatric MEG system. Our goal is to see if we can predict the SEF responses in these patients on an individual basis. To the extent that this is possible, we will be able to identify the nature of the cortical abnormality in children with CP due to PVL and in the long-term premature infants while in the NICU.

## **Functional Modeling of the Pediatric Airway in Children with Obstructive Sleep Apnea**

Principal Investigator: Eliot Katz, MD, Boston Children's Hospital

Co-Investigators: Edward Lee, MD, Boston Children's Hospital  
Andrew Wellman, MD, Brigham and Women's Hospital

Obstructive sleep apnea (OSA) is a common and serious cause of metabolic, cardiovascular and neurocognitive morbidity in children. Airway narrowing often includes a combination of adenotonsillar hypertrophy, mucosal edema, turbinate hypertrophy, micrognathia, and/or maxillary constriction. Adenotonsillectomy is typically the first-line therapy for childhood OSA and generally results in improvement, but approximately 40% of patients will have residual OSA, resulting in considerable morbidity. Adjuvant therapies for OSA are frequently performed, including rapid maxillary expansion, turbinectomy, and nasal septal repair, but there is no consensus on which patients require additional therapy. Surgical and/or medical interventions for OSA cannot be evaluated experimentally on the same patient, and therapeutic trials are logistically and ethically challenging. Tools to predict the response to therapy in childhood OSA are urgently needed to ensure complete resolution of OSA, and to avoid unnecessary interventions. Magnetic resonance imaging can be used to obtain an airway surface mesh suitable for analysis with computational fluid dynamics, yielding an airway flow and pressure

profile related to sleep-disordered breathing. Thus, virtual surgical manipulations of MRI data in combination with fluid dynamics could be used to predict therapeutic efficacy. We propose to obtain airway MRI and polysomnography data in a sample of children with OSA, before and after adenotonsillectomy. Computational fluid dynamics will be utilized to model upper airway flow through the collapsible airway mesh in order to predict response to surgery. Modeling techniques could determine the optimal surgical and/or medical intervention, thereby reducing unnecessary procedures and treatment delays.

### **Hybrid Optical X-ray CT for Head and Neck Cancer Diagnosis and Surveillance**

Principal Investigator: Anand Kumar, PhD, Massachusetts General Hospital

Co-Investigators: Stefan Carp, PhD, Massachusetts General Hospital  
Qianqian Fang, PhD, Massachusetts General Hospital  
Rajiv Gupta, MD, PhD, Massachusetts General Hospital

Head and neck squamous cell carcinoma (HNSCC) is the 6th leading cancer world-wide and results in considerable morbidity and mortality and mandates constant surveillance after treatment, severely impacting the quality of life of patients. In addition to the physical exam, CT and MRI are used to assess the extent of disease. Surgical resection, when feasible, in conjunction with chemo and radiation therapy, is the main treatment modality. While these imaging techniques offer high spatial resolution, they generally suffer from poor contrast for distinguishing tumors from normal tissue. As a result, the mortality rates from recurrent tumors remain stubbornly high. Near infra-red optical imaging can provide both intrinsic (blood oxygenation) and extrinsic (fluorescence) contrast that can delineate the tumor region based on hemoglobin and vascular permeability. While standalone optical systems have previously been employed to image breast cancers, head and neck cancers and for sentinel lymph-node mapping, the optical images are often poor in resolution and lack anatomical specificity. We propose to build a new Hybrid Optical X-ray CT (HOX-CT) for primary diagnosis, intra-operative tumor margin detection, and surveillance after treatment. Building upon our previous success of fabricating a dual ring system that seamlessly integrates into Siemens volume CT scanner, we will further incorporate optical components in this ring system. We will also adapt our state-of-the-art multi-modality optical imaging reconstruction algorithms to provide spatially co-registered anatomical and functional images. We will validate the performance of this system using phantom experiments and demonstrate the proof-of-concept by staging HNSCC in clinical subjects.

### **Relationship Between Multiparametric MRI and Prostate Cancer Aggressiveness**

Principal Investigator: Neil Martin, MD, MPH, Brigham and Women's Hospital

Co-Investigators: Fiona Fennessy, MD, PhD, Brigham and Women's Hospital  
Philip Kantoff, MD, Dana-Farber Cancer Institute  
Clare Tempny, MD, Brigham and Women's Hospital

Active surveillance is increasingly recognized as a way to limit morbidity associated with the diagnosis and treatment of low-risk prostate cancer. We currently lack non-invasive imaging modalities to characterize prostate cancer aggressiveness or prognosis for men undergoing active surveillance. Multi-parametric (MP)-MRI has been shown to correlate with physiologic processes and may relate to tumor grade. In this study, we propose to first relate MP-MRI findings to paired biopsy findings to determine whether the MRI can predict un-sampled higher-

grade disease. For the second Aim, we will explore how tumor whole-transcriptome mRNA expression relates to MP-MRI findings. These data will be crucial in determining how to integrate MP-MRI in the care of men undergoing active surveillance for prostate cancer. The funding of this pilot grant will be essential in integrating MP-MRI into a developed but not yet opened DF/HCC active surveillance protocol.

### **Imaging Pancreatic Amyloid with PET**

Principal Investigator: Marc Normandin, PhD, Massachusetts General Hospital

Co-Investigators Susan Bonner-Weir, PhD, Joslin Diabetes Center  
Keith Johnson, MD, Massachusetts General Hospital

Post-mortem analyses detect pancreatic amyloid aggregates in most type-2 diabetes mellitus (T2DM) patients, but rarely in type-1 patients and non-diabetics. Despite the lapse of a century since this initial discovery, the causal or correlative role of amyloidosis in T2DM pathology has yet to be fully resolved.

Like the pancreas in T2DM, the Alzheimer's disease brain exhibits amyloid deposits at autopsy. The amyloid aggregates prototypical of Alzheimer's and T2DM are not identical, but sufficiently alike that the same histological stains are used for both. [<sup>11</sup>C]PiB is a recently developed PET tracer used to image cerebral amyloid and derived from Thioflavin-T, which is used to stain pancreatic amyloid. To our knowledge, pancreatic amyloid imaging has not been attempted.

We aim to assess the feasibility of imaging pancreatic amyloid deposits using PET with the amyloid-targeting radiotracer [<sup>11</sup>C]PiB. We will confirm that [<sup>11</sup>C]PiB penetrates pancreatic tissue and binds to amyloid by comparing microPET/CT and *ex vivo* measurements of radiotracer uptake with histological assays in transgenic mice expressing self-aggregating human amyloid. PET/CT will noninvasively measure pancreatic [<sup>11</sup>C]PiB uptake in healthy humans and T2DM patients, and binding will be related to metrics of disease severity.

These experiments will determine the potential for noninvasive measurement of pancreatic amyloid with [<sup>11</sup>C]PiB PET. The pilot data collected here will provide initial validation of our method and the basis for future grant applications to verify findings in a larger cohort and explore amyloid deposition in longitudinal studies to elucidate the role of amyloidosis in the onset and progression of T2DM.

### **Pilot Evaluation of <sup>11</sup>C-D-Deprenyl Uptake in Chronic Pancreatitis: A Potential Diagnostic PET-MRI Biomarker**

Principal Investigator: Nisha Sainani, MD, Brigham and Women's Hospital

Co-Investigators: Peter Banks, MD, Brigham and Women's Hospital  
Clas Linnman, PhD, McLean Hospital  
Darwin Conwell, MD, Brigham and Women's Hospital

Definitive diagnosis of early-stage chronic pancreatitis (CP) remains elusive due to the inability of conventional imaging techniques to detect early inflammation, and the inability to safely obtain histologic biopsy. Secretin-stimulated endoscopic pancreatic function testing and ERCP are considered the "nonhistologic" gold standards for diagnosis of CP; however, they are

invasive and require endoscopy. We propose a pilot study to evaluate [<sup>11</sup>C]-D-deprenyl PET-MRI as a non-invasive diagnostic tool for chronic pancreatitis.

MRI/MRCP has emerged as a valuable, non-invasive diagnostic tool in assessing changes in pancreas ductal and parenchymal architecture associated with both acute (AP) and chronic pancreatitis. [<sup>11</sup>C]-Ddeprenyl (DDE) tracer positron emission tomography (PET) provides highly accurate direct imaging of musculoskeletal inflammation. Simultaneous DDE-PET and MRI/MRCP may provide unprecedented spatial resolution of the morphological changes and early inflammatory response associated with CP.

In this pilot study we aim to compare qualitative and quantitative DDE-PET/MRI imaging findings in cohorts of patients with alcohol-induced acute and chronic pancreatitis to imaging findings in healthy control subjects. We expect to find a statistically significant increase in DDE uptake in the pancreas of AP and CP patients, reflecting the underlying acute and chronic inflammation. If proven, this pilot study will establish the proof of principle and preliminary data necessary to develop future studies, evaluating the accuracy and utility of DDE-PET/MRI in the diagnosis and management of early mild CP.

This proposed collaboration spans several Harvard teaching hospitals and disciplines (Gastroenterology, Radiology, and Molecular Imaging), which we believe is ideal for funding from the Harvard Catalyst.

### **Early Detection of Corneal Ectasia with *In Vivo* Brillouin Optical Imaging of Corneal Biomechanical Properties**

Principal Investigator: Giuliano Scarcelli, PhD, Massachusetts General Hospital

Co-Investigators: Roberto Pineda, MD, Massachusetts Eye and Ear Infirmary  
Seok Hyun Yun, PhD, Massachusetts General Hospital

The biomechanical properties of the cornea are essential for its function. Corneal collagen fibers provide the mechanical strength to withstand the intraocular pressure; if corneal tissue becomes abnormally weak, corneal ectasia (i.e. thinning and bulging) ensues, causing severe vision degradation. Abnormal weakening of the cornea occurs due to degenerative ocular conditions, e.g. keratoconus, affecting ~1/2000 of the general population or as a complication of LASIK surgery. Concerns about post-LASIK ectasia prevent about 15% of prospective patients from benefitting from laser vision correction. When clinical symptoms manifest, corneal ectasia is often at an advanced stage that leads to corneal transplant. If inherent corneal weakness were detected early, corneal collagen crosslinking could stop the degenerative bulging and at-risk subjects could be consulted to avoid LASIK surgery. Early detection requires an imaging technique that uses elasticity as a contrast mechanism; current clinical instruments only provide morphological information. This proposal addresses this need by bringing Brillouin imaging to corneal applications. Brillouin imaging can map the elastic modulus of material without contact and with 3D resolution. A pilot clinical study will be performed to compare normal to keratoconus corneas (Aim 1) and normal to post-LASIK ectasia corneas (Aim 2). Brillouin imaging has the potential to revolutionize current diagnostic paradigms for keratoconus and screening protocols for LASIK surgery. This study will collect crucial data to design large-scale clinical studies to prove the technology effectiveness. This proposal is the result of collaboration between the inventors of Brillouin imaging and an expert in ophthalmology and corneal refractive surgery.

## **Advanced Imaging Concept Development Awards**

### **Mapping Dopamine Transmission with Simultaneous PET/MR**

Principal Investigator: Marc Normandin, PhD, Massachusetts General Hospital

Co-Investigators: Diego Pizzagalli, PhD, McLean Hospital  
Joseph Mandeville, PhD, Massachusetts General Hospital

Anhedonic depression is characterized by abnormal affect and reward processing putatively mediated by serotonin (5HT) and dopamine (DA). Preliminary [<sup>11</sup>C]raclopride PET scans suggest blunted DA reward response, but less is known of 5HT dysfunction. We propose advanced neuroimaging techniques toward understanding 5HT signaling pathologies in the disorder.

Hybrid PET/MR combines PET's molecular specificity with fMRI's sensitivity and temporal resolution, but relationships between neurotransmission and fMRI appear complex. Using dopamine as a prototype system, we applied basic pharmacological principles to model excitatory effects of DA D1 receptors opposing neuronal inhibition by D2 receptors. Replicating the procedure for the excitatory and inhibitory 5HT receptors will produce an fMRI model tailored to that neurotransmitter system.

We propose to apply the fMRI analysis in conjunction with existing PET methodology in simultaneous PET/MR experiments of patients with anhedonic depression. These studies would utilize [<sup>11</sup>C]P943, whose binding is sensitive to 5HT levels, and fenfluramine challenge to provoke elevation of synaptic 5HT. This paradigm parallels the use of [<sup>11</sup>C]raclopride and [123I]IBZM to image amphetamine-induced DA release in schizophrenia. These studies advanced the dopaminergic hypothesis of schizophrenia by mapping not only receptor distribution but also the functional responsiveness of the system. The proposed [<sup>11</sup>C]P943 studies with fenfluramine would similarly advance understanding of pathological 5HT responsiveness in depression, with the added benefit of synergistic views into underlying neuronal processes owing to use of PET/MR technologies not available when the amphetamine studies in schizophrenia were conducted. The results will inform our understanding of depression pathophysiology and potential avenues for treatment.

### **Digital Infrared Thermal Imaging (DITI) for Early Detection of Necrotizing Enterocolitis (NEC) in Premature Newborns**

Principal Investigator: Richard Parad, MD, MPH, Brigham and Women's Hospital

Co-Investigators: Judy Estroff, MD, Boston Children's Hospital  
Amir Lahav, ScD, PhD, Brigham and Women's Hospital  
Steven Ringer, MD, PhD, Brigham and Women's Hospital

NEC is the most common life threatening intestinal emergency in premature infants. Pathophysiology is poorly understood, but intestinal injury, systemic sepsis and multi-system organ failure lead to significant mortality and morbidity. NEC affects 5% of NICU admissions (10,000 infants/yr in the US). 75% are <36 weeks gestation or birthweight <2000g. Among the 40% who require surgery, common complications are wound dehiscence, abscess, intestinal strictures, and short bowel syndrome, and survivors are at increased risk for adverse neurodevelopment outcomes. Mortality nears 50% in surgical NEC.

Although abdominal radiography (AR) is the accepted standard for NEC diagnosis and serial imaging aids management, AR has poor specificity and sensitivity, especially in early disease stages. A more sensitive test which allowed earlier diagnosis would improve outcome and reduce unnecessary treatment of infants with uncertain diagnosis.

Recent technical improvements in DITI cameras, which allow non-invasive measure of infrared radiation, are improving breast cancer detection. We hypothesis DITI to be more sensitive than AR in detecting the bowel inflammation which would precede AR NEC findings (abnormal bowel gas or intramural or free air).

Children's and BWH Radiology (Judy Estroff(Co-I)) and BWH Neonatology (Richard Parad(PI), Amir Lahav(Co-I), Steven Ringer(Co-I)) would perform DITI concurrent with AR in evaluating NICU patients with suspected NEC (50/yr). In a pilot study, if 10 infants with AR diagnosed and surgically confirmed NEC demonstrate concordance with abnormal DITI patterns, we propose a prospective study of serial DITI to evaluate sensitivity and specificity of this imaging modality.

### **Arthroscopic Optical Imaging for Improved Management of Articular Cartilage Injury**

Principal Investigator: Ryan Porter, PhD, Beth Israel Deaconess Medical Center

Co-Investigators: Brett Bouma, PhD, Massachusetts General Hospital

The management of articular cartilage injury remains an important challenge to orthopaedic clinicians, since ineffective management can lead to the development of osteoarthritis in the injured joint. The inherent challenge can be partly attributed to the status of articular chondrocytes within the apparently "normal" cartilage surrounding a defect. It is now understood that these cells can undergo apoptosis following joint trauma. A devitalized border of native cartilage is less likely to integrate with repair tissue formed or implanted within the defect. However, zones of apoptosis cannot be detected and addressed by conventional arthroscopic evaluation. Recent advancements in near infrared fluorescence imaging have shown much promise for the minimally-invasive imaging of pathological features with cellular resolution. Arthroscopic management of articular cartilage injuries could similarly benefit from this modality. Specifically, the imaging of cartilage apoptosis could better identify the region of tissue debridement prior to defect filling. A protocol for intraarticular staining and arthroscopic detection of apoptotic chondrocytes could be readily translated to clinical practice. The goal of this project is to develop a proof-of-principle apparatus and validate it for detecting apoptotic chondrocytes using a bovine cartilage explant model for joint injury.

### ***In Vivo* Optical Imaging Studies of Aneuploidy as Biological Predictor of the Progression of Barrett's Epithelium to Adenocarcinoma**

Principal Investigator: Le Qiu, PhD, Beth Israel Deaconess Medical Center

Co-Investigators: Lev Perelman, PhD, Beth Israel Deaconess Medical Center

Previously we demonstrated that spectroscopic information in light scattered by nuclei could reveal precancerous cellular changes and developed new endoscopic scanning technique called endoscopic polarized scanning spectroscopy (EPSS) that can perform rapid optical scanning and multispectral imaging of the entire esophageal surface and provide diagnoses in near real time. By detecting and mapping suspicious sites, guided biopsy of invisible,

precancerous dysplasia becomes practicable. The results of our study with the EPSS instrument could help clinicians to diagnose esophageal cancer at an earlier stage, when the condition is still treatable. The EPSS instrument gives information on the location of high grade dysplasia (HGD), a traditional predictor of adenocarcinoma. In addition to dysplastic changes, EPSS is also sensitive to other subcellular changes in epithelium related to aneuploidy. Thus, we hypothesize that EPSS should also detect and provide valuable *in vivo* information on the second risk factors of the progression of Barrett's epithelium to adenocarcinoma, aneuploidy. To accomplish the task of this real time risk factor imaging of adenocarcinoma, we will design and build a new and improved portable EPSS instrument dedicated to the *in vivo* optical studies of these biological predictors and establish new algorithms for imaging both disease predictors. The new imaging technology will guide the gastroenterologists taking biopsies more efficiently and even make on-site decision for ablation of suspicious area which could largely reduce both the risk and cost of otherwise multiple procedures.