Training the Trainers: How to Answer Radiation Biology Questions Before, During, and Following a Radiation Terrorism Event

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RSNA/AUR/APDR/SCARD
Radiology Research Development Grant

Many authorities recognize the increasing likelihood of the occurrence of a terrorist-generated radiological or nuclear event. In order to develop successful response plans, emergency personnel (hospital staff, first responders, etc) need to have received a primer in radiation biology so they can adequately recognize, and respond confidently to, a radiological event and know how to get adequate assessment and support. The onus for this education falls on many of those currently employed within the radiological fields, who themselves may lack a full understanding of the biological underpinnings of such an event. We propose to develop a new and comprehensive course, provided by some of the leading radiation biologists in the U.S. that can be distributed and used to “train-the-trainers” in the fundamentals of relevant radiation biology topics. This course will form a useful part of a toolkit to educate both media and public in the event of a radiological emergency.

This grant will enable the creation of a unique multidisciplinary educational resource that will not only serve the broader community in preparation for a response to a terrorist incident, but also will serve as a valuable and concise summary of the pathways of radiation interactions and injury.

Technical and Professional Skill Development Within Radiation Oncology

Abstract not available.

Photo not available

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GE Healthcare/RSNA
Educational Scholar Grant

Towards a Comprehensive and Accurate 3D Visual Simulation Tool for External Beam Radiation Therapy Planning

The 3D simulation educational project began in response to the increasing technical complexity of clinical setups in radiation oncology treatments. The simulation tool is a web-based application that can be accesses from any PC with internet connection. It provides a detailed 3D virtual reality display of the actual patient, the treatment room and radiation delivery systems. Through an intuitive and interactive graphical user interface, the user can manipulate the radiation delivery system motions and simulate treatment delivery of any treatment plan using actual patient surface data as if the user is inside the treatment room. This is a unique approach to external beam radiation therapy planning and is currently unavailable on any of the commercial treatment planning systems.

The simulation tool can be implemented in any radiation oncology clinic to improve the overall quality and efficiency of radiation therapy patient treatments by addressing the following needs: Patient Safety: The high-resolution 3D models of various radiation delivery systems in the simulation tool allows the radiation oncology treatment planner to examine relative positions of all device components and associated accessories relative to the patient with a few millimeters accuracy. Any unforeseen issues in patient setup and treatment can be resolved before the start of the actual treatment; Patient Education: The tool can be used to educate patients about their specific treatment procedure prior to them being on the treatment table, and therefore, helps to ease patient tension and fear of radiation devices; and Trainee's Education: Radiation oncology training programs can use the tool to train their staff and students and help them build confidence in radiation therapy equipment functionality without learning under the stress of the daily busy clinical hours.

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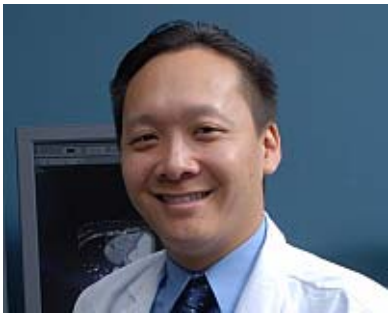
Philips Medical Systems/RSNA
Education Seed Grant

PHILIPS

Fellowship in Cardiovascular Imaging



The purpose of the Cardiovascular Imaging Fellowship is to receive training train that will enable the independent operation a non-invasive CVI service, including the expert acquisition, processing, and interpretation of CV computed tomography (CT) and magnetic resonance (MR) imaging. The specific goals of the fellowship are: To participate in the image acquisition and interpretation of CT and MR imaging of patients with a broad spectrum of cardiovascular diseases. To develop an in depth understanding of CT and MR technology as applied to imaging of the cardiovascular system. To become proficient in 3D and other post processing techniques, including the measurement of biometric data, and to understand their role in optimizing the interpretation and reporting of CVI studies. To participate in original scientific investigations with one third of the time devoted for academic purposes. Some of the projects include characterization of the pedal arterial anatomy with use of multi-detector CT, assessment of morphological changes in stent-graft and the abdominal aortic aneurysm wall following endovascular repair, and writing a book chapter that will review the latest advances in CT with respect to cardiac imaging. Finally, to gain experience in the teaching of cardiovascular imaging to radiology trainees.

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GE Healthcare/RSNA
Fellowship Training Grant

Clinical Fellowship in Cardiovascular Imaging: Cardiac MR and CT Emphasis

Abstract not available.

Photo not available

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RSNA
Fellowship Training Grant

Johns Hopkins University Cardiovascular Imaging Fellowship

Abstract not available.

Photo not available

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Fellowship Training Grant

Radiologic Informatics Fellowship Program at Brigham and Women's Hospital

Abstract not available.

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RSNA
Fellowship Training Grant

Beyond the Diffusion-Perfusion Mismatch: MR Imaging of Oxidative Metabolism in Acute Stroke

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Tyco Healthcare/Mallinckrodt/
RSNA
Research Scholar Grant

Intravenous thrombolysis is the only FDA-approved treatment for acute stroke. Only 1%-7% of patients are treated, largely because most present after the currently required limit of three hours after symptom onset. Extending the three-hour window could make this potentially lifesaving treatment available to far more patients. Recent studies have shown that thrombolysis indeed can be safe and effective up to nine hours after onset, if MRI is used to select appropriate candidates. In these studies, a mismatch between lesions in diffusion-weighted (DWI) and perfusion-weighted (PWI) images is presumed to reflect tissue that is threatened by ischemia but is still salvageable, and patients with a mismatch are deemed eligible for thrombolysis.

The concept of the diffusion-perfusion mismatch is useful, but based only indirectly on pathophysiology. Imaging-based measurements of oxygen metabolism, specifically oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen consumption (CMRO2), may be more accurate in delineating at-risk and irreversibly injured tissue. Novel MRI techniques are capable of measuring OEF and CMRO2 in only a few minutes.

In this research, OEF and CMRO2 measurements will be added to the MRI examinations of acute stroke patients. Patients will be a subset of those participating in an ongoing randomized, placebo-controlled study of normobaric supplemental oxygen therapy (NBO), which may extend the viability of at-risk brain tissue, presumably by supporting oxidative metabolism. MR images obtained at presentation and at multiple follow-up time points will be analyzed with two goals: First, to assess the effectiveness and limitations of NBO in preserving oxidative metabolism in threatened brain tissue. Second, to assess whether MR-based measurement of OEF and CMRO2 is more accurate than DWI/PWI in identifying and distinguishing irreversibly damaged and at-risk tissue, and therefore potentially more effective in selecting patients for thrombolysis and in extending the time window.

Assessment of Emerging Technology: Comparison of Breast Tomosynthesis and Digital Mammography in the Evaluation of Heterogeneously Dense and Extremely Dense Breasts

Photo not available

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AGFA/RSNA
Research Scholar Grant

Purpose: To assess the clinical utility of emerging digital tomosynthesis (DT) technology and improve breast cancer detection in women with heterogeneously dense (HD) and extremely dense (ED) breasts. To evaluate mass conspicuity on DT compared to DM in HD and ED breasts. To assess reader preference and workflow issues of DT compared to DM.

Design and Methods: 50 patients with HD and ED breasts and BI-RADS 4 or 5 interpretation will undergo two view DT and DM prior to core needle biopsy or excisional biopsy of mass, for histologic proof. Masses will be detected by imaging (ultrasound or mammogram) or palpation. For patients with more than one mass per breast, each mass will be separately analyzed.
50 randomized cases, divided into 2 subsets, will be independently interpreted by 3 MQSA accredited radiologists. Readers will record mass size, location, conspicuity and likelihood of malignancy. After four week delay, readers will interpret corresponding DM or DT image sets in random order. After another four week delay, readers will evaluate DT and DM in side by side comparison and rank preference for DT or DM. Time for interpretation of each case and standard time motion analyses will be recorded. Statistical significance testing for mass conspicuity, reader preference and interpretation time will be performed. Diagnostic confidence of malignancy will be evaluated with ROC analysis.

Potential Significance of this work in Radiological Sciences: DT is a new DM method in which a series of low dose x-ray images is acquired over a range of angles relative to an imaged object. It can be used to reconstruct the 3D structure of the entire breast. If improved mass conspicuity in HD and ED breasts on DT is proven, this innovative technology could significantly impact the detection and characterization of breast masses in women with dense breasts.

Correlation Between Perfusion Metrics Measured with Perfusion-Weighted MRI and Tissue Oxygenation Measured with BOLD MRI with VEGF Expression and Microvessel Density in Hepatocellular Carcinoma

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Siemens Medical Solutions/RSNA
Research Scholar Grant

Hepatocellular carcinoma (HCC) is a typical angiogenic tumor, with a recent significant increase in incidence in the US. Treatment of advanced HCC is still limited, and several systemic therapies are being assessed, including anti-VEGF (vascular endothelial growth factor) drugs. The objective of this proposal is to develop MRI methods for quantification of angiogenesis and oxygenation and to correlate the MR findings with histologic quantification of angiogenesis in HCC. We will use contrast-enhanced MRI to quantify tumor perfusion parameters using a first pass pharmacokinetic model and blood oxygenation level-dependent (BOLD) MRI to measure oxygen consumption in cirrhotic patients with HCC before they undergo cadaveric or living-related liver transplantation. Quantitative perfusion parameters (blood volume and Ktrans) and BOLD R2* (apparent transverse relaxation rate) values will be calculated in HCC lesions and surrounding non tumorous liver using regions of interest measuring signal intensity over time and a dual input single compartmental model integrating Gadolinium concentrations. Quantitative MR parameters will be correlated with VEGF expression and microvessel density in HCCs and surrounding liver parenchyma obtained on liver explants.

With this study, we are aiming to validate functional MRI as a non invasive tool for quantification of HCC angiogenesis. MRI could be used for predicting and monitoring response to targeted anti-VEGF drugs currently investigated in HCC and to transarterial chemoembolization. In addition, MRI could have a prognostic value by predicting the degree of HCC angiogenesis and the response to antiangiogenic drugs and chemoembolization, and could have a prognostic value. This would benefit tens of thousands of Americans over the next decade.

Advanced MR Imaging after External Beam Radiation Therapy of Prostate Cancer

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GE Healthcare/RSNA
Research Scholar Grant

Biochemical failure (defined as PSA nadir value plus 2 ng/dl) following external beam radiation therapy (EBRT) of prostate cancer is a clinical dilemma for which adequate management in not well established. It may represent isolated local recurrence, systemic recurrence, both, or neither. The standard method of evaluating local control is transrectal ultrasound-guided (TRUS-guided) biopsy of the prostate, which is invasive and has limited accuracy after radiation treatment. Our goal is to determine if 3-Tesla spectroscopic (MRSI) and diffusion tensor (DTI-MRI) MR imaging will non-invasively identify the patients who can be cured by salvage therapy, while potentially identifying other patients who require systemic treatment or who have adequate disease control and do not need additional therapy.

Specific aims:
1) determine the accuracy of 3-Tesla endorectal MRI in detecting locally recurrent prostate cancer in patients with biochemical failure after EBRT by correlating areas of low signal intensity on T2-weighted images, spectroscopic voxels showing a choline-to-creatine ratio greater than 1.5 on MRSI, and areas of decreased water diffusion on DTI-MRI with the presence or absence of cancer at post-radiation transrectal ultrasound-guided biopsy;

2) determine the prognostic value of post-treatment 3-T endorectal MRI in men with prostate cancer treated with EBRT by correlating the volume of reduced water diffusion and the number of spectroscopic voxels showing a choline-to-creatine ratio greater than 1.5, as well as maximum and mean metabolite levels, with disease-free survival (defined as absence of local recurrence and/or metastases).

This will be a prospective cross-sectional study followed by a cohort of 36 consecutive adult patients referred for evaluation and management of biochemical failure after EBRT for prostate cancer. Prostate biopsy histopathology will be used as standard of reference in determining the presence or absence of local prostate cancer recurrence. Systemic disease will be considered present if periodical and systematic medical chart review produces evidence of such through pathology reports, imaging studies, and/or clinical notes.

We expect to promote MRSI and DTI-MRI as prognostic tools to be used in the post-radiation prostate cancer patient population and to develop a new line of investigation in multiparametric MR imaging of prostate cancer patients.

Assessing Global Gene Expression Programs of Cancer Using Non-Invasive Imaging

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Bracco Diagnostics/RSNA
Research Scholar Grant

Abstract not available.

Monitoring Chemotherapy Response in Metastatic Liver Lesions with Quantitative ^{1}H MRS

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Carestream Health/RSNA
Research Scholar Grant

Metastatic liver tumors are commonly found in patients with advanced cancers. There is a great need in oncology for non-invasive evaluation of these lesions to assess therapeutic response and to help develop new therapies. Magnetic resonance imaging (MRI) and spectroscopy (MRS) can meet this need. Contrast-enhanced MRI is regularly used for measuring tumor size and vascularity in lesions of the liver and other organs. More recently, MR spectroscopy has been used to evaluate tumor response in the brain, breast and prostate. The feasibility of single-voxel 1H spectroscopy in liver tumors has been demonstrated, but rigorous quantitative methods, required for longitudinal studies, have yet to be established. The goal of this proposal is to develop new methods for performing quantitative MRS of liver lesions and to determine if such measurements can be used to predict the response of metastatic lesions to chemotherapy.

The proposed project consists of two phases. The initial technical development phase, several strategies for for managing respiratory motion (respiratory triggering vs. breath-holding) and performing spectroscopic quantification (internal vs. external referencing) will be implemented and compared. These methods will then be evaluated with a small reproducibility study performed with normal subjects. The second phase will be a clinical pilot study, in which ten patients with metastatic liver lesions will be followed through their chemotherapy regimens with serial MRI/MRS scans. The success of this project will provide a new tool that clinicians can use to evaluate therapy response and researchers can use to help test novel therapies. The methods will also be applicable for other clinical liver applications such as diagnosis and staging, and can be developed further for use in other abdominal cancers that cannot currently be evaluated with MRS.

Quantitative Proton MR Spectroscopy of Perinatal White Matter Injury: Correlation with Neurodevelopmental Outcome, Axonal Injury and Cytokine Inflammation

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GE Healthcare/RSNA
Research Scholar Grant

Recent studies have demonstrated that the incidence of the diffuse non-cystic form of perinatal white matter injury in the neonate has increased resulting in more cognitive and behavioral deficits compared to the classic forms of cerebral palsy. The pathogenesis of perinatal white matter injury is currently thought to be related to interactions between maternal/fetal infection, cytokines and hypoxia-ischemia which results in both the generation of reactive oxygen specific agents (oxidative stress), apoptotic oligodendrocyte cell death, and diffuse axonal injury. However, in vivo data interrelating these mechanisms is lacking. In this project, we will use advanced quantitative proton MRS as a potential way to provide an in vivo link between perinatal white matter injury, poor neurodevelopmental outcome, axonal injury and cytokine inflammation. Specifically, we will be focusing on NAA (N-acetyl-aspartate) and myo-inositol (mI).

To understand the importance of these MRS findings and how they relate to axonal injury and cytokine inflammation, we propose (1) To correlate neonatal NAA levels with both neurodevelopmental and neuroimaging outcome. For the neurodevelopmental outcome, the patients will be evaluated at 2 years of age. (2) To correlate myo-inositol levels with plasma and CSF cytokine levels in the neonatal period; (3) we will correlate in vitro both NAA levels with immunocytochemical markers of axonal injury and myo-inositol levels with cytokine markers in the human white matter.

This project is novel because it will focus on quantitative short echo MRS which have not been specifically used to evaluate perinatal white matter injury in relation to neurodevelopmental outcome, in vivo cytokine levels, and in vitro markers of axonal injury and cytokine inflammation. We hope to not only improve our imaging capability to diagnose perinatal white matter injury, but also to improve our understanding of both mechanistic and prognostic factors which play a role in the pathogenesis of perinatal white matter injury.

Quantification of Hepatic Steatosis with Magnetic Resonance Imaging

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AGFA/RSNA
Research Scholar Grant

The goal of this proposal is to develop new MRI technologies that accurately and confidently quantify fatty infiltration of the liver (hepatic steatosis), within a short breath-hold. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, afflicting 20% of people in the United States. NAFLD is closely linked with insulin resistance and its incidence is paralleling the current epidemics of obesity and typeII diabetes. The earliest manifestation and hallmark of NAFLD is steatosis. Accurate and early diagnosis relies on liver biopsy, which is expensive, risky, and provides a subjective measure of steatosis with high sampling variability. Clinical trials for new therapies for NAFLD are hindered by the lack of an accurate non-invasive measure of steatosis. We seek to address this critical unmet need by quantifying steatosis using MRI. Our approach is based on a water-fat separation method developed by our group, known as IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation), that provides robust separation of water and fat, even in challenging magnetic environments such as the abdomen. Combined with3D spoiled gradient echo imaging, we will develop a quantitative method that measures true fat fraction, corrected for relaxation parameters (T1, T2*) and noise bias. We will validate this method in an animal model of steatosis, the obese Zucker rat, and reduce scan time to reasonable breath-hold times using multi-echo and parallel imaging techniques. Finally, we will leverage support from the RSNA to obtain preliminary data inpatients with NAFLD to draft and submit an NIH grant proposing a larger clinical study of these methods. Successful completion of this proposal will significantly impact early diagnosis and management of NAFLD, as well as drug discovery, by providing an accurate non-invasive measure of steatos is a capability previously unavailable.

Contribution of Visual Attention and Imagery to Nonlinearity of fMRI Response to Paired Stimuli

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RSNA
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Functional magnetic resonance imaging (fMRI) has traditionally been limited by the temporal resolution of the neurovascular responses to brain activation it can measure. Since the BOLD signal underlying the fMRI response represents changes in perfusion related to neuronal activity, which occur on a timescale of seconds, fMRI has been of limited utility for investigating neuronal events that occur on much faster timescales.

Newer techniques in fMRI research, including paired pulse protocols and fMRI adaptation, circumvent this problem by measuring responses to the output of controlled sequences of neural events or summation of responses in different neuronal populations. A shared assumption of these techniques is that fMRI responses to multiple stimuli represent a summation of responses to individual events.

However, nonlinearity of temporal summation of the fMRI response to sequential visual stimuli has been demonstrated, rendering interpretation of studies employing these techniques problematic. This nonlinearity has been attributed to neuronal adaptation and nonlinearity of neurovascular coupling.

The contribution of visual attention and imagery to temporal nonlinearities of fMRI responses has not yet been studied systematically, and would affect interpretation of fMRI paradigms using multiple visual stimuli. This study will assess the contribution of visual attention and imagery to temporal nonlinearity of fMRI by using event-related designs with millisecond stimuli at which neuronal adaptation is not operative. By modulating visual attention to stimuli and by controlling for visual imagery, it is theorized that a contribution to this nonlinearity, independent from neuronal adaptation and that of neurovascular coupling, can be quantified.

Evaluating the contribution of attention to nonlinearity of paired or repeated stimuli could affect interpretation of a broad class of fMRI experiments, and would help characterize the neurophysiology of attention in distributed neural networks.

Urinary Oxygen Tension Measurement in Humans Using MR Imaging

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Philips Medical Systems/RSNA
Research Fellow Grant

Hypoxia of the renal medulla is a key factor implicated in many forms of kidney disease, including acute tubular necrosis, diabetic nephropathy, contrast or drug-induced nephropathy, and papillary necrosis. Our broad, long-term goal is to develop an imaging tool to identify patients with pre-clinical renal dysfunction related to renal medullary hypoxia and thereby allow for early diagnosis and patient-specific treatment monitoring. Specifically, we propose to study a novel MR imaging method that exploits the known high correlation between renal pelvis urinary oxygen tension and renal medullary oxygen tension. The urinary oxygen tension in the renal pelvis equilibrates with that of the adjacent medulla, and reflects medullary perfusion and metabolic function. At our institution, we have recently developed a modified single-shot fast spin echo pulse sequence that quantifies oxygen tension in fluids based on its longitudinal relaxivity (R1=1/T1). This technique has been validated in phantom models and in vivo for the assessment of cerebral spinal fluid oxygen tension. Our current proposal is to validate the use of this method for measuring urinary oxygen tension in humans.

Specific Aims:

1. To validate the ability of MR imaging to quantify urinary oxygen tension in vivo. This aim will test the Hypothesis that MR imaging can reliably measure urinary oxygen tension in volunteers.
2. To quantify the effect of supplemental inhaled oxygen and diuretic (furosemide) on urinary oxygen tension of healthy subjects. This aim will test the Hypothesis that MR imaging can monitor temporal changes in urinary oxygen tension.

This study will provide preliminary data and experience for the development of a novel approach to assess urinary oxygen tension, and thereby renal medullary oxygenation. This tool may be useful to assess the association between renal medullary hypoxia and common renal diseases, therefore facilitating diagnosis and rational intervention.

Computer-Assisted Risk Estimation (CARe) from Breast Tomosynthesis Images

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Siemens Medical Solutions/RSNA
Research Fellow Grant

The current gold standards for breast cancer risk estimation, the Gail and Claus models, have certain limitations in clinical practice. They are based primarily on non-modifiable risk factors; for this reason they lack the flexibility to adjust risk levels after risk reduction interventions. In addition, being designed from population statistics, they are not accurate in predicting cancer incidence for individual women. On the other hand, evidence suggests that breast parenchymal patterns are related to a woman's cancer risk; being indicative of changes in modifiable risk factors such as hormonal effects, diet, and body mass index. Recent studies demonstrated a potential to improve the Gail model by including image-based breast density descriptors. However, due to tissue superimposition in projection mammography, accurate estimation of parenchymal properties is not possible. Tomosynthesis is a novel x-ray imaging modality in which 3D images of the breast are reconstructed from a limited number of projection images; the 3D nature of tomosynthesis allows for more accurate estimation of parenchymal properties.

Our long-term hypothesis is that tomosynthesis risk biomarkers combined with demographic and clinical information can outperform the Gail and Claus models. The proposed Computer-Assisted Risk Estimation (CARe) study aims to: (i) determine the value of parenchymal texture descriptors as a surrogate of cancer risk, (ii) develop a better model for breast cancer risk estimation using tomosynthesis texture and demographic data, and (iii) investigate the potential of tomosynthesis to provide superior risk assessment compared to mammography.

The improved performance and low cost of breast tomosynthesis will likely fuel the rapid and broad dissemination of tomosynthesis as breast cancer screening modality. The ability to improve breast cancer risk estimation based on tomosynthesis parenchymal analysis could provide a biomarker for customizing detection, tailoring individual treatment and forming preventive strategies, especially for women associated with a higher risk.

Combination Immunotherapies for Pediatric Glioma

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Toshiba Medical Systems/RSNA
Research Resident Grant

The main hypothesis of this proposal is that a combination of immunotherapies with low dose ionizing radiation will overcome the existing barriers to anti-tumor immunity, resulting in tumor response, rejection by the host immunity and potential cure of pediatric gliomas. Presently there is no known cure for pediatric brainstem gliomas. Even low-grade tumors have a poor prognosis with survival less than 18 months from diagnosis due to the growth properties of these tumors that are highly invasive. We have developed a mouse model where the animal develops a brain tumor (called GL261 glioma model) that behaves like their human counterpart. Similar to human brain tumors, the mouse brain tumors are not rejected by the host immunity. We found that invading glioma cells defeat the host immune surveillance system, at least in part, by down-regulating expression of specific molecules (called MHC) to escape recognition by the host. Irradiation of established GL261 tumors in the brain can recover the expression of these important MHC molecules on the glioma cells. Vaccination of the animals with modified autologous tumor cells when combined with radiation of large intracranial well-established, invasive brain tumors, produced “cures” in up to 60% of the animals (Newcomb et al, 2006). Radiation alone had only a minor temporary effect, similar to the disappointing results encountered clinically. These results indicate that combining radiation with immunotherapy has a great therapeutic potential and warrant further studies. We propose to use the GL261 glioma model to test a novel immunotherapy approach based on the administration of an antibody directed to the co-stimulatory molecule 4-1BB/CD137 (BMS-469492, obtained from Bristol-Myers Squibb). Co-stimulation via this pathway has been shown to increase and sustain the anti-tumor immune response in several animal models. Specifically, we will 1) determine the therapeutic effects (survival, cure) of the combination of BMS-469492 with whole brain radiation therapy (WBRT) and vaccination with GM-CSF-producing autologous tumor cells (mGVAX) and 2) determine the cell subset(s) mediating the therapeutic immune response by in vivo depletion experiments.

Since the BMS-469492 antibody is already in clinical studies, this promising approach could be rapidly translated into the clinic and provide a new treatment option for pediatric brain tumor patients. Because of the limited amount of radiation used (400 cGy x 2), a clinical trial would enable previously irradiated patients to be eligible at the time of tumor progression, the typical course for glioma patients, to a future Phase I/II trial of the combination therapy.

Radiosensitization of Gliomas Through Targeting of the N-linked Glycosylation Pathway

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Research Resident Grant

Glioblastoma Multiforme is an aggressive primary brain tumor that is treated with surgery, radiation, and chemotherapy, but ultimately recurs locally and has a median survival of less than 15 months. Novel molecular therapeutics are currently being developed to target cellular receptor tyrosine kinases (RTKs) which regulate tumor cell growth, proliferation, and resistance to ionizing radiation. Examples of these receptors include the ErbB family of RTKs, the IGF-1R, and the VEGF family of RTKs. Specific disruption of each RTK has demonstrated anti-tumor effects in pre-clinical studies for some tumor cell lines, however, the absence of general clinical effectiveness shows that the benefit of these agents is restricted to as of yet unidentified subgroups of patients. Previous in vitro work investigating ErbB RTK (EGFR, ErbB2, ErbB3, and ErbB4) network signaling has demonstrated parallel and compensatory cellular signaling produced by this receptor family that results in cytoprotective responses and resistance to anti-tumor therapies. Evidence from gene therapeutic approaches demonstrates that disruption of multiple RTKs reduces tumor cell resistance, enhances cellular radiosensitivity, and produces a greater cell kill. We have recently demonstrated that blockade of N-linked glycosylation is a feasible strategy to disrupt RTK expression and activity across receptor family types, with the goal of enhancing tumor cell death. In this project we propose a systematic investigation of an alternative method of blocking RTK signaling in malignant glioma cells. We demonstrate that blockade of N-linked glycosylation, a pathway involved in RTK expression, reduces RTK protein levels and disrupts RTK activity across multiple receptor family types. Furthermore we show that the inhibition of N-linked glycosylation radiosensitizes glioma cells and that this strategy has the potential for clinical utility. This research will contribute to a better understanding of the pathways and mechanism of receptor glycoslation, the role of RTKs in adaptive and protective responses to radiation, and have the potential to identify novel therapeutic agents for the treatment of malignancy.

Combining Total Body Irradiation with Immunotherapy to Generate Therapeutic Anti-tumor Immune Responses

The induction of effective anti-tumor immune responses will enhance existing conventional cancer therapies and may provide hope for durable responses in patients with aggressive malignancy. Others and we have demonstrated significant enhancement associated with adoptive transfer of tumor specific T cells with the use of lymphodepletion prior to transfer of T cells. Indeed, the use of chemotherapeutic or radiation induced lymphodepletion prior to adoptive transfer has demonstrated promising results in early clinical trials. The aim of this work is to define some of the mechanisms whereby Total Body Irradiation enhances the immunogenicity associated with T cell adoptive transfer through characterization of the activation of the innate immune system. Specifically we are looking at how circulating endotoxins following Total Body Irradiation, a phenomenon well described in the transplant literature, enhances adoptive transfer immunity. By gaining a deeper understanding of the immunogenicity associated with Total Body Irradiation lymphodepletion we hope to enhance clinical immunotherapy approaches for patients with refractory malignant disease.

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Investigating the Mechanism of Cancer Stem Cell Radioresistance

Tumors are composed of heterogeneous populations of cancer cells that differ in their capacity to proliferate, metastasize, and reconstitute tumors after in vivo transplantation. While these observations have generally been attributed to stochastic effects of genomic instability, recent work indicates that at least a subset of leukemias and solid malignancies contain populations of cancer stem cells (CSCs) that can give rise to more CSCs and to non-tumorigenic cancer cells (NTCs) with limited proliferative potential. One important implication of the cancer stem cell hypothesis is that CSCs may be more resistant to cytotoxic therapies than NTCs. My research plan is based on the hypothesis that CSCs of carcinomas are radioresistant compared to NTCs due to a combination of radiobiologic parameters and differences in genomic gene expression programs.

In preliminary experiments using murine MMTV-Wnt-1 breast tumors (for which we have previously identified the CSC-enriched sub-population), I have observed accumulation of CSCs after in vivo irradiation. In this work, I will confirm and extend these results and will then test the generalizability and clinical relevance of CSC radioresistance by performing similar experiments using human carcinoma xenograft models. Next, I will investigate the mechanism(s) of CSC radioresistance by examining radiobiologic parameters such as hypoxia, cell cycle distribution, apoptosis, and DNA repair. To elucidate gene expression responses of CSCs and NTCs, I will also perform microarray gene expression profiling of the two cell types before and after exposure to ionizing radiation.

This work is of significant potential importance to radiation oncology, since elimination of CSCs will likely prove to be the critical factor in achieving cure for many malignancies. Confirmation of carcinoma CSC radioresistance and identification of its mechanism(s) would have important implications for how therapeutic efficacy should be assessed and how the therapeutic ratio of ionizing radiation could be enhanced.

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Radiation-Induced Immunotherapy: Characterization of The Systemic, Anti-Tumor Immune Response Generated Following Coadministration of an Immunoadjuvant, CpG-Oligodeoxynucleotides, with Radiation Therapy

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Cesare Gianturco/
RSNA
Research Resident Grant

Researchers in cancer immunotherapy espouse that advances in cancer treatment are achievable through the activation of an anti-tumor, host immune response, which could eliminate cancer cells through the recognition of tumor-specific antigens. Despite the theoretical appeal of cancer immunotherapy, successful implementation of clinically effective tumor-specific immune responses has not been achieved on a broad scale. Recently, interest in the utilization of radiation therapy for the purposes of augmenting anti-tumor immunotherapy has been stimulated by the development of more potent and less toxic immunomodulating agents. CpG-oligodeoxynucleotides (CpG-ODN) are synthetic molecules that mimic immunostimulatory structures present in bacterial unmethylated CpG motifs, and are capable of inducing immune activation. The aim of this proposal is to determine whether treatment of the primary tumor site with a combination of localized irradiation and the immunoadjuvant CpG-ODN induces a systemic, anti-tumor immune response, capable of eliminating metastatic disease. Additionally, attempts will be made to identify the immune cells involved in this anti-tumor response.

It is hypothesized that treatment of the primary tumor site with the combination of CpG-ODN and radiation therapy may activate a systemic anti-tumor immune response, capable of eliminating metastatic disease beyond the radiation treatment field. If obtainable, this anti-tumor immune response could function systemically to eliminate tumor metastasis throughout the body, providing a treatment option for patients who present with detectable metastatic disease and for those at risk of harboring occult metastatic disease. In this manner, the combination of CpG-ODN and radiation therapy may augment the local control observed with radiation therapy and additionally provide treatment for both detectable and clinically occult metastatic disease.

Computational Fluid Dynamic Modeling of Upstream Flow Modifiers on Coiled Intracranial Aneurysm Recurrence

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RSNA
Research Resident Grant

The use of detachable coils for the endovascular treatment of intracranial aneurysms has improved disability-free survival compared to surgical aneurysm clipping. However, aneurysms recur more frequently after coiling. Although the exact mechanism for this is unknown, several theories have implicated local hemodynamics as a contributing factor.

The hypotheses of this study are (1) that differences exist between the local hemodynamics of stable versus recurrent previously coiled aneurysms and (2) that altering upstream arterial geometries can induce the favorable hemodynamics associated with stable aneurysms.

These hypotheses will be investigated by simulating the hemodynamics in patients with stable and recurrent intracranial aneurysms using patient specific anatomical and physiological parameters. The local hemodynamics (blood flow patterns, shear stress etc.) will be determined using computational fluid dynamics (CFD) simulations based on data from three dimensional rotational angiography and phase contrast magnetic resonance imaging. The second part of this study will also use CFD to investigate if alterations in arterial geometries proximal to a coiled aneurysm can favorably affect local hemodynamics.

The results of this research may be useful clinically in patient selection for endovascular coiling. This work may also be helpful in determining which patients are more likely to have recurrent aneurysms. Patients found to have favorable local hemodynamics may require less frequent surveillance angiograms while patients at increased risk could be followed more closely. If alterations in upstream geometries are found to be associated with a decreased incidence of aneurysm recurrence, methods to favorably alter arterial configurations at the time of aneurysm coiling could be developed.

Characterization of HER4, a Multifunctional Signaling Protein Involved in Breast Cancer Radiation Response

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Research Resident Grant

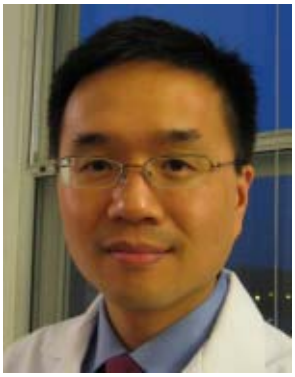
PHILIPS

In recent years both traditional cytotoxic chemotherapeutics and molecularly targeted agents have been shown to synergize with radiation to produce improved cellular kill. Use of these agents has the potential to improve cancer control and/or decreased the dose of radiation required to achieve similar results. Understanding the cellular signaling pathways underlying this radiosensitization effect may allow for the a priori identification of a specific drug for concurrent chemoradiation in individual patients.

Human epidermal growth-factor receptors (HERs) have become important radiosensitizing targets. HER1-4 comprise a subclass of the receptor tyrosine kinase-family involved in growth and development. HER4, a multifunctional signaling protein, interacts with other proteins via an array of structural elements. However, how each element contributes to the ability of activated HER4 to sensitize cells to radiation remains unclear. Furthermore, understanding how HER4 interacts with its signaling partners may illuminate the finding that HER4 expression in human cancer carries both positive (inducing differentiation, apoptosis, and cell-cycle arrest) and negative (promoting growth, transformation, and lymph-node spread) prognostic information.

In preliminary work, we have found that the subcellular localization of HER4 changes following delivery of a single dose of radiation and that HER4 induces radiosensitization in breast cancer cell lines. These findings have led to the hypothesis that HER4 is involved in the response of breast cancer cells to radiation. The work funded by this award aims to define the role of HER4 signaling pathways in radiosensitization and understand how changes in subcellular localization affect HER4 radiosensitization. These studies may identify downstream signaling partners which can later be used as correlative markers in clinical trials of radiation and may impact clinical care by allowing us to understand how different tumors respond to radiation. One can imagine being able to predict not only which tumors necessitate higher doses of radiation, but also which tumors will respond to lower doses. Further investigation of these questions is outside the scope of this proposal, but will form the basis for future studies.

Noninvasive Characterization of NFkB Activation in Non-Alcoholic Fatty Liver Disease



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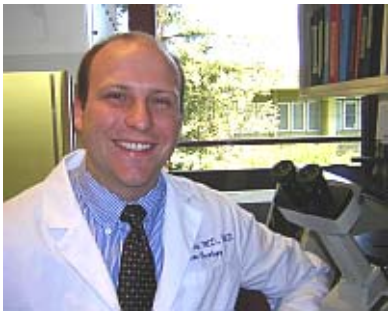
TOSHIBA

Non-alcoholic fatty liver disease (NAFLD) is closely associated with obesity and diabetes and may affect up to 24% of the general population. Current imaging modalities can detect steatosis, but only liver biopsy can distinguish fatty liver from its inflammatory counterpart, non-alcoholic steatohepatitis (NASH). A major barrier to developing early diagnostic tests for NAFLD is a limited understanding of its molecular pathogenesis. The overall goal of this research project is to characterize the role of the transcription factor NFkB in NAFLD.

Specifically, we will use an NFkB-dependent luciferase reporter gene construct as a readout of NFkB activity in both cell culture and dietary mouse models. Experiments will also test thiazolidinediones (TZD), a class of commonly used oral anti-diabetic agents which has shown promise as treatments for NAFLD, for possible effects on NFkB. Finally, the cell culture model will be used in an automated screen of libraries of small interfering RNA (siRNA) in order to identify human kinases and phosphatases necessary for NFkB activation. By capitalizing on recently developed bioluminescence imaging technologies, this work aims to lay the groundwork for future development of novel imaging-based diagnostic tests and disease-modifying therapies for NAFLD.

The Role of Hypoxia During the Induction of Immune Responses In Vitro and In Vivo



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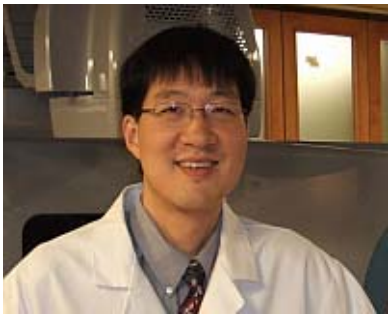
Hypoxia selects for more malignant cancer phenotypes and is associated with worse clinical prognosis. Hypoxia stimulates cytokine secretion in dendritic cells (DC) and, at the same time, may inhibit DC migration into draining lymph nodes (DLN). However, it remains unclear whether the hypoxic tumor environment influences the ability of DC to cross present antigen in order to stimulate an immune response. During cross presentation, DC endocytose antigen which is then processed through the ER associated degradation (ERAD) pathway. Recent work has demonstrated that hypoxic stress upregulates the ERAD pathway likely via the unfolded protein response (UPR). Therefore, hypoxia may affect the cross presentation of antigen via the ERAD pathway.

Here, I hypothesize that hypoxia affects the ability of DC to cross present antigen and, subsequently, to induce an immune response. In Aim 1, I will determine if DC can cross present a model ovalbumin (OVA) antigen under hypoxic stress. Furthermore, I will determine if hypoxia affects cross presentation via the ERAD pathway. Finally, I will determine how hypoxia affects the other steps involved in cross presentation: endocytosis of antigen, TAP mediated transport of peptides into the ER and presentation of these peptides by MHC. In Aim 2, I will determine if hypoxia affects the generation of an immune response in vivo by immunizing mice with DC cultured under hypoxic conditions. If DC exposed to hypoxia can induce an immune response, I will determine if DC promote a CD8+ T cell response.

By understanding how hypoxia affects the ability of DC to stimulate an immune response, we will learn how the tumor microenvironment may protect cells from immune recognition. Furthermore, by discovering which areas of tumors are poorly immunogenic, we can develop immunotherapies that target the antigens expressed in these “ignored” tumor regions. Such strategies may better target the radioresistent hypoxic tumor cells.

Cost-Effectiveness Analyses of Radiotherapy for Gastrointestinal Malignancies



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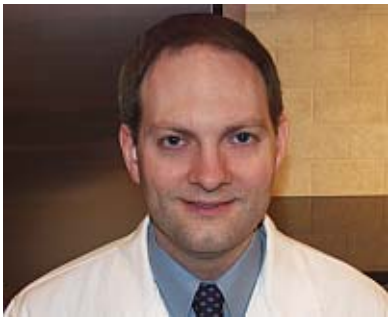
The goal of this research study is to analyze the economic impact of treatment for gastrointestinal malignancies where radiotherapy is used either alone or in combination with surgery or chemotherapy. The focus will be on GI disease sites where major Phase III randomized controlled trials have shown a benefit with the use of radiotherapy in conjunction with other treatment modalities. Cost data will be obtained from Medicare fee schedules, the SEER-Medicare database, and from the published literature. Costs will be reported in US dollars from the perspective of the third-party healthcare payer. Models will be built that include all direct costs of care from the time of diagnosis until death, including the costs of initial work-up, treatment, and managing toxicities. The time horizon will vary depending upon the available clinical data. In cases where clinical outcome data are only available for a limited follow up time, Markov processes will be constructed to model annual disease progression to extrapolate outcomes at extended follow-up times. Clinical outcome data will be obtained from published literature. The reference strategy will be the previous standard of care before the current treatment study was published. The primary outcome measure will be the Incremental Cost-Effectiveness Ratio (ICER). One-way, multi-way, and probabilistic sensitivity analyses will be performed to evaluate the effect of uncertainty on the outcome. Final results will be compared with generally accepted cost-effective thresholds, and the overall financial impact to the US healthcare system will be estimated. This study will result in a better understanding of the economic impact of the role of radiotherapy in the treatment of the major GI malignancies, and can serve as a reference against which future cancer therapies can be compared.

Percutaneous Femoroplasty for Preventing Hip Fracture: Procedural Development and Finite Element Analysis



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Osteoporosis affects millions of individuals worldwide, and has no cure. Hip fracture is a devastating complication of osteoporosis that is associated with high morbidity and mortality. Relatively costly medical therapies to prevent osteoporotic fracture have variable efficacy, and surgical interventions post fracture can result in significant peri-operative complications and difficult prolonged recovery periods. Estimated Medicare costs for hip fracture approaches $3 billion annually.

The present proposal aims to develop and investigate a new relatively inexpensive minimally invasive image guided procedure for preventing hip fractures due to falls. We hypothesize that augmentation of osteoporotic femoral necks by controlled economic delivery of polymethylmethacrylate bone-cement, termed femoroplasty, will be mechanically effective in reducing stresses in the femoral neck under fall conditions.

To test this hypothesis, percutaneous femoroplasty will be performed on osteoporotic cadaveric femurs. Biomechanical strain gage measurement of femoroplasty treated and matched non-treated controls will be conducted in a configuration simulating fall on the greater trochanter. Finite element (FE) models will then be constructed from CT scans obtained before and after femoroplasty that permit differentiation of cortical and trabecular bone in accordance with variations of the bone mineral density. FE analysis of these models will be performed using computer program solvers to further characterize the biomechanical performance of femurs with and without femoroplasty.

The significance of our project is that it aims to advance the possibility of introducing a practical and inexpensive minimally invasive prophylactic procedure for prevention of hip-fracture, using currently available technology. The procedural steps involved rely completely on currently available skills and devices, while the target population is manifestly underserved for want of effective interventions. Many who are at risk for the devastating consequences of hip fracture would benefit from an effective, minimally invasive, and inexpensive treatment that addresses this important problem.

Role of Lithium and Specific GSK-3ß Inhibitors in Neural Protection During Cranial Irradiation

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Cranial irradiation in the treatment of adult and pediatric cancers commonly causes neurological deficits such as decreased cognition and memory. Intellectual impairment, memory loss, and dementia have been reported in adults after exposure of CNS tissue to radiation during cancer treatment. Patients receiving radiotherapy also had a significant reduction in performance IQ. These effects have been linked to increased apoptosis of neuronal cells. Lithium has been shown to prevent brain injury following stroke and to reduce the incidence of Alzheimer's disease through modulation of the apoptosis. In addition, lithium significantly reduces the cytotoxic effects of radiation on neuronal cells and improves learning and memory in mice treated with whole brain irradiation. In this proposal, we aim to understand the mechanisms by which lithium exerts its neuroprotective effects against cranial irradiation. We believe this effect occurs through modulation of neuronal apoptosis, in particular through the GSK3□ enzymatic pathway. We also propose that specific inhibition of the GSK3□ pathway will result in decreased radiation-induced neuronal apoptosis. Elucidating such pathways may provide the impetus for the development of novel therapeutic strategies for neural protection in whole brain radiation. This will allow for the development of neuroprotective drugs for use during whole brain radiation.

Diagnosis and Staging of Liver Fibrosis by Quantitative Texture Analysis of Contrast-Enhanced Magnetic Resonance Images

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Hepatitiis C virus (HCV) infection is a major cause of liver-related death. Appropriate management of HCV-infected patients requires accurate assessment of liver fibrosis. Because biopsy, the current gold standard for diagnosis and staging of liver fibrosis, has risks and limitations, there is a need for noninvasive alternatives. Combined contrast-enhanced magnetic resonance (MR) imaging with superparamagnetic iron oxides (SPIO) and low-molecular-weight gadolinium (Gd) chelates has been shown to visualize liver fibrosis as high-signal reticulations against low-signal liver background. These reticulations may be assessed qualitatively to estimate fibrosis severity, but such methods suffer from observer-dependency and other limitations of human vision. These reticulations can also be assessed using computational methods that quantify image texture. Quantitative texture analysis would permit objective evaluation of liver fibrosis and may improve diagnostic and staging accuracy. Such a method would represent an important clinical advance for early diagnosis of liver fibrosis and longitudinal surveillance. It may also represent a new indication for MR imaging and provide a new role for radiologists in the management of chronic liver disease.

In this prospective cross-sectional clinical study, we will develop a quantitative texture-analysis method to objectively evaluate liver fibrosis in HCV-infected patients. Adult patients with documented HCV infection and a recent liver biopsy will be imaged with MRI at 1.5T. Single-contrast (SPIO) and combined-contrast (SPIO+Gd) images will be obtained using T2*-weighted spoiled gradient recalled echo and T2-weighted echo train spin echo sequences. The reticular patterns of fibrosis will be quantified by texture features derived from (1) pixel intensity histograms, (2) co-occurrence matrices, (3) sum-of-Gaussian models, (4) spatial frequency-scale analyses, and (5) geometric analyses. A multiple regression technique will be used to build a fibrosis prediction model based on the most discriminatory MR texture features. The accuracy of the prediction model will be assessed by goodness-of-fit, correlation and correspondence analyses, and sensitivity-specificity analysis. The method's diagnostic and staging accuracy will be tested and validated against histological fibrosis stages from liver biopsies.

Determining the Relationship Between IL-1beta, TNF-alpha, and IL-6 Response to External Beam Radiation Therapy and Treatment Related Fatigue in Patients with Prostate Cancer

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Research Resident Grant

Cancer patients undergoing chemotherapy, radiation, or both experience significant fatigue during treatment that begins during treatment and declines following treatment. Cancer treatment related fatigue (CTRF) has a profound negative impact on physical functioning, quality of life (QOL) and the patient's ability to receive the prescribed treatment. For patients undergoing potentially curative radiotherapy, such unscheduled breaks can also contribute to tumor re-growth. To date the molecular mechanisms underlying the initiation and perpetuation of CTRF are not well established. We hypothesize that treatment induced inflammatory cytokine production plays an important etiological role in CTRF. Several lines of evidence support our hypothesis. First, in addition to fatigue, cancer patients undergoing treatment often experience several other symptoms including anorexia, cachexia, pain, sleep disturbance, depression, and anemia, which can impact the subjective sensation of fatigue. Considerable evidence generated in animal models and in clinical populations implicates the inflammatory cytokines IL-1, TNF-a and IL-6 in the etiology of these symptoms. In this regard CTRF may be homologous to sickness behavior, a normal response to infection or tissue injury. Total body and localized radiation have been shown to induce the production of inflammatory cytokines both in experimental systems and in clinical populations. The purpose of the proposed study is to determine the relationship between fatigue and plasma inflammatory cytokine levels in prostate cancer patients undergoing external beam radiation therapy (RT) for prostate cancer. Understanding whether CTRF is initiated by the production of IL-1, TNF-α, and IL-6 may lead to new treatment strategies that will improve physical functioning, QOL and the patient's ability to receive the prescribed treatment.

Human-Computer Interface Differentials in Target Delineation: A Multi-Institutional Study

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RSNA
Research Resident Grant

In conformal radiotherapy, even minor geometric uncertainties to result in substantial dose deviations, potentially resulting in decreased dose to tumor or increased exposure to radiosensitive tissue. Target volumes and organs at risk for treatment planning are necessarily defined by human users, introducing a possible source of uncertainty due to variation in target delineation. This multi-institutional repeated measure user survey will combine objective evaluation of specific target delineation parameters with user reported data for comparison between standard mouse-keyboard interfaces and a novel pen-display device (DTZ-2100, Wacom Technology). Anonymized DICOM files will serve as “case sessions” for target delineation series of various anatomic sites, and are packaged within a proprietary program developed at NKI-AVL called Big Brother. Big Brother contains a contouring interface and standardized tool-set containing common features of commercial imaging software, and allows remote electronic data collection of objective target delineation parameters. Participants from five designated institutions will contour structures using both standard mouse-keyboard and pen-display interfaces on separate distinct occasions over a 9 month period, affording collection of intra-and inter-user agreement and variance data. Recorded information electronically will be remotely extracted from the contouring session for analysis, after being collected electronically via the internet from participating institutions. Big Brother includes a wide array of volumetric and target delineation efficiency measures allowing evaluation of efficiency, suitability, reproducibility and target volume variability as a function of hardware interface or operator. By using established margin generation recipes to account for differentials in user-hardware interface, uncertainty reduction and tumor control probability/normal tissue complication probability may be optimized. Similarly, allowing target delineation/visual data manipulation tasks to be completed in a more expedient may increase radiotherapy workflow, decrease costs, and minimize user-derived variability. The long-term plan of this project is to quantify, analyze, and develop training methods to optimize and standardize target delineation while maximizing workflow.

Imaging Cardiac Angiotensin-Converting Enzyme (ACE) Activity with ^{99m}Tc-Lisinopril in Transgenic Rats Overexpressing Cardiac ACE

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Philips Medical Systems/RSNA
Research Resident Grant

Congestive heart failure (CHF) has become a significant social burden in Western society, with high morbidity and mortality and accelerating financial costs. Accumulating evidence from clinical and experimental studies indicates that the renin–angiotensin system (RAS) and its primary effector peptide, angiotensin II (Ang II), are linked to the pathophysiology of interstitial fibrosis, cardiac remodeling, and heart failure. In patients with CHF, inhibition of the RAS with angiotensin-converting enzyme (ACE) systems has proven to have favorable effects on left ventricular (LV) remodeling and patient outcomes.

Building on previous work in synthesizing a novel radiotracer and an ACE inhibitor (^{99m}Tc-lisinopril), I propose a project to explore the imaging signal changes associated with increased myocardial ACE and the contribution of ACE to pathologic remodeling in a transgenic rat model overexpressing cardiac ACE. Based on preliminary data in rats and in explanted hearts from patients with CHF, I believe that the characterization of this ACE inhibitor that binds specifically to myocardial ACE in the heart (at high percentage injected dose per gram) will lead to a new generation of imaging probes for monitoring disease progression and the effectiveness of treatments for CHF.

If successful, data from this research would lay the groundwork for preclinical studies to determine the utility of this technique in prospectively identifying CHF patients with increased myocardial ACE activity, before the transition to replacement fibrosis and remodeling. If the finding of increased ACE is reversible (eg, with ACE inhibitors), noninvasive imaging with SPECT would allow monitoring of both disease progression and the effects of medical and interventional therapies before collagen replacement ensues. Imaging techniques that can identify patients with increased ACE before the transition to replacement fibrosis and remodeling may result in preserved LV function, thereby improving overall prognoses and outcomes.

Hyperpolarized Helium-3 MRI Assessment of Bronchiolitis Obliterans in Pediatric Lung Transplant Recipients

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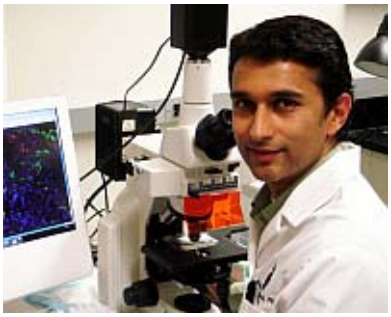
Philips Medical Systems/RSNA
Research Seed Grant

Chronic allograft dysfunction due to bronchiolitis obliterans is the major cause of long-term morbidity and mortality in pediatric lung transplant recipients. Early diagnosis and initiation of treatment can improve survival and may ameliorate the course of disease. Hyperpolarized helium-3 magnetic resonance imaging (^{3}He-MR) is a promising new technology for noninvasively visualizing the airways and alveolar spaces that has been extensively used in our laboratory for evaluating adults with emphysema. It offers information on lung microstructure and function not afforded by traditional imaging methods and pulmonary function tests and has yet to be established in a pediatric population with airway diseases.

Because early detection of bronchiolitis obliterans has the potential to reduce morbidity and mortality, we are interested in investigating the use of ^{3}He-MRI for diagnosing this disease in pediatric lung transplant recipients. Approaches include evaluation of standard techniques using ventilation and diffusion ^{3}He-MRI and a newly developed technique-in vivo morphometry. The hypothesis is that ^{3}He-MRI will allow reliable clinical assessment of impaired pulmonary ventilation in pediatric lung recipients with posttransplant bronchiolitis obliterans.

CT and clinical function tests are the standards for establishing the diagnosis of bronchiolitis obliterans. The goal is to demonstrate that ^{3}He-MRI is as at least as sensitive as CT and spirometry in the diagnosis of small airway disease. In particular, determining that ^{3}He-MRI could replace CT has the potential to impact the care of young patients by reducing exposure to ionizing radiation. The optimal techniques for lung ^{3}He-MRI in children have not been established. If we can identify the ^{3}He-MRI technique that provides the best estimate of bronchiolitis obliterans compared with CT, we can provide a valid biomarker of bronchiolitis obliterans, and potentially this can be applied to other airway diseases in children.

Vascular Phenotyping of Brain Tumors Using Magnetic Resonance Microscopy



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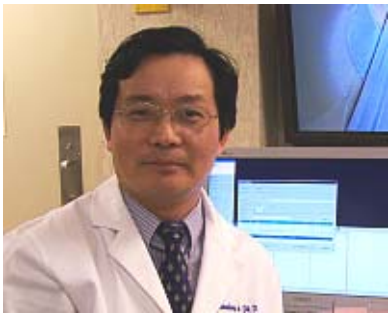
Toshiba Medical Systems/RSNA
Research Seed Grant

The initial success of anti-angiogenic agents in clinical trials has created a crucial need for developing radiological techniques and imaging markers for assessing their efficacy in patients. Due to its sensitivity to various aspects of the vasculature, MRI with conventional FDA approved contrast agents has the potential to be a non-invasive, *in vivo* marker of angiogenesis with widespread clinical availability. However, the “angiogenic” image contrast obtained from contrast-enhanced MRI critically depends on the complex interplay between the biophysics of the MR signal and the underlying tumor microvasculature. It is the PI’s goal to elucidate the factors that bring about “angiogenic” contrast in clinical MRI. Since, this is an issue of profound significance to the radiological sciences, the PI’s vision is to model the biophysical tumor environment, with the aim of developing a quantifiable association between the observed MR signal change, and underlying microvascular geometry. Most models employ geometrical approximations of tumor microvasculature as it is computationally convenient, and circumvents the challenge of obtaining accurate morphological information about the microvasculature. However, such approximations may be inadequate when imaging tumors with their anomalous vascular trees. In such cases, we need models that take the *de facto* tumor vasculature into account. The high-resolution 3D images of the vasculature of brain tumors acquired with MR microscopy from this proposal will be directly employed in new models of MR contrast mechanisms, fulfilling the PI’s long-tem goal of understanding these complex phenomena. Then MRI can live up to its full potential as a reliable *in vivo* clinical surrogate of tumor angiogenesis. In summary, this proposal describes novel methods for imaging tumor angiogenesis in a preclinical brain tumor model, with a focus on characterizing the tumor vascular architecture during tumor progression and antiangiogenic therapy, *ex vivo* using 3D MR microscopy in conjunction with laser scanning confocal microscopy.

Instant Magnetosonoporation (MSP) Cell Labeling for MRI Tracking of Stem Cell Migration



Stem cells are being explored for infusion or transplantation into tissue for purposes of repair, revascularization, and other therapeutic measures. Non-invasive magnetic resonance imaging (MRI) is a useful tool to serially track the migration of magnetically labeled stem cells. The overall goal of this study is to develop a novel, instant cellular magnetic labeling technique, termed magnetosonoporation (MSP). The concept of MSP is based on the hypothesis that ultrasound-induced sonoporation can increase the permeability of cell membrane, thus facilitate the transfer of MR contrast agents into the cells. The proposed project includes two specific aims. First, we will develop an experimental ultrasound instrument and optimize MSP-mediated cell labeling parameters. Second, we will validate the feasibility of using in vivo MRI to track the migration of MSP-labeled neural stem-progenitor cells to gliomas. We expect this MSP-based cell labeling technique will be more efficient, convenient and safer compared to the currently existing cell labeling methods. The success of this study will facilitate the use of MRI as a non-invasive imaging tool to monitor the migration of stem cells, and thus to explore new insights into the early diagnosis and efficient treatment, such as cell-based gene therapy.

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FUJIFILM Medical Systems/RNSA
Research Seed Grant

Utility of an Open Source Web Based Application for Radiology Decision Support and Operational Efficiency

Abstract not available.

Photo not available

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Philips Medical Systems/RSNA
Research Medical Student Grant

Perfusion MR Imaging Methods for Characterization of Prostate Cancer: Preliminary Experience

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*Kiran is enrolled at the University of Michigan Medical School

Canon USA/RSNA
Research Medical Student Grant

Canon

Purpose: To develop methods for quantification of prostate cancer perfusion metrics using dynamic contrast-enhanced (DCE) MRI.

Methods & Materials: In this study, we will evaluate patients diagnosed with prostate cancer who underwent DCE-MRI. The protocol includes multiplanar high resolution T2 weighted-imaging and DCE T1-weighted imaging, using 3D FLAH sequence after dynamic contrast injection of 0.1 mmol/kg of Gd-DTPA, with a temporal resolution of approximately 5 sec. Post-processing will be performed using locally developed software. Color-coded parametric voxel-based maps using Gd concentration vs. time curves will be obtained. By applying a multi-compartmental modified Tofts model, vascular characteristics of normal prostatic tissue and prostate cancer will be extracted using ROIs and arterial input function (using the external iliac artery as a surrogate for the aorta). The calculated parameters will include vascular permeability (microvascular permeability-surface area product [Ktrans]), extravascular-extracellular space volume (Ve), and relative blood volume (rBV). An experienced observer will measure the parameters on parametric maps using ROIs placed in the normal peripheral zone, normal central gland, and tumor for each patient. The ROI placement will be correlated to T2-weighted imaging and histopathology (biopsy and/or prostatectomy). These parametric estimates will be compared between areas of tumor, normal peripheral zone and central gland, and will be correlated to histological grade (Gleason score) and PSA levels.

Clinical Significance: This study will enable us to acquire pilot data on perfusion quantification methods in prostate cancer, which will be used for extramural grants.

Evaluation of Iocoregional Recurrence (LRR) Before and After Implementation of a Computed Tomography (CT)-Based Treatment Planning in Post-Mastectomy Radiation Therapy (PMRT)

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FUJIFILM Medical Systems/RSNA
Research Medical Student Grant

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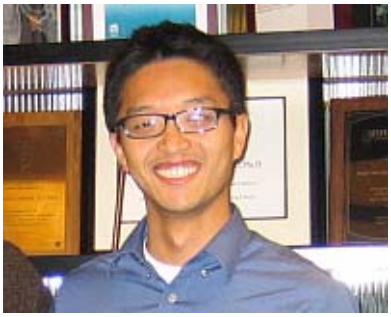
Abstract not available.

The Mighty Mouse: Ubiquitous Expression of Tri-Fusion Imaging Multimodality (Bioluminescence, Fluorescence, PET) Reporter Gene in Transgenic Mouse



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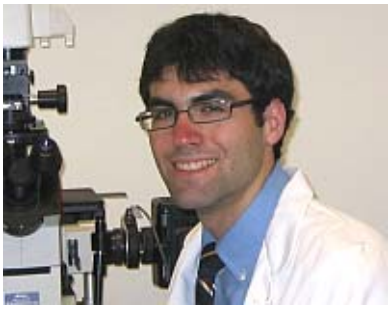
RSNA
Research Medical Student Grant

As biology moves towards a "systems biology" approach, so must imaging of molecular/cellular events in living subjects move towards a "systems imaging" approach. Imaging using reporter gene expression in living animals with various imaging modalities is a rapidly advancing field. In this project, we will create a transgenic mouse with high level and ubiquitous expression of a tri-fusion reporter protein in collaboration with the Stanford Transgenic Research Facility. The triple fusion reporter vector harbors a bioluminescence [a mutated thermo-stable firefly luciferase (*mTfl*)] reporter gene, a fluorescence reporter gene [a monomeric red fluorescence protein (*mrfp1*)] and a positron emission tomography (PET) reporter gene [truncated herpes simplex virus type 1 sr39 thymidine kinase (*ttk*)]. This tri-fusion reporter gene will be driven by the chicken β-actin promoter, thus all cells of the transgenic mouse will produce strong bioluminescence, fluorescence, and PET signals when the proper substrate (PET/bioluminescence) or light (fluorescence) is provided. We will first test the activity levels of all the three reporter proteins of the *β-actin-mtfl-mrfp-ttk* vector in different cell lines. Then various imaging and histology techniques will be performed to characterize the transgenic mice. This transgenic mouse model will be crucial in the future stem cell, cancer, tissue engineering and other research areas as this mouse can serve as the source of donor cells of any type for many applications.

Characterizing and Modulating the Cancer Stem Cell Phenotype



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Research Medical Student Grant

Our goal is to characterize cancer stem cells in the clinic and test the hypothesis that these cells are a prime determinant of treatment success. Our first task has been to establish the controls necessary to confer maximal rigor to our investigations. We have discovered that HT29 cells, a biologically aggressive and radioresistant colorectal cancer cell line, express the CD133 stem cell marker. We have also detected CD133 expression in HCT116 and OVCAR5 cells. This marker was detectable via immunoblotting and via flow-assisted cytometric sorting (FACS). We have also discovered that histone deacetylase inhibitors (HDIs) efficiently inhibit the proliferation of and downregulate CD133 expression in HT29 cells. HDIs have been approved for clinical use and validated as monotherapy against specific cancers in clinical trials. Our findings therefore raise the intriguing possibility that HDIs may be combined with standard anticancer strategies to target cancer stem cells and other mechanisms of treatment resistance.

Our immediate goals are to test whether HDIs radiosensitize HT29 and other cancer stem cells such as HCT116 and OVCAR5 cells. We will investigate whether HDIs modulate other aspects of the cancer stem cell phenotype, such as high efficiencies in tumor engraftment in animal models, and high degrees of chemotherapy resistance. Furthermore, we will establish assays that should enable us to isolate cancer cell populations with and without expression of cancer stem cell markers, which will in turn facilitate hypothesis testing, the testing of treatment strategies, and the mechanisms by which HDIs modulate the cancer stem cell phenotype. The results of these studies will establish a solid foundation from which we can proceed into the clinic to reach our ultimate goal of characterizing cancer stem cells and provide more effective treatments for afflicted patients.

Utility of Silicone Rubber Contrast-enhanced MicroCT in Evaluating the Angioarchitecture of Malignant Prostatectomy Specimens

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A 50-year-old male has a 42% lifetime risk of developing prostate cancer (PCa). Currently, this cancer is the 2nd leading cause of death in North America.

Cancer detection rates on first (initial), second, third, and fourth biopsy were 22%, 10%, 5%, and 4%, in a multi-center study. Image-guided biopsies based on tumor vascularity could potentially increase the accuracy of PCa diagnosis. Although there is some information available on the mean vascular density (MVD) of PCa, no information exists on the functional vascularity of PCa that reflects the vascularity required for image-guided biopsy. Computed tomography (CT) analysis of silicone rubber-enhanced microvasculature can potentially provide this information. Microfil MV-122 (Flow Tech, Inc., Carver, MA) is one such polymer that is ideal for amplifying the 3D hierarchy of blood vessels, as it preserves surrounding tissues and may be used to visualize vessels as small as 17 um. CT analysis has already proven successful in the vascular assessment of kidneys, ovaries, mammary glands, and lungs.

A protocol combining Microfil MV-122 and CT analysis for the evaluation of prostatectomy specimens in vitro will be this project's primary goal. Such a protocol could improve the detection of vascular patterns indicative of malignant processes and help cancer detection by the use of ultrasound and magnetic resonance imaging with contrast agents. Malignant vascular features that this project could reveal would greatly aid these techniques, which are currently constrained by a lack of reliable vascular signs for confirming a diagnosis.

We will inject the contrast agent into the prostatectomy specimens and scan them using microCT. We hypothesize that morphological differences will be observed when comparing benign and malignant prostatic tissues. In malignant tissues, these differences are believed to include increased MVD, typically seen in more aggressive and higher Gleason PCa, loss of vascular hierarchy, and changes in vessel diameter and tortuosity.

Cosmetic Outcomes and Complications After Breast Conservation Treatment in Early-Stage Breast Cancer: Electron Boost Versus Iridium Implant

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Research Medical Student Grant

Breast conserving treatment (BCT), offered to early-stage breast cancer patients, involves radiation treatment following breast conserving surgery (BCS). Radiation treatment consists of external-beam photon radiotherapy of the whole breast, followed by radiation boost to the tumor bed; this boost is currently delivered using external electron beams and was historically delivered via iridium-192 implants. With the development of accelerated partial breast irradiation (APBI), the use of breast implants through MammoSite® and other brachytherapy systems has regained interest. APBI involves delivery of radiation to the tumor bed alone over 5-7 days following BCS. Compared to external tangent beams to the whole breast, APBI has been rationalized according to clinical and pathological data suggesting that most cancer recurrences localize near the primary lesion. Additionally, by delivering radiation directly to affected tissues and irradiating less normal tissue, APBI is believed to have reduced toxicity and complications.

APBI has been hypothesized to shorten the treatment duration, improve clinical outcomes, and cause fewer complications; however, such long-term data does not exist. Thus, this retrospective cohort study will examine cosmesis and complications in a group of patients treated with iridium-192 implant boost with 20-year follow-up as a proxy for patients treated with APBI and will compare this group via a 1:1 case-match model to patients who received standard whole-breast tangential external-beam radiotherapy. This study will utilize long-term findings in the iridium boost group to extrapolate the long-term outcomes associated with APBI, thereby helping radiation oncologists design treatment modalities.

Main outcome measures include cosmesis ratings and complications. Survival and local recurrence data will also be reported. Patient data will be collected and abstracted for 20 years following treatment completion, or until patients are deceased or lost to follow-up. Cosmesis and complications data for both groups will be compared via Cox regression models and the Pearson's Chi Square test.

Quantitative Analysis of FDG-PET-MRI Fusion and DTI to Determine the Epileptogenic Region in Children with Tuberous Sclerosis

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Tuberous sclerosis (TS) is a devastating hereditary neurologic disorder which affects approximately 1:25,000 live births. Roughly 80% of patients with TS have epilepsy that can lead to mental retardation. Typically seizures change over time, as more than one tuber can become epileptogenic. When this happens, medication is often ineffective in controlling these seizures. In addition, these patients often are not considered surgical candidates due to the multifocal nature of their epilepsy. Thus, there appears to be a critical window of time to achieve seizure control and good developmental outcome— ideally when a single tuber is epileptogenic, before multifocal epilepsy and intractability ensue. Surgical resection is now considered a viable option at leading epilepsy centers, but currently there is no satisfactory presurgical method of reliably differentiating epileptogenic tubers from inactive tubers.

The specific aim of this study is to utilize the modalities of magnetic resonance fused positron emission tomography (FDG-PET-MRI) and diffusion tensor imaging (DTI) as a novel combination to improve preoperative identification of epileptogenic tuber(s) through the identification of specific patterns of abnormality. We will evaluate quantification values of FDG-PET-MRI in the area within the putative epileptogenic tuber and compare this to the corresponding values in the surrounding normal brain tissue, as well as non-epileptogenic tubers. Furthermore, this data will be combined with DTI diffusivity (ADC) and fractional anisotropy (FA) values to further elucidate the epileptogenic tissue.

It is our ultimate hope that by comparing values from PET-MRI fusion and DTI of epileptogenic tubers and non-epileptogenic tubers, the multimodal imaging findings can greatly aid the surgeon by providing a virtual map which can be used to clearly identify epileptogenic tubers and also preserve normal brain tissue during surgical treatment of TS.

Analysis of Cardiac MR Imaging Sequences for Optimal Detection of Intracardiac Thrombi

Photo not available

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Research Medical Student Grant

Stroke is ranked third among all causes of death in the United States. Approximately 700,000 people experience a new or recurrent stroke each year. Detection of left-sided thrombus is important due to the increased risk of cardioembolic stroke. Currently, transthoracic echocardiography(TTE) is most often used to detect intracardiac thrombi. However, due to several technical limitations such as window size, inability to visualize all cardiac chambers, and reduced image quality in some patients, transesophageal echocardiography(TEE) is performed for further evaluation. TEE does not suffer from the acoustic window limitations and is the gold standard, however, it is invasive and requires conscious sedation. A recent, non-invasive modality, cardiac magnetic resonance(CMR) offers high temporal and spatial resolution visualization of the cardiovascular system.

42 patients who underwent CMR with a diagnosis positive for intracardiac thrombi were enrolled. Clinical information and results of imaging studies are retrospectively reviewed. CMR studies were performed on a 1.5T scanner. Contrast-enhanced studies were performed after intravenous administration Gd-DTPA (0.2 mmol/kg). Two-dimensional echocardiography was performed using commercially available equipment and by experienced cardiologists. TEE was performed after oral administration of 0.02 mg of lidocaine with a 5-MHz phased multiplanar probe. Contrast agents were administered to some patients to improve endocardial border definition. Signal-to-noise ratio(SNR) and contrast-to-noise ratio(CNR) will be calculated for both thrombi:blood and thrombi:myocardium. Two radiologists blinded to the identity and diagnosis of the patients will then review MR sequences for conspicuity and clinical confidence for thrombus.

The study will evaluate and quantify the ability to accurately detect intracardiac thrombi with different MR sequences to each other and echocardiography. The clinical management of these patients is greatly dependent on accurately detecting thrombi.

Predicting Patient Responsiveness to Stroke Therapy Using Diffusion Tensor Imaging

In the six months after a stroke occurs, patients recover partial or complete function of an ability that was lost due to the stroke. This is now believed to be the result of neural plasticity or the reorganization of the brain to compensate for the cortex damaged because of the stroke. This study will focus on cortical reorganization in the motor cortex using DTI in hopes that it will help us understand the recovery process better and to improve current treatments for strokes. Our study will look at the reorganization of the internal capsule in particular and how its axons project to the cortex (motor, somatosensory, premotor, frontal and parietal). We will compare the organization of these projections in normal patients with those of patients whom have recovered from a stroke to try to correlate the reorganization with the amount of function recovered.

This study will use data that is already being collected under a research protocol overseen by Dr. Robert Levy and Dr. Todd Parrish. All data will be acquired at baseline and 12 weeks following therapy. Subjects will be controlled for intracranial volume, motor performance, age, sex, and lesion location. All data will under go statistical analysis and thresholding which will account for multiple comparisons and a priori regions of interest where changes are expected in the internal capsule and motor cortex.

The expected results will demonstrate regions of the brain that respond to therapy and are correlated with clinical improvements in motor performance as measured by standard behavioral testing. It is further believed that these results may allow one to predict based on lesion location, age, gender, and baseline performance how the patient will recover. This powerful and exciting study has the potential to alter how stroke patients are managed in the future.

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Determination and Utilization of Optimum Oblique Cutplanes of the Prostate for Use in Radiotherapy Contouring

The early history of 3D conformal therapy parallels the history of computed tomography (CT), the main 3D imaging modality used for treatment planning. The use of early CT scanners with limited speed, and treatment planning systems with limited memory, caused the radiation therapy community to gravitate to the 3 mm thick transverse slice as the de-facto standard for prostate contouring. Prostate and local organ segmentation was therefore conducted on transverse planes by manual, semi-automatic or automatic delineation. The visualization and utilization of non transverse images had widely varying spatial resolution in two axes which caused distracting digitization features, and ultimately lead to the abandonment of alternate image planes for contouring purposes. In spite of the rapid and extensive expansion of imaging technology, specifically with respect to CT, the segmentation process in radiation therapy has changed little.

We propose to capitalize on the isotropic, high spatial resolution multislice fan-beam and cone-beam CT images to improve how the prostate and normal organs are segmented and how segmentations are quantitatively reviewed. We intend to develop a process that utilizes oblique planar cuts through the CT datasets, allowing clinicians to contour on the oblique cuts, and generate the segmentation surface using sophisticated triangular surface mesh interpolation techniques. We hypothesize that the successful development of this model will improve the accuracy of segmentation (by allowing the treatment planner to select optimal planes for contouring), as well as the efficiency of planning (by allowing the use of fewer contours to define the segmentation surface) eventually allowing 4D and adaptive radiotherapy techniques to become more clinically manageable.

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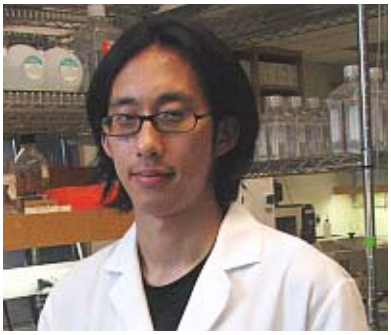
MRI of Neural Stem Cell Migration in Response to Excitotoxic Injury in the Adult Mouse Brain



Recent findings that neurogenesis occurs in the adult mammalian brain have led to the exciting prospect that endogenous neural stem cells (NSCs) can be manipulated to replace neurons in areas of neurodegeneration and central nervous system injury. Several studies have demonstrated that neurogenesis is stimulated in response to various types of injury, including excitotoxic injury. The development of non-invasive imaging methods to monitor endogenous NSC behavior in vivo would represent a major advance for evaluating endogenous NSC therapies in live animals and humans. Used extensively in the Turnbull lab, iron-oxide agents are currently favored for cellular contrast in MRI, and we and other labs have been able to label NSCs in situ, using micron-sized particles of iron oxide (MPIOs), to visualize migration of NSC progeny from the subventricular zone to the olfactory bulb. Quinolinic acid (QA) is an endogenous excitotoxin that has previously been used in rodent neurogenesis studies. My specific aim is to develop and evaluate in vivo micro-MRI approaches to monitor migration of NSC progeny in the excitotoxically-injured adult mouse brain, using QA as our lesion model and MPIOs as our contrast agent of choice.

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Detection of Skeletal Muscle Denervation in Living Aging Rodents with Positron Emission Tomography

Growing evidence supports a role for neural degeneration in the chronic, age-related structural and functional decline of skeletal muscle. An accurate, noninvasive technique for assessing muscle innervation could be invaluable by enabling delineation of the natural history of muscle innervation and evaluating the effects of interventions aimed at preventing and delaying denervation in specific subjects. Despite many advances that have occurred in functional and molecular imaging in the last few decades, imaging the neurofunctional aspect of muscle remains elusive. Positron emission tomography (PET) is a three-dimensional imaging technique that has been used to elucidate organ function noninvasively. The neurofunctional radiotracer 18F-flurobenzyltrozamicol (FBT) binds to the vesicular acetylcholine transporter (VAChT), and has been found to be an effective marker of skeletal muscle innervation.
The hypothesis of this project is that alterations in mouse skeletal muscle innervation with aging can be quantified using the noninvasive imaging procedure 18F-FBT-PET, which will correlate with expression of the vesicular acetylcholine transporter (VAChT). This hypothesis will be tested by quantifying hindlimb muscle innervation using 18F-FBT-PET. To investigate whether 18F-FBT-PET is sufficiently sensitive to detect differences in muscle innervation, mice will be subjected to transient (sciatic crush) or permanent (transection) nerve injury. Time-activity curves in lower hindlimb muscles and differences in 18F-FBT uptake between experimental denervation and young and old mice will be measured. Changes in muscle volume with aging will be analyzed by MRI.

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The contribution of denervation to sarcopenia remains elusive, particularly in humans. Validation of 18F-FBT-PET as a novel, accurate, noninvasive measure of skeletal muscle innervation in rodents will provide valuable data that can be rapidly translated into a research and clinical tool in animals and humans to evaluate interventions aimed at preventing and/or ameliorating the potential significant contribution of muscle denervation to sarcopenia and subsequent physical disability in older adults.

Designing Active Feedback-Enhanced Contrast for Improved Lesion Detection by MRI

Limited contrast in magnetic resonance imaging (MRI) often obscures the subtle physiological changes leading to a pathologic state. A conceptually new approach for enhancing MRI contrast due to small variations in MRI parameters has recently been developed that exploits nonlinear feedback fields induced by the spins themselves. Feedback-enhanced MRI has been shown to improve contrast by 15–24 times in epileptogenic lesions and malignant brain tumors, which are difficult to visualize using conventional methods. However, the underlying feedback interactions are typically weak at the lower field strengths used in human MRI.

This proposal aims to translate feedback-enhanced contrast for clinical applications by designing an active feedback device to amplify the effect of the feedback fields under the conditions encountered in clinical MRI scanners. Active feedback MRI differs fundamentally from conventional MRI in that the interplay between the magnetization and the feedback field allows the spins to direct their own evolution. In this way, heightened sensitivity to underlying susceptibility variations and their relative contribution to the total magnetization may be achieved to yield new and enhanced contrast. With the added control provided by active feedback, new pulse sequences will be designed to sensitize the feedback field to microscopic susceptibility variations while overcoming macroscopic field inhomogeneity. During the three-month grant period, an active feedback device will be constructed, and active feedback-enhanced contrast will be validated on simple phantom samples at 3T. Projected long-term applications of active feedback-enhanced contrast for improved lesion detection include detecting small cortical dysplasias in patients with refractory epilepsy, delineating tumor boundaries in patients with malignant brain tumors, and highlighting small concentrations of molecular imaging contrast agents such as superparamagnetic iron-oxide nanoparticles with amplified, positive contrast. Preliminary results on tissue samples and small animals from microimaging are shown to assess the feasibility of the proposed research.

Photo not available

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Taxanes Increase the Radiation Pneumonitis Response in Esophagus Cancer Patients

Taxanes are plant-derived chemotherapeutic agents that are currently considered to be among the most effective anticancer drugs. Recent investigations on the risk of radiation pneumonitis (RP) with taxane-based chemotherapy in breast cancer patients with sequential or concurrent irradiation have yielded conflicting findings. These investigations used subjective clinical assessments to identify RP and did not utilize or provide three dimensional (3D) radiation dose information from the patients included in their studies. Because RP is an inflammatory reaction within irradiated lung tissue in response to radiation injury, [18F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging may serve as a quantitative indicator of lung inflammatory intensity after thoracic radiotherapy. A correlation between the RP clinical symptoms and the inflammation intensity measured by FDG PET/CT was recently found. The primary aim of this study is to elucidate the risk of RP in patients who receive concurrent or sequential taxane-based chemotherapy with thoracic radiotherapy. 120 patients treated at the University of Texas M. D. Anderson Cancer Center for esophageal cancer who received CT treatment planning and follow-up FDG PET/CT imaging between 1 and 3 months after thoracic radiotherapy completion will be selected for this study. We will measure the pulmonary inflammation intensity with post-irradiation FDG PET/CT and score the pulmonary toxicity using the common toxicity criteria for adverse events version 3 (CTCAEv3). A secondary aim is to further characterize the use of FDG PET/CT as a non-invasive quantitative assessment of pulmonary inflammatory response to treatment and for risk stratification prior to treatment. This aim will demonstrate the role of FDG PET/CT imaging in quantifying toxicity response among groups with differing risks and will support its use in the future to studies introducing new chemotherapy agents or radioprotectors. Our long-term objective is the reduction in radiation induced pulmonary complications in thoracic radiotherapy patients.

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MRI Assessment of Diffusion Changes in Hepatocellular Carcinomas Post Chemoembolization

Abstract not available.

Photo not available

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Relationship of Cerebrovascular Outcomes and Carotid Intraplaque Hemorrhage Detected By Magnetic Resonance Direct Thrombus Imaging

Abstract not available.

Photo not available

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Research Medical Student Grant

Biliary Spills and Collections: Causes, Diagnosis, and Management by Interventional Radiology

This research project evaluates the outcome of patients with bile leaks and bilomas managed with image-guided percutaneous interventions. The patient population includes those with internal and external bile leaks occurring from November 1999 through August 2007. These patients are classified by the location of the bile duct injury and bile collections. The study was retrospectively designed to analyze patients that resolved completely with the interventions and those who required further endoscopic and/or surgical procedures. The image-guided interventions discussed in this study serve as safe, effective, and minimally invasive alternatives to conventional surgical and endoscopic procedures previously used to repair these biliary injuries. Guidelines and recommendations on management and end point results for each of these conditions are expected as end points of the study.

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Development of Reader Criteria for Early Diagnosis of Alzheimer's Disease Using Arterial Spin Labeled MRI

Abstract not available.

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Research Medical Student Grant

Identification of Molecular Markers Associated with Poor Prognosis in Tumors of the Uterine Cervix

Abstract not available.

Photo not available

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Imaging Pancreatic Cancer Vascular Phenotypes to Determine Tumor Genotype-Specific Responsiveness to TGF-ß Inhibitor Using Intravital Fiber-Optic Confocal Microcatheter and Fractal Analysis

Abstract not available.

Photo not available

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TRIP-MRI Monitoring of Hepatic Tumor Perfusion Changes Following Therasphere and SIR-Sphere Radioembolization

Abstract not available.

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