A single frame of a 4D MRI study that displays streamlines of velocity vectors in the heart and the aorta in a patient who has had a surgical repair of the aortic valve and root. Note the complex spiral in the ascending aorta and acceleration across the aortic valve.
## Creating Breakthroughs in Medical Imaging

### Lucas Center Overviews

- Centers of Excellence
- Research Overview
- Radiological Sciences Laboratory and Center for Advanced MR Technology (RSL & CAMRT)
- Information Science in Imaging at Stanford (ISIS)
- Molecular Imaging Program at Stanford (MIPS)
- Canary Center
- CCNE

### Clinical Translation

- Clinical Collaborations Foster Translational Research

### Research Faculty and Personnel

- Radiology Research Personnel, Students, and Visitors
- New Research Faculty & Clinical Investigators
- Faculty Awards
- Trainee Awards

### Education and Training

- NIH-supported Training Programs
  - Advanced Techniques for Cancer Imaging and Detection (T32)
  - Stanford Molecular Imaging Scholars (R25)
  - In Vivo Cellular and Molecular Imaging (P50)
  - Predoctoral Training in Biomedical Imaging at Stanford (T32)
- Continuing Medical Education
- Lucas Center MR Systems Training and Support

### Research Group Updates

- Advanced X-Ray and CT Techniques
  - Inverse Geometry CT and Conventional CT (Pelic)
  - X-Ray Guidance of Interventional Procedures (Fahrig)
- Image Analysis, Bioinformatics, Computational Modeling
  - Laboratory of Imaging Informatics (Rubin)
  - Cancer Systems Biology Laboratory (Plevritis)
  - Imaging Bioinformatics (Paik)
  - Radiology 3D Visualization & Analysis Laboratory (Napel)
- Magnetic Resonance Research
  - Interventional and Open MRI (Butts Pauly)
  - Magnetic In Vivo Spectroscopy and Multinuclear Imaging (Spielman)
  - Body MR Imaging (Hargreaves)
  - High Field MR (Rut)
  - Functional Imaging (Glover)
  - Clinical Center for Advanced Neuroimaging (Bammer/Zaharchuk/Moseley)
- Molecular Imaging
  - Multimodality Molecular Imaging Lab (Gambhir)
  - Cancer Molecular Imaging Chemistry Lab (Cheng)
  - Cellular and Molecular Imaging Lab (Rao)
  - Molecular Imaging Instrumentation Lab (Levin)
  - Cardiovascular & Molecular Imaging Lab (Wu)
  - Molecular Imaging of Nocieption & Inflammation Laboratory (Biswal)
  - Cellular Pathway Imaging Laboratory (Paulmurugan)
- Translational Molecular Imaging Lab (Willmann)

### Facilities

- Radiology Imaging Facilities
- Stanford 3D Medical Imaging Laboratory
- Animal Model Management
- Small Animal Imaging Center (SCRI)
- Lucas Center MR Systems 1.5T, 3T, and 7T Whole Body Magnets
- Cyclotron Suite Update

### Abstracts

- Advanced X-Ray and CT Techniques
- Image Analysis, Bioinformatics, Computational Modeling
- Magnetic Resonance Research
- Molecular Imaging

### Publications and Presentations

- Peer-Reviewed Presentations at Scientific Meetings
- Other Scientific Meeting Presentations
- Published Papers
- Books & Book Chapters
- Papers Submitted or in Press

### Funded Research Projects

- NIH Supported Research
- NIH Collaborations (Sub Contracts)
- California Supported Research
- Professional Society and Foundation Supported Research
- Other Government Supported Research
- Industry Supported Research

### CBIS Seed Funding

### Collaborators

217
Creating Breakthroughs in Medical Imaging

Creating Breakthroughs

It is hard to believe that it has been over 20 years since the Richard M. Lucas Center for Imaging was conceptualized and its construction initiated. The pace of discovery and innovation continues to be extremely rapid so that each year we reinvent the Center and its programs.

This year, we are reinventing the Center by renovating its interior and by siting the most up-to-date instrumentation in our building. Our renovations will begin in May of 2011 and represent a $7.1M investment on the part of the Department. Over the years, we have maintained all of our MRI scanners at their latest software/hardware releases. However, one 1.5T and one 3.0T scanner can no longer be upgraded, and we plan to replace them with the latest whole body 3.0T instruments. We will also add equipment to hyperpolarize MRI signal, a technology that allows us to chemically modify compounds to increase the MRI signal by many orders of magnitude thereby markedly increasing signal detection. In addition, we will upgrade our 7.0T whole body scanner with new hardware and electronics; renovate an office area to provide additional space; and modernize an animal surgery lab.

In preparation for a new program in PET/MR, our renovations will also allow the siting of one of the earliest PET/MRI hybrid scanners in the world by 2012. Combining the superior soft-tissue contrast and high spatial resolution of MRI with the high sensitivity of positron emission tomography (PET), our PET/MR Program will advance the diagnosis of disease and the monitoring of treatment. There are currently no integrated whole body PET/MR systems in the United States.

The people and programs of the Lucas Center continue to be highly recognized throughout the imaging world. I am delighted that a new program has been established: “Modeling the Role of Differentiation in Cancer Progression,” which is one of the National Cancer Institute’s 11 new Centers for Cancer Systems Biology (CCSB). Our new Center complements our other 3 existing NIH-funded Centers of Excellence: the Center for Advanced Magnetic Resonance Technology at Stanford (CAMRT), the In Vivo Cellular and Molecular Imaging Center at Stanford (ICMIC), and the Center for Cancer Nanotechnology Excellence Focused on Therapy Response (CCNE-TR). We are the only U.S. radiology department with 4 large multidisciplinary NIH-funded centers.

CCSB research focuses on uncovering the disruption of normal processes underlying cellular differentiation in cancer for the development of novel molecular therapies. Research from the CCNE-TR includes a new magnetic cell sorter to isolate very rare cells from blood. ICMIC scientists are combining PET imaging with in vitro diagnostics to analyze patient response to anti-cancer therapies. Recent CAMRT innovations include the application of hyperpolarized 13C MRSI acquisition methods to measure treatment response in prostate and liver cancers; the improvement of cerebral blood flow techniques; the integration of imaging techniques to quantify fat, tissue perfusion, and blood flow; and the application of real-time fMRI for controlling brain regions associated with depression.

In this golden age of medical imaging, we are grateful for your support, which has helped us become leaders in biomedical imaging. You have made the Lucas Center synonymous with excellence in the development of world-leading technology and imaging programs.

Gary M. Glazer, MD
Emma Pfeiffer Merner Professor in the Medical Sciences
Professor and Chairman
Department of Radiology
Stanford University School of Medicine
The Stanford Department of Radiology now leads four NIH-funded Centers of Excellence and is the only academic radiology department in the country with four NIH-funded Centers of Excellence under the leadership of a single department. Our four Centers have contributed significant advances to improve health care, diagnosis, treatment, and monitoring for patients worldwide. In addition to technological, biochemical, and biological innovation in the imaging sciences, we have formally trained more than 500 individuals (including residents, fellows, postdocs, and graduate students) since our first Center, the Center for Advanced MR Technology, was established in 1995.

In 2009, all four of our Centers of Excellence completed the competing renewal process; all four of these Centers did remarkably well and are in various stages of initiating new excellence cycles. The following text gives a brief summary of each of these programs.

The Center for Advanced Magnetic Resonance Technology at Stanford (CAMRT - P41)
The CAMRT, now in its sixth year of operation as a National Research Resource and directed by Gary Glover, PhD, is funded by a grant from the NIH National Center for Research Resources. This Resource has five core technology development areas that include reconstruction methods (Dwight Nishimura and John Pauly, EE Department, core directors), hardware development (Brian Rutt, core director), neuro imaging methods (Gary Glover, core director and PI, Mike Moseley, Roland Bammer), diffusion and perfusion-weighted imaging methods (Mike Moseley, core director), Body imaging (Brian Hargreaves, core director), spectroscopic and multicellular imaging development (Dhan Spielman, core director). In addition to development of technology projects, the CAMRT provides support for collaborations and service use of the facilities, with users in the Radiology department as well as 75 faculty and more than 200 other users from at least 14 departments. For further details, please see http://rl.stanford.edu/research/camrt.html and the CAMRT/RSI-Overview (page 6-7).

The In Vivo Cellular and Molecular Imaging Center at Stanford (ICMIC@Stanford - P50)
The ICMIC, directed by Sam Gambhir, MD, PhD, and initially funded in 2005, brings together more than 50 faculty across the Stanford campus from more than 15 different departments, including the Department of Radiology. As one of a small number of in vivo cellular and molecular imaging centers (ICMIC) in the country, the ICMIC/Stanford studies disease by connecting preclinical models with clinical management through advances in multidisciplinary molecular imaging. The goals of the program are to fundamentally change how biological research is performed with cells in their intact environment in living subjects and to develop new ways to diagnose diseases and monitor therapies in patients. Areas of active investigation are cancer research, microbiology, immunology, developmental biology and pharmacology. The ICMIC benefits from the highly regarded infrastructure provided by the Department of Radiology, the CAMRT, and the RSL in the Richard M. Lucas Center for Imaging. For further details, please see http://mips.stanford.edu/public/grants/icmic/ and the MIPS Overview (page 10).

The Center for Cancer Nanotechnology Excellence (CCNE - U54)
Stanford Nanotechnology is one of a few (less than 10) institutions in the nation supported by the NIH to develop a major nanotechnology center: the Center for Cancer Nanotechnology Excellence Focused on Therapy Response (CCNE-TR). This center, established in 2006 and led by Sam Gambhir, MD, PhD, includes scientists from Stanford and five other sites across the country. The goal of this Center is to use nano-technology for the benefit of cancer patient management. Our new Center for Cancer Nanotechnology Excellence and Translation (CCNE-TR), approved for funding in 2010, builds on the success of the CCNE-CT and brings together scientists and physicians from Stanford University, University of California Berkeley/Lawrence Berkeley National Lab, University of California Los Angeles, University of Southern California and the Massachusetts Institute of Technology. Our goals with the new CCNE-TR build on our vision that in vivo diagnostics, used in conjunction with new cancer therapy, will significantly improve cancer patient management. It is through the use of nanotechnology that we will be able to significantly advance both in vitro diagnostics through proteomic nanosensors and in vivo diagnostics through nanorobots for molecular imaging. Both the CCNE-TR and the CCNE-TR will run simultaneously for ~1 year as we begin ramping up the CCNE-TR to focus molecular imaging methods (Gary Glover, core director and PI, Mike Moseley, Roland Bammer), diffusion and perfusion +weighted imaging methods (Daniel Butts Pauly, Fahrig); 2 S10s (Fahrig, Moseley) ; 1 Training Grant (Pki) ; 2 D03 projects (Cheng, Levine); 2 foundation grants (flamberg, Gold), and 4 industry grants (Gambhir, Levine, Marks, Hofmann). While most of these projects are led by experienced faculty with long standing research programs, we note that 2 faculty (Rubin, Yasuawalu) were awarded their first NIH-funded R01. Congratulations to all Radiology researchers, including faculty, postdocs, students, and staff members – all of whom contribute to the success of our present Center.

The Center for Cancer Systems Biology (CCSB - U54)
The Center for Cancer Systems Biology (CCSB), led by Sylvia Plevritis PhD, promotes the discovery of molecular mechanisms underlying cancer progression by studying cancer as a complex biological system that is driven, in part, by impaired differentiation. Our CCSB’s overarching goal is to better understand the self-renewing properties of cancer and its cellular hierarchy for the purposes of identifying effective therapeutic strategies. Our approaches integrate a vast high-throughput experimental datasets at the genomic, transcriptomic and proteomic levels, in order to reveal coordinated biological progression. This multidisciplinary Center brings together Stanford faculty from the Schools of Medicine, Engineering, and Human Sciences, with expertise ranging from molecular biology and oncology to mathematics, statistics, and computer science. It is one of twelve centers, nation-wide, newly funded by the NIH/NCI Integrative Cancer Biology Program (http://icbp.ncl.nih.gov/icbp) to promote the analysis of cancer as a complex system by merging experimental and computational methods. For further details of the CCSB, please see http://icbp.stanford.edu/ and the ISIS Overview (page 8-9).

Once again, we had a very successful year. Our research productivity and extramural funding (see abstract pages 61-138) funded projects pages 209-214) ranks the best and most productive radiology departments anywhere. In addition to funding mechanisms, we have approved an additional $15M for 2010-11 (with $5M for 2010-11) through the 2009 American Recovery and Reinvestment Act (ARRA). These funds have allowed us to retain or hire research scientists and establish new projects as the ARRA funding tapers off and comes to an end.

2010 Success: During 2010, we have enjoyed remarkable progress. Our faculty secured funding for 23 New (or Competing Renewal) sponsored projects. These newly funded projects include the following: 3 Center Grants (Gambhir, Glover, Plevritis); 8 new or renewed ROIs (Bannmer, Butts Pauly, Fahrig, Gold, Robin, Spielman, Yasuawalu, Waj, 1 RC Grant (Waj); 3 R01s (Daniel, Butts Pauly, Fahrig), 2 Stfs (Fahrig, Moseley). 1 Training Grant (Pki); 2 D03 projects (Cheng, Levine); 2 foundation grants (flamberg, Gold), and 4 industry grants (Gambhir, Levine, Marks, Hofmann). When you take all these projects into consideration, we are in a very favorable position to keep growing our research program.

Research Overview
Norbert Pelc, ScD, Associate Chair for Research
Susan Kowopida, MS, PhD, Director, Strategic Research Development

Figure 2 presents a history of the Stanford Radiology awards from 2003 - 2010 (noting that from 2005 to 2006 NIH represented approximately 95% of sponsored project funding. Since 2007, this profile has shifted such that NIH funded projects represented our largest source of funding, now representing about 75% of total funding. Industry makes up the next largest group, representing 14% of all awards received. In the current economic environment, including concerns about NIH funding and due to an increase in our overall research activity, we will likely observe changes in these patterns.

Figure 2 gives an overview of proposal activity from the Department from 2000 through 2010; it is worth noting that from 2005 to 2006 NIH represented approximately 95% of sponsored project funding. Since 2007, this profile has shifted such that NIH funded projects represented our largest source of funding, now representing about 75% of total funding. Industry makes up the next largest group, representing 14% of all awards received. In the current economic environment, including concerns about NIH funding and due to an increase in our overall research activity, we will likely observe changes in these patterns.

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Figure 1: Shows Stanford Radiology awards history. Total 2010 awards equals $37M (purple line). Of that $37M, $26M (75%) is due to NIH funded projects (yellow line). Industry makes up the next largest group, while still our largest source of funding, now represents 75% of total funding. Industry makes up the next largest group, while still our largest source of funding, now represents 75%

Space: On campus, the Richard M. Lucas Center for Imaging will shortly undergo a third remodel to accommodate new and upgraded facilities, office space for new faculty, additional space for research, and space for the students and staff associated with new faculty. At our off-campus research site on California Avenue, the Canary Center at Stanford, which opened in June 2009, is nearing capacity. With our new building and advanced nanotechnology, we are poised to expand our research, continue our active dialogue with the University and Hospital leadership for facilities to support our programs.

We are pleased to present the Lucas Family Foundation Trustees with the 2010 Lucas Annual Report. In the next few pages, you will read about our 4 NIH-supported Centers of Excellence (Page 4), and the three Stanford Radiology sections that make up our research effort: 1) the Radiological Sciences Lab (RSL), led by Gary Glover, PhD, PI; 2) the Molecular Imaging Program at Stanford (MIPS), led by Sanjiv (Sam) Gambhir, MD, PhD, and 3) Information Sciences in Imaging (ISI), led by Richard Lucas, PhD, who also founded our company, Imageguided Technologies, Inc., which supports the majority of the infrastructure of our sponsored projects on pages 209-234).

It is with continued support of the Lucas Family Foundation and the California Foundation that we are able to maintain leadership in research, train the next generation of imaging clinicians and scientists, and, above all, deliver the most advanced diagnostic and therapeutic techniques to benefit our patients and patients worldwide.
The Lucas Center has been home to the Radiological Sciences Laboratory (RSL), a section of the Radiology Department since the building’s dedication in 1992, and in conjunction with the Electrical Engineering Department has hosted the Center for Advanced MR Technology, an NIH-funded National Research Resource since 1995. The Center also houses a cyclotron and radiopharmacy labs as well as other wet labs for the Molecular Imaging Program under Dr. Sanjiv Gambhir. The Center’s state-of-the-art imaging facilities support research of the RSL and others in the Radiology department as well as hundreds of on-campus and extramural researchers as a core facility. The Center has always been, and remains, an exciting and lively nexus for fundamental imaging research.

THE RADIATION SCIENCES LABORATORY

The RSL comprises 9 faculty, approximately 35 graduate and postdoctoral students, approximately 30 scientific staff and 7 administrative assistants, as well as the Lucas Center/RLSL Administrative Services Director, Donna Cronister. The faculty serve in a wide variety of advisory roles to government and foundation agencies such as the NIH and in policy-making positions for international scientific societies such as the ISMRM and RSNA. Many of our faculty, scientific staff and students have garnered prestigious awards for their exceptional research achievements.

The Lucas Center has a mission to provide a stimulating environment for the translation of emerging technologies and advanced therapeutics to improve patient care. The RSL’s core infrastructure is supported in a multi-year award from the National Institutes of Health’s National Center for Research Resources (NCRR) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) (5P41-RR-001698). The Center’s mission has remained as research projects have been introduced, matured and been replaced with new developments and opportunities.

Michael Moseley:

- Editorial Boards:
  - Journal of Magnetic Resonance Imaging (JMRI)
  - Cerebrovascular Diseases (CVD), Journal of Cerebral Blood Flow and Metabolism (CBFPM), International Journal of Stroke (IJS)
- Advisory Boards:
  - AHA: American Heart Association
  - AHA/ASA Stroke Council Writing Committee (Definition of Stroke)
- Study section service
- NIH CSR: Service on 6 study sections
- Israeli Science Foundation. January 2010, Reviewer.
- ISMRM “Seed Grant” Grant Review Committee. 2010.
- Grants Funded: NIH S1 $1029697-01 “Upgrade of the Stanford GE-Variant Experimental MR1 scanner to the Current Model”.

Norbert Pelc:

- Postdoc Sam Mazin won a Kaufman Entrepreneur Postdoctoral Fellowship
- Chair, A/PM Science Council
- Awarded NIH T32 Training Grant: “Predoctoral Training in Biomedical Imaging at Stanford University”.

Priti Balchandani:

- Awarded a new NIH R01 “Metabolic Imaging of the Cardioprotective Effects of Alcohol and ALDH2 Activators”
- Priti Balchandani awarded 2010 International Society for Magnetic Resonance in Medicine (ISMRM) Junior Fellow award

THE NATIONAL CENTER FOR ADVANCED MR TECHNOLOGY AT STANFORD (CAMRT)

The CAMRT is a National Biotechnology Research Resource, sponsored by the NIH’s National Center for Research Resources (NCRR) with Dr. Glover as PI. The Center was initiated in 1995 with the broad goal of developing and making available a spectrum of cutting edge MR imaging research tools for scientists who would otherwise not have access, as well as to train students and others in MRI. Over the years that goal has remained as research projects have been introduced, matured and been replaced with new developments and opportunities.

The five-year grant was up for its third renewal last year as was reported in the 2009 Annual Report. The review was conducted with a site visit by an NIH review panel in October 2009, and we were gratified to receive a score of 5, which, on a scale of 1-9, is Perfect! This recognition by our peer reviewers/colleagues is a testament to CAMRT’s continuing international excellence and prominence in MRI physics development and collaborations. The grant was restructured somewhat in consultation with our National Advisory Board’s recommendations to include a new Hardware Core headed by Brian Rutt, which will be described next year (the new funding cycle started in July 2010 and so is not included here). We therefore have now entered our sixteenth year of continuous support of the National Center.

Outstanding progress has been made in all six of the core technology development areas that include reconstruction methods (John Pauly), EE Department, core director), imaging of brain activation (Gary Glover), diffusion and perfusion weighted imaging methods (Mike Moseley), imaging of cardiovascular structure and function (Brian Hargreaves), spectroscopic imaging development (Dan Spielman) and interventional MRI technique development (Kim Butts). Much of this exciting research is chronicled in the scientific reports that follow. These reports are acknowledged with funding from P41 RR00974.
ISIS Overview

Information Sciences in Imaging at Stanford
Sandy Napel, PhD and Sylvia Plevritis, PhD, Co-Directors

ISIS (Information Sciences in Imaging at Stanford), the newest section of the Radiology Department, is committed to harnessing new knowledge and new imaging techniques by integrating and analyzing them with related clinical and molecular data. ISIS is working toward this goal by exploring the full spectrum of information-intensive activities in imaging (e.g., image management, storage, retrieval, processing, analysis, understanding, visualization, navigation, interpretation, reporting, and communications) and in non-imaging domains (e.g., pathology, molecular and genetic markers, family history, prior medical reports, and clinical outcomes).

The expertise of the ISIS faculty spans image quantization, imaging informatics, molecular imaging bioinformatics, and systems biology. The ISIS core faculty includes Sandy Napel, Professor of Radiology and co-Director of the Radiology 3D Laboratory, Sylvia K. Plevritis, Associate Professor of Radiology, David S. Paik, Assistant Professor of Radiology, and Daniel L. Rubin, Assistant Professor of Radiology. ISIS is co-led by Drs. Napel and Plevritis. ISIS also has an affiliate faculty member Professor Robert J. HerTens whose expertise helps ISIS bridge between clinical imaging and information systems. Over the past year, ISIS has recruited an Administrative Program Manager Danae Barnes, and is in the process of finalizing its search for a Clinical Research Coordinator.

ISIS Overview

• RadBank Data Warehouse: RadBank, led by Dr. Rubin, is an open and community-driven database of qualitative and quantitative imaging biomarkers. To date, RadBank has been used to find cases of particular imaging findings, diagnoses, and molecular features derived from the image, and to identify cohorts for new research.

• RadBank Data Warehouse: RadBank, led by Dr. Rubin, is an integrated data warehouse that brings together radiology reports with pathology and clinical information and in the future molecular data) to enable researchers, clinicians, and educators to find cases of particular imaging findings, diagnoses, modalities, and other information. To date, RadBank has been used to identify teaching cases, to perform retrospective research, and to identify cohorts for new research.

• Imaging Biomarker Ontology (IBO). The IBO has developed an initial draft of the Imaging Biomarker Ontology and is working to refine and expand it to cover the domain of how quantitative measurements are captured from imaging data, with an emphasis on molecular imaging. IBO aims to enable intelligent and semantically-searchable warehousing of quantitative measurements from molecular imaging analogous to the way in which microarray data is currently captured in public databases, thereby enabling imaging to realize its potential in translational bioinformatics research.

• Standards for Interchange of Nanoparticle Data: As part of a national working group, the Paik Lab has been developing standards for the computational representation of data about nanoparticles that are used for diagnostic imaging and/or therapy delivery. These efforts have helped guide development of the NanoTAB, a data exchange format for nanomaterial composition and characterization.

Four key grants have been awarded to ISIS over the past year:

• Modeling the Role of Differentiation in Cancer Progression: In one of two national Centers for Cancer Systems Biology funded by the NIH, Dr. Sylvia Plevritis will direct a $12.8 million dollar multidisciplinary program over the next 5-year period to study the role of differentiation in hematologic malignancies. This program integrates a diversity of high-throughput data, including genomic, transcriptomic, and proteomic, to elucidate molecular networks driving cancer progression.

• Computerized Quantitative Imaging Assessment of Tumor Burden: Dr. Rubin is Principal Investigator of one of the centers in the newly established Quantitative Imaging Network (QIN), composed of researchers who will develop approaches to validate and standardize imaging data and related imaging metadata for quantitative measurements of responses to cancer therapies. Stanford’s part of the QIN will be to create computer algorithms to measure tumor burden in patients, and to identify and quantify novel imaging biomarkers that can provide earlier indicators of treatment response to cancer therapies.

Cancer Intervention and Surveillance Network (CISNET): Sylvia Plevritis’ CISNET programs over the past ten years have received an additional 5 years of funding to mathematically model the impact the early detection strategies on population trends in cancer incidence and mortality. Dr. Plevritis had two grants funded by CISNET: one to evaluate the role of CT in screening for lung cancer; and the other to evaluate risk-stratified screening strategies for breast cancer.

Integration of Imaging and Molecular Phenotypes for Improved Management and Understanding of Lung Cancer: In a pilot project supported, in part, with a grant from General Electric Medical Systems and led by Drs. Sandy Napel and Sylvia Plevritis, ISIS has effectively launched its first effort to integrate imaging and molecular features from lung cancer patients who undergo surgical resection. The imaging features are obtained from CT and annotated using much of the technology from our CBIR project (see above). In addition, PET data has been collected and annotated. Illumina gene expression microarray expression was generated on the human tissue specimens. Currently, an association map between the CT and PET image features and the tissue molecular profile is being created.

Finally, ISIS has acquired a Discovery Lab that will enable experimental validation of computationally derived results; this lab is located in LUCAS P169 and is under the supervision of Dr. Plevritis.

Through these efforts, we believe that ISIS has made progress that will enable the realization of its three main goals: (1) an evidence-based diagnostic decision support system, whereby patient-specific image, clinical and, if available, molecular data, can be compared to the database to suggest the most likely diagnoses, prognoses, and most relevant treatments, (2) biological discovery, i.e., synthesis and potential testing of hypotheses regarding the underlying biology in the development, progression and hopeful eradication of specific diseases, and (3) the translation of these developments into clinical practice using computers and image storage systems that are ubiquitous in healthcare enterprises today.
The Molecular Imaging Program at Stanford (MIPS) (http://mips.stanford.edu) continues to experience significant growth. Many faculty within the Department of Radiology and from other Departments continue to help build the program. The faculty received several new grants from the NIH as well as other agencies over the last year. We were fortunate to have our NCI-funded In Vivo Cellular Molecular Imaging Center (ICMIC) P50 grant renewed which now starting its 6th year. We are in the fifth year of the NCI Center for Cancer Nanotechnology Excellence (CCNE) U54 grant. We had another major NCI U54 Center grant awarded focused on Cancer Nanotechnology that will start in first year in a few months. We are also in the fifth year of the NIH K25 training grant, Stanford Molecular Imaging Scholars (SMIS), to train the next generation of cancer molecular imaging post-doctoral scholars. This grant has been submitted for a renewal. An NIH post-doctoral training grant (T32) for cardiovascular molecular imaging is in its second year. In addition, all labs continue to grow with many new students, postdoctoral fellows, and outstanding research staff joining the program. In addition, many visiting scientists from all around the world are coming to our program to learn more about molecular imaging.

Funding from the Canary Foundation to develop a new center for early cancer detection in the previous year is helping build bridges with many investigators on campus. Significantly increased funding from the Canary Foundation is expected with continued growth of the program. New off-campus space on California Avenue is facilitating the effort to early cancer detection including facilities for blood/tissue based detection of disease. We are convinced that more investments are needed in the earlier detection of all disease, including cancer. The ability to detect disease earlier will allow much better potential for cure. This center, pioneering in vitro diagnostics (e.g., using patient blood samples) as well as new imaging strategies with high sensitivity to detect very low burden disease. It is hoped that in the near future it could become a world leader in the important field of early cancer detection.

We continue to have several seminar series on campus to help educate scientists about molecular imaging. The molecular imaging seminar series (http://mips.stanford.edu/public/mips_ads) is now in its fifth year and has a large collection of videos available on-line of talks from the last few years. This year we also initiated students presenting from the Department of Pediatrics. The Nanotechnology seminar series (http://mips.stanford.edu/public/nanobiochem_seminar/adp) which focuses on new applications of nanotechnology to cancer continues to draw large attendance from all over campus. Several speakers from around the country have already presented in the series and all lectures are available on-line.

There are now 21 MIPS faculty that are full members of the program with many more associate members from all over campus. Many of the full members are from the Department of Radiology. The number of graduate students, MSTP students, post-doctoral fellows, research scientists, technicians, and administrative staff continues to grow and is currently approximately 150. We expect significant growth over the next 2-3 years with the new center on early cancer detection and occupancy of the space on California Avenue.

Construction of a new Molecular Imaging/Nuclear Medicine clinic is about to finish with a grand opening expected in September 2010. This new facility will consolidate all of the PET-CT and SPECT equipment and new radiochemistry facilities will be added. New cardiac and optical imaging equipment is also expected to be placed into this new clinic. We have also designed the clinic so that large animal imaging can be performed there. Research trials that combine state-of-art imaging with in vitro diagnostics (e.g., blood proteomics) should also be possible in this new facility.

We also continue to grow our industrial partnerships with key leaders in the molecular imaging community. Several projects to develop new imaging agents/strategies are underway with General Electric Research, General Electric Healthcare, Schering-Plough as well as Bayer-Schering. A new relationship with Lilly has just started. It is likely that additional industrial partners will enter into collaborative research relationships over the next several years. These will be key to help translate these new technologies from the lab to the patient bedside. Several faculty are also involved in new startup-company efforts with intellectual property from their laboratories at Stanford. These include efforts in diagnostics, small animal imaging and clinical imaging.

The Canary Center at Stanford for Cancer Early Detection celebrated its first year anniversary in June 2010. The mission of the Canary Center, which occupies ~30,000 square feet of the building at 1501 S. California Ave, is to house and foster research programs focusing on the development of blood and imaging tests to detect early lethal types of cancer. The center represents a novel alliance between the Canary Foundation, the Department of Radiology, the Canary Center, and the School of Medicine. The Center also actively fosters intellectual and programmatic alliances with the Schools of Engineering & Humanities and Sciences.

The Center mission is based on the striking association between early cancer diagnosis and improved survival rates. Chances of survival are far greater when cancer is detected in its earliest stages while still localized to the organ of origin and amenable to treatment. To optimize the detection of cancer at this stage, the Center is taking a binary approach including: 1) identifying blood biomarkers that can be detected by simple blood screening tests and developing technologies for these biomarkers, and 2) developing molecular imaging tests to confirm and localize early cancerous lesions. The extraordinary technical challenges associated with this dual strategy include the refinement of molecular imaging agents to specifically detect pre-invasive malignant tumors the size of a blueberry (< 5 mm). They also include the development of new treatment approaches that can reliably detect minute (<0.1 ng/ml) quantities of cancer-specific proteins released into the bloodstream by these small lesions. Cost-effective solutions are expected by applying a relatively cheap blood test followed by a more expensive imaging study, although in some cases the blood test and the imaging test will be performed concurrently. Having both tests run simultaneously should lead to a greater overall accuracy.

To accomplish these goals, the Center was specifically designed to house state-of-the-art core facilities and collaborative research programs in molecular imaging, proteomics, chemistry, and bioinformatics. The center is engaged in the design and refinement of molecular imaging agents for early detection, which then undergo preclinical testing using both in vivo and ex vivo model systems, including patient blood and tissue samples. Dr. Jelena Levi has been recruited to direct the Chemistry Core. The Molecular and Cell Biology Core works closely with both the Proteomics and Chemistry Cores to screen and refine agents that can bind cancer-specific targets in tissues and thus complements the efforts of the Chemistry and Proteomics Cores. We will also ensure that both core facilities conduct imaging tests for cancer early detection. Dr. Richard Kimura has been recruited to head the Molecular Cell Biology Core. A significant effort has been put forward over the past year to equip the Center cores and laboratories with state-of-the-art instrumentation to promote and facilitate innovative research efforts. Two new mass spectrometers are already in place and the acquisition of 1-2 more is planned.

Collaborative research efforts fostered at the Center are made possible by creating a truly multidisciplinary team of faculty members. Current faculty members focus on imaging technologies, chemistry and disease mechanisms/cell biology. Two new faculty members have been recruited and are anticipated to join the Center in the fall of 2010. These two new faculty members will bring in complementary proteomics expertise. Additionally, Canary Center research programs are actively interfacing with other facilities and programs on campus, including MIPS and CCNE-TR in order to leverage the latest developments in molecular imaging and nanotechnology into the early detection effort.

Collectively, these initiatives form a direct pipeline for the translation of early cancer detection into clinical trials and practice. A specific example of a novel molecular imaging strategy that is expected to help the goal of early cancer detection is ultrasound with targeted microbubbles. These gas filled microbubbles can be chemically coupled to targeting ligands that allow the bubbles to bind to cancer vasculature. This will allow molecular imaging using a conventional anatomic imaging strategy (ultrasound). This is expected to allow detection of tumors in the 3.5 mm range. A specific example of a novel strategy being pursued for blood biomarker detection is based on magneto-nanorays being developed as part of the Stanford CCNE-TR. This novel technology is allowing the detection of many different biomarkers at levels that are 10-100 fold better than the most sensitive ELISA tests currently available.

The original Center for Cancer Nanotechnology Excellence (CCNE) was established in 2006 with funding from the National Cancer Institute (NCI). The Stanford CCNE-TR, based in the Radiology Department, is a consortium of public and private universities, non-profit institutions, foundations, and for-profit corporations. It brings together scientists from different disciplines including chemistry, materials science, engineering, radiology, molecular biology, cancer biology, and oncology. Most of our CCNE-TR members had never previously collaborated. These new collaborations have resulted in a remarkable scientific team that has come together to help fuel the center and its relatively rapid progress. In its fourth year of funding, the CCNE-TR continues as a highly interactive and successful center that develops novel diagnostic cancer nanotechnologies and has made significant advancements in moving the center’s nano-medical discoveries towards clinical translation.

Figure 1 signifies the strength of these collaborations as measured by our scientific output. All involved in this CCNE are highly committed to the success of this program. The level of productivity as shown in Figure 1 is a strong testament to the dedication of our faculty, staff, students, and post-doctoral fellows. Our center is constantly growing both in its research scope and also in its physical boundaries thanks to the significant investment in our center from Stanford University, the School of Medicine, the Stanford Cancer Center, the Radiology Department, the Lucas Foundation, and the National Cancer Institute (NCI). We believe that nanoscience applied to cancer research is a critical approach for the elimination of cancer and, thus, are convinced that nanotechnology will make a significant impact on cancer diagnosis and management in potentially revolutionary ways. In vitro diagnostics used in conjunction with in vivo molecular imaging can markedly impact future cancer patient management by providing a synergy that neither strategy alone can offer.

Nanotechnology can significantly advance both in vitro diagnostics through proteomic and circulating tumor cell nanosensors and in vivo diagnostics through nanoparticles for molecular imaging. The areas of earlier cancer detection and the prediction and monitoring of response to anti-cancer therapies are both very important applications of nanotechnology with near-term clinical translational potential. Through an integrated, cohesive five-year plan that builds on our first four years of significant progress, we are pursuing the use of in vitro protein nanosensors and in vivo nanoparticles for next generation molecular imaging.

The CCNE-TR is committed to clinical translation of our nanotechnologies by leveraging our large network of clinical trials and patient samples at USC, FHICRC, UCLA, Cedars Sinai Medical Center, and Stanford. Towards this, we are working on clinical translation of our technologies via our research and developments for in vitro proteomic nanosensors and in vivo molecular imaging.

Very recently, we received news that our new Center for Cancer Nanotechnology Excellence and Translation (CCNE-T) will also be supported by NCI. This program will continue expanding the work of the CCNE-TR with a concerted focus to move our nanotechnology successes into clinical use. For approximately two years both centers will continue while the CCNE-TR phases out and the CCNE-T becomes firmly established. In this highly interdisciplinary center, faculty from radiology, bioengineering, materials science, oncology, and numerous other departments collaborate in an effort to use nanotechnology to improve cancer-patient management. For the new CCNE (CCNE-T) we engage faculty from UCLA, UC Berkley, USC, and MIT to collaborate with our Stanford faculty. Key investigators on this U54 include Drs. David Agus, Demir Akin, Jonathan Berek, Alice Fan, Dean Felsher, Sanjiv Sam Gambhir (PI), Luke Lee, Paul Marusich, Ed Myers, David Paik, Steve Quake, Jianhong Ruo, Brian Rutt, Robert Sinclair, Mark Stolowitz, Mary Tang, Shan Wang (Co-PI), Irv Weissman, Robert Wilson and Anna Wu.

The primary focus of the CCNET is to develop and use nanotechnology for earlier cancer detection and to monitor response to anti-cancer therapy. This NCI-funded center supports projects focused on: (a) the production of next generation smart nanoparticles; (b) magnetonanotechnology for blood proteomics and cell sorting; (c) multiple nano-platforms to interrogate single circulating tumor cells; (d) molecular imaging with photoacoustics and nanoparticles and monitoring response to therapy using imaging and magnetono-sensors.
Clinical Translation
In this new section for the Lucas Report, we highlight clinicians who lead their own research programs and who have developed strong collaborations with basic scientists in the Lucas Center. It is through these collaborations that we are able to influence change in the clinical environment and present advanced imaging solutions for the benefit of our patients and patients worldwide. It is also through such clinical collaborations that our trainees begin to understand the needs and limitations of clinical imaging. We encourage our trainees to enhance their training experience through mentoring opportunities with clinical scientists. Each year we will highlight clinical faculty in this section to recognize our commitment to translating research concepts into clinical use.

**Bruce Daniel, MD, Associate Professor of Radiology**
Chief of Breast MRI Service

Dr. Daniel is interested in new MRI techniques for imaging the breast. He is also interested in MR-guided interventions for breast and for prostate cancer. Through his research interests, Dr. Daniel has developed collaborations with several of our Lucas Center scientists and has been instrumental in introducing new imaging techniques into everyday clinical use. Techniques spawned from this research have been used over the last 12 years to image thousands of patients with known or potential breast cancer. These advanced breast imaging techniques continue to be used everyday at Stanford. These include 3D spiral MRI with dual slab excitation, temporal sensitivity encoding acceleration, and independent slab phase modulation for ultra-fast 3 T dimensional dynamic contrast-enhanced MRI, as well as high resolution 3D MRI with water-selective spectro-spatial excitation. Ongoing research into ultra-high resolution MR imaging and methods to image breast cancer without injecting contrast material hold great promise for clinical translation in the future. In interventional MRI, Dr. Daniel has performed several hundred MR-guided procedures and MR-guided cryoablation, all of which use pulse sequences and other techniques developed at the Lucas Center. Other translational research areas include the development of miniaturized MR-compatible robotics.

**Nancy Fischbein, MD, Associate Professor of Radiology**
Neuroradiology Section

Dr. Fischbein, a neuroradiologist with a particular focus on head and neck imaging as well as imaging of patients with acute neurological problems such as ischemic stroke and brain hemorrhage, has developed numerous collaborations with basic science faculty in the Lucas Center. Dr. Fischbein has collaborated with faculty and post-doctoral scholars at the Lucas Center to improve the diffusion-weighted imaging (DWI) assessment of cholestoma at with PROPELLER and RS-EPI techniques. She has also assisted in the investigation of new techniques for diffusion and perfusion, such as SENSE/GRAPPA and ASL, and their applications to acute neurological illness. These collaborations provide a critical link that allows us to translate advanced MR imaging probes into daily clinical use.

**Garry Gold, MD, Associate Professor of Radiology**
Musculoskeletal Section

Dr. Gold, who is PI on an NIH-funded R01 for the study of osteoarthritis, an Arthritis Foundation grant, and a multi-investigator industry funded project to develop advanced MR applications, collaborates daily through his research with Lucas Center faculty. Through his research and basic science collaborations, Dr. Gold has been able to introduce a number of new solutions for musculoskeletal imaging into clinical use. These include improved MR imaging around metallic implants, isotropic 3D imaging, and sodium MRI for detection and characterization of osteoarthritis. Dr. Gold’s background and training in Electrical Engineering and as a practicing radiologist makes him an ideal collaborator for faculty, postdocs, and graduate students who are interested in discussing and understanding biomedical imaging limitations and requirements for clinical applications.

**Robert Herfkens, MD, Professor of Radiology**
Associate Chair for Clinical Technology, and Director of MRI, Destination Digital (PADS); Co-director of PET/CT

Dr. Herfkens combines his high technology interests with his clinical skills and leadership in MRI and CT. Through Dr. Herfkens’ efforts as Associate Chair for Clinical Technology, the Department of Radiology has transformed its analog film environment to a paperless digital department. In addition to his technology interests, Dr. Herfkens’ research interests include cardiovascular imaging with CT and MRI, utilizing fast imaging techniques for physiologically based evaluation. He works closely with cardiovascular surgery and cardiology to provide innovative tools for improved clinical evaluation of patients with cardiovascular disease.

**Andrew Quon, MD, Assistant Professor of Radiology**
Nuclear Medicine Section (MIPS)

Dr. Quon, with expertise in multimodality fusion imaging, has given presentations and received awards at major Radiology and Nuclear Medicine conferences for his work on PET/CT imaging. His research with molecular imaging scientists in the Lucas and Clark centers provides opportunity to introduce new imaging probes into clinical use. Dr. Quon’s current projects include: i) evaluation of the radiotracer NaF for orthopedic disease; ii) evaluation of 18F-FDE, a thymidine analog, for post-therapy monitoring of diffuse large B cell lymphoma; iii) a pilot study using the novel radiotracer 18F-3FU to assess modulation of 5FU receptors by bevacizumab; and iv) comparison of the effects of regadenoson and adenosine on myocardial blood flow using 13NH3 PET.

**Shreyas Vasanawala, MD, PhD, Assistant Professor of Radiology**
Pediatric Radiology Section (Lucile Packard Children’s Hospital)

Dr. Vasanawala is PI on an NIH-funded research program that focuses on reducing exam time in pediatric MR imaging. As children cannot tolerate long exams, they are often scanned under anesthesia or subjected to the ionizing radiation of CT scans. Dr. Vasanawala works closely with Lucas Center physicists and engineers and, through his funded research and collaborations, has begun to realize MR imaging solutions that address his goal of improving imaging for children. These efforts, in collaboration with Dr. Brian Hargreaves, include developing novel pediatric-specific hardware to speed image acquisition. In collaboration with Dr. Marcus Alley, Dr. Vasanawala also develops novel MRI pulse sequence and image reconstruction approaches for faster more patient-friendly MRI to image congenital heart disease. When the hardware and software approaches are combined in synergistic fashion, comprehensive cardiac MRI examination times may be reduced from over one hour to less than ten minutes.

**Gregory Zaharchuk, MD, PhD, Assistant Professor of Radiology**
Neuroradiology Section

Dr. Zaharchuk is PI on two projects: an NIH-funded R01 evaluating arterial spin labeling (ASL) to detect venous imaging of multiple sclerosis.

**Graham Sommner, MD, Professor of Radiology**
Body Imaging Section

Dr. Sommner has worked closely with a number of Lucas Center faculty over the past 20 years, pursuing advanced processing techniques for CT and MR data. He has also collaborated on NIH-funded studies involving the evaluation of renal function and structure with MRI, and studies of prostate and pancreatic tumor ablation under MRI guidance. These collaborations have led to several important areas of clinical translation. Advanced 3D processing of CT data developed in conjunction with Lucas faculty has led to the development of 3D CT urography, an advanced GU imaging technique developed at Stanford, which has been adapted throughout the world. MRI renal functional research has led to entirely new MRI applications in renal MRI and in the evaluation of renal transplants and pediatric kidneys. Collaborative work on prostate ablation has led to the development of devices ideally suited for prostate tumor (BPH, cancer) ablation under MRI guidance. Clinical studies using these technologies are now in progress.

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Research Faculty and Personnel
Radiology Research Faculty, Staff, and Students

Faculty & Staff

Our group photo represents approximately half of the Radiology research personnel found in various locations on the medical school campus.

Faculty

- Lucas Annual Report 2010
- Radiology Research Faculty, Staff, and Students
- Faculty & Staff Trainees
- Scientific Staff
- Visitors
- Graduate Students

Administrative & Support Staff

- Wei Xiong
- Jean Stevens
- Susan Singh
- Judy Schwimmer, MBA, MA
- Monique Schareck, MHA
- Billie Robles, BS
- Lanzie Rivera
- Patricia Riley
- John Reuling
- Kala Raman, MS
- Donna Niernberger, RN
- Teresa Newton, BA
- Susan Kopiwoda, MS, MPH
- Joe Hubbard, BS
- Mandalay Ka, BA
- Susan Kevorkian, MS, MPH
- Marlye Lesmer
- John Mendoza
- Amy Morris, BA
- Terence Newton, BA
- Donna Nienhuis, RN
- Kala Raman, MS
- John Reading
- Patricia Riley
- Laniu Rivera
- Billie Rubles, BS
- Jazie Ruiz, PhD
- David Rusd
- Monique Schramm, MHA
- Judy Schlimmer, MBA, MA
- Susan Singb
- Jean Stevens
- Wei Xiong

Scientific Staff

- Demi Akin, DVM, PhD
- Marcus Alley, PhD
- Sunny Bhandari, MS
- Wendy Baumgartner, VRT, LAVT
- Rhema Bergeron, BS
- Nicole Brandon, MD
- Thomas Brown, PhD
- Carmel Chu, PhD
- Edin Chu, PhD
- Dance Chu, MS
- Frederic Chi, PhD
- Gary Chi, PhD
- Anandush Dharubahan, MS
- David Dick, PhD
- Alaina D’Swarn, PhD
- Ailsa Fu, PhD
- Aramutti Gandguy, PhD
- Steven Gain, MS
- Andrew Gentles, PhD
- Gayatri Ghoshchian, PhD
- Fangchi Hui, PhD
- Fangchi Hui, PhD
- Pan Hertz, RVT
- Samantha Holdsworth, PhD
- Linda Horst, RT
- Fangjun Jia, PhD
- Linda Horst RT
- Samantha Holdsworth, PhD
- Ailsa Fu, PhD
- Ailsa Fu, PhD
- Pan Hertz, RVT
- Samantha Holdsworth, PhD
- Linda Horst, RT
- Fangjun Jia, PhD
- William Johnson, RT, CV
- Richard Kimme, PhD
- Moritz Kircher, PhD
- Kronish Kode, BS
- Kishan Kodubala, MS
- Andrea Koo, PhD
- Andrew Korov, MD
- Brian Kucute, PhD
- David Kudlow, PhD
- Lisa Kudlow, PhD
- Michelle Kudman, PhD
- Jesse Kuznetzov, PhD
- Sonal Khan, PhD
- Seb-Rajendrakoth Kothapak, PhD
- Feng Lan, PhD

Visiters

- Chien-Huei Ahn, PhD
- Byong-Chul Ben Ahn, MD, PhD
- Colin Carpenter, PhD
- Andreas Fischbach, MSc
- Hayk Greenpan, PhD
- Jian Jiang
- Baris Kandemir
- Daniel Koppinger, PhD
- Honggang Liu, PhD
- Tanik Massoud, PhD
- Christine Niebler, PhD
- Carsten Nielsen, MSc
- Chang-Hyun Oh, MD
- Catherine Panny
- Shihuo Qi, PhD
- Yi Yu Song, PhD
- Zhengming Xiang, MD, PhD
- Zhaohong Zhang, PhD

Research Faculty and Personnel

<table>
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<tr>
<th>Faculty</th>
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New Research Faculty

Heike Daldrup-Link, MD, Acting Associate Professor of Radiology, Lucile Packard Children's Hospital

Dr. Daldrup-Link, who was previously an Associate Professor of Radiology and Pediatrics at the University of California, San Francisco, (UCSF) and joined the Stanford Department of Radiology September 1, 2010. She earned her medical degree from the University of Munster, Germany, in 1994 and completed a radiology residency and fellowship in pediatric radiology and molecular imaging at the Technical University of Munich, Germany, in 2004. While at UCSF as a research fellow, Dr. Daldrup-Link studied uses of contrast media for image enhancement. She currently leads several projects including “Monitoring of Stem Cell Engraftment in Atherosclerotic Aorta with MR Imaging” (R01); and “Novel Imaging Approach to Monitor Chondrogenic Differentiation of iPSC Cells” (R21). Dr. Daldrup-Link is also a practicing radiologist with an interest in pediatric oncology, molecular imaging, general pediatric radiology, and teaching. Along with other professional memberships, Dr. Daldrup-Link is also a member of the board of directors of the Society for Pediatric Radiology (SPR) and a permanent member of the NIH Cancer Immunology and Immunotherapy Study Section. Her recently published textbook, *Essentials of Pediatric Radiology: A Multimodality Approach*, provides a concise overview of both basic and complex topics encountered by pediatric radiologists in their daily practice.

Michael Zeineh, MD, PhD, Assistant Professor of Radiology, Neuroradiology Section

Dr. Michael Zeineh joined the Department as an Assistant Professor in the Neuroradiology Section on September 1, 2010. After completing his undergraduate training at California Institute of Technology, Dr. Zeineh completed an MD & PhD program at the University of California, Los Angeles (UCLA). His PhD work focused on using high-resolution structural and functional MRI to investigate the neural underpinnings of memory formation and retrieval. While a radiology resident at Stanford, he received a two-year Radiological Society of North America (RSNA) Research Fellowship to pursue high-field imaging in neuroradiology. Dr. Zeineh was also awarded General Electric (GE) seed funding to support his ongoing research as a neuroradiology fellow. His research is driven by the challenge to noninvasively characterize the microscopic pathology underlying neurologic disease, particularly those with a significant component of pathology invisible to conventional imaging methods. Dr. Zeineh utilizes high-field MRI, advanced susceptibility based processing, and diffusion tensor imaging with the following applications: 1) MR imaging and characterization of amyloid plaques in the brains of Alzheimer’s patients; 2) early in vivo biomarker imaging for Alzheimer’s disease; 3) improved imaging of seizure foci in localization-related epilepsy; 4) identifying network derangements and microstructural alterations in Parkinson’s disease; 5) imaging biomarkers for multiple sclerosis with quantitative imaging (measurement of myelin content); and 6) general applications of ultra-high field MRI for neurologic disease.

Jafi Lipson, MD, Assistant Professor of Radiology, Breast Imaging Section

Dr. Jafi Lipson joined the Department August 1, 2010, as an Assistant Professor in the Breast Imaging Section. A graduate of Harvard College, UCSF School of Medicine, and UCSF Radiology Residency, Dr. Lipson completed her medical training as a Stanford Breast Imaging Fellow in June, 2010. Her research interests include medical informatics applications in breast imaging and breast radiologic-pathologic correlation. Her prior research activities focused on CT radiation dose and the associated risk of cancer. As a T32 research fellow and mentored by Dr. Rebecca Smith-Bindman, Dr. Lipson conducted a study of four Bay Area hospitals in which she reviewed 1,200 CT examinations and dose reports, estimated the effective dose from each examination, and calculated the associated risk of cancer attributable to that effective dose. Her study culminated in an article entitled “Radiation Dose Associated with Common Computed Tomography Examinations and the Associated Lifetime Attributable Risk of Cancer” (Arch Intern Med. 2009 Dec 14;169(22):2078-86), which is one of only a few articles that have raised national attention regarding the issue of medical radiation and the need for clinical practice guidelines to track and reduce dose. Dr. Lipson’s current projects include the creation and evaluation of an Annotated Breast Map, which is an automated, WIKI-form summary of a patient’s breast history; integration of the BI-RADS lexicon for mammography, ultrasound, and MRI into the RSNA RadLex lexicon; and classification and quantification of dynamic contrast enhanced breast MRI patterns of response to poly (ADP-ribose) polymerase (PARP) inhibitor therapy in the neoadjuvant treatment of triple-negative and BRCA-associated breast cancer.

New Clinical Instructors

We also welcome six new Clinical Instructors whose primary and critical role is to provide excellence in radiological clinical care, teaching, and institutional service appropriate to their training and clinical interest areas. Please welcome our new clinical instructors whose commitment and dedication to patient care are highly valued and provide critical service and discipline in all clinical areas of the Department of Radiology.

Bo Yoon Ha, MD, Neuroradiology
Medical Education: Seoul National Univ., South Korea

John Chang, MD, PhD, Body Imaging
Medical Education: Univ. of Illinois at Urbana-Champaign, IL

Arvind Souik, MD, Pediatric Imaging
Medical Education: Univ. of California, Davis

Hedieh Eslamy, MD, Pediatric Imaging
Medical Education: Tehran Univ. of Medical Sciences, Iran

Payam Massaband, MD, VA Radiology
Medical Education: Univ. of Southern California, Keck School of Medicine

Martin Laufer, MD, VA Radiology
Medical Education: Univ. of California, San Diego School of Medicine

SNM Scientist Award, and a Stanford Cancer Center 2009 Developmental Cancer Research Award in Translational Science. With his interests, background, and training, Dr. Iagaru will find many opportunities for collaboration, teaching, and introducing his successful research into the clinical practice of Nuclear Medicine.
### Faculty Awards

<table>
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<tr>
<th>Recipient</th>
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<tr>
<td>Scott Atlas, MD</td>
<td>Societade de Radiologia de Pernambuco in Recife, Brazil award Dr. Atlas for his “important contributions to radiology and to education in Brazil”</td>
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<tr>
<td>Roland Bammer, PhD</td>
<td>John Calley Award for Best Basic Science Research Paper at the 2010 Society for Pediatric Radiology (SPR), “3D SAP-EPI in Motion-Corrected Fast Susceptibility Weighted Imaging (SWI)” (Roland Bammer, PhD, Samantha J Hislopworth, PhD, Stefan Skare, PhD, Kristen Yee, MD, Patrick D Burns, MD)</td>
</tr>
<tr>
<td>Roland Bammer, PhD</td>
<td>2010 John Calley Award for Best Basic Science Research Paper at the 2010 Society for Pediatric Radiology (SPR), “TI-Weighted 3D SAP-EPI for Use in Pediatric Imaging” (Roland Bammer, PhD, Samantha J Hislopworth, PhD, Stefan Skare, PhD, Kristen Yee, MD, Patrick D Burns, MD)</td>
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<tr>
<td>Kim Butts Pauly, PhD</td>
<td>Elected to the Board of the International Society for Therapeutic Ultrasound</td>
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<tr>
<td>Bao Do, MD</td>
<td>RSNA Certificate of Merit: “RadIF: An NLP-generated Teaching File” (Bao Do, MD, Aya Kamnaya, MD, Andrew Wu, MD, Sandip Biswal, MD)</td>
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<tr>
<td>Bao Do, MD</td>
<td>RSNA Certificate of Merit and Selected for Radiographics: “XRAYHEAD MSK ONLINE: A Radiology Teaching File Based on RSNA’s RadLex” (Andrew Wu, MD, Kate Stevyns, MD, Sandip Biswal, MD, Christopher Beaulieu, MD, PhD, Garry Gold, MD, Daniel Rubin, MD)</td>
</tr>
<tr>
<td>Rebecca Fabing, PhD</td>
<td>Media Coverage: “Mummies and Medicine: Scanner sees past Veil of Time” Front Page, San Francisco Chronicle, August 21, 2009</td>
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<tr>
<td>Michael Fedeler, MD</td>
<td>2010 Society of Gastrointestinal Radiologists (SGR) Walter B. Cannon Medal Award</td>
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<tr>
<td>Sanjiv Sam Gambhir, MD, PhD</td>
<td>American College of Cardiology Foundations Parnely Prize</td>
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<tr>
<td>Sanjiv Sam Gambhir, MD, PhD</td>
<td>Endowed Professorship - Virginia and D. K. Ludwig Professor for Clinical Investigation in Cancer Research</td>
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<tr>
<td>Sanjiv Sam Gambhir, MD, PhD</td>
<td>Radiological Society of North America (RSNA) Outstanding Researcher Award</td>
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<tr>
<td>Gary Glover, PhD</td>
<td>University of Minnesota’s Outstanding Achievement Alumni Award given for his “outstanding contributions in refining medical magnetic resonance technologies to improve patients’ lives and expanding our knowledge of biomedical imaging”</td>
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<td>Gary Gold, MD</td>
<td>American Society of Biomechanics 2009 Clinical Biomechanics Young Investigator Award (Senior Author), “Using real-time MRI to quantify altered joint kinematics in subjects with patellofemoral pain and to evaluate the effects of a patellar brace or sleeve on joint motion”</td>
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<td>Gary Gold, MD</td>
<td>GE Healthcare Thought Leadership Award</td>
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<td>Andrei Iagaru, MD</td>
<td>2009 Alavi-Mandell Award for the Journal of Nuclear Medicine publication: “A Novel Strategy for a Cocktail 18F Fluoride and 18F FDG PET/CT Scan for Evaluation of Malignancy: Results of the Pilot Phase Study”</td>
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<tr>
<td>Andrei Iagaru, MD</td>
<td>2010 Society of Nuclear Medicine (SNM)/American College of Nuclear Medicine (ACNM) Best Essay Award: “Combined 18F NaF and 18F FDG PET/CT Scan for Evaluation of Malignancy: Beyond the Pilot Study”</td>
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<tr>
<td>Andrei Iagaru, MD</td>
<td>Norman D. Poe Memorial Scholarship Award, presented at the 34th Western Regional SNM annual meeting</td>
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<td>Delma Ikeda, MD</td>
<td>Visiting Professor, Kansas City Radiological Society</td>
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<td>Aya Kamnaya, MD</td>
<td>Finalist, New Investigator Award, American Institute of Ultrasound in Medicine, San Diego, CA March 25, 2010, 2010</td>
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<td>Nischita Kohary, MD</td>
<td>Invited member of 6 US interventional radiologists to create the interventional radiology component of the new American Board of Radiology certifying examination for diagnostic radiology</td>
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<td>Craig Levin, PhD</td>
<td>Physics in Medicine and Biology Featured Article by Editors of Institute of Physics: “Bayesian reconstruction of photon interaction sequences for high-resolution PET detectors”</td>
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<td>Margaret Lin, MD</td>
<td>Clinical Educator of the Year - awarded by Stanford Radiology graduating Residents</td>
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<td>Sandy Napel, PhD</td>
<td>Elected to the College of Fellows of the American Institute for Medical and Biological Engineering (AIMBE)</td>
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<td>Norbert Pelz, ScD</td>
<td>Elected to the position of Third Vice President of the Radiological Society of North America (RSNA)</td>
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<td>Peter Paullius, MD</td>
<td>Association of University Radiologists (AUR)-Philips Academic Faculty Development Program</td>
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<tr>
<td>Daniel Rubins, PhD</td>
<td>RSNA Certificate of Merit: “J-Viewer: A Free Javascript Library for Creating Web (and iPhone) Teaching Files with Simple PACS Functionality” (Bao Do, MD, Nishant Parekh, Andrew Wu, MD, Sandip Biswal, MD, Daniel Rubin, MD)</td>
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<td>Brian Ratt, MD</td>
<td>Named a Fellow of the American Institute for Medical and Biological Engineering</td>
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<td>Daniel Sce, MD, PhD</td>
<td>Western Angiographic and Interventional Society, President 2010</td>
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<td>Shreyas Vasanawala, MD, PhD</td>
<td>ISMRM-GE Healthcare 2010 Thought Leader Award: innovation in pediatric MRI</td>
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<td>Jaegun Willmann, MD</td>
<td>2009 Radiology Editor’s Recognition Award with Distinction</td>
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<td>Jaegun Willmann, MD</td>
<td>2009 Walter Frederich Award of the German Society of Radiology for outstanding research in Radiology</td>
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<tr>
<td>Jaegun Willmann, MD</td>
<td>2010 Roscoe E. Miller Award for best paper presentation at the Annual Meeting of the Society of Gastrointestinal Radiology: “Monitoring Anti-Angiogenic Therapy in Colon Cancer with Molecular Ultrasound and a Novel Clinically Translatable Ultrasound Contrast Agent”</td>
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### Trainee Awards

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<tr>
<td>Priti Balchandani, PhD</td>
<td>2010 International Society for Magnetic Resonance in Medicine (ISMRM) Junior Fellow award</td>
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<td>Pat Baus, MD</td>
<td>National Finalist for the 2010-11 White House Fellowship Program</td>
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<tr>
<td>Rachel Bitton, PhD</td>
<td>2010 International Society of Magnetic Resonance in Medicine (ISMRM) Student Stipend</td>
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<tr>
<td>Rachel Bitton, PhD</td>
<td>California Breast Cancer Research Program Grant: “MRI-guided Focused Ultrasound in Breast Cancer Treatment”</td>
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<tr>
<td>Abdelkader Bousliman, PhD</td>
<td>Trainee Award: Postdoctoral Fellowship from the Swedish Research Council</td>
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<td>Hongguang Liu, MD, PhD</td>
<td>Molecular Imaging Center of Excellence (MICoE) Young Investigator Award: “Noninvasive molecular imaging of radioactive tracers using optical imaging techniques”</td>
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<td>Andrew Lee Bio-X Graduate Student Fellowship Award</td>
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<td>Frances Lau, PhD</td>
<td>California Breast Cancer Research Program Grant: “Noninvasive imaging of Cardiac Stem Cells in a Large Animal Model”</td>
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<td>Ealgoo Kim, PhD</td>
<td>Trainee Award: 2-year Postdoctoral Scholarship from TLL, Inc., Seoul, South Korea</td>
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<td>Stephenie Curr, MD</td>
<td>Society of Interventional Radiology (SIR) Foundation Dr. Constantin Cope Medical Student Annual Scientific Meeting Research Award: “Common Ilia Visc Diam and Risk of Deep Venous Thrombosis”</td>
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<td>Bao Do, MD</td>
<td>RSNA Trainee Research Prize for mentored resident: “A Natural Language Processor to Detect Uncertainty and Recommendations in Radiology Reports”</td>
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<td>Christine Draper, PhD</td>
<td>Society of Nuclear Medicine's Correlative Imaging Council/Walter Wolf award: “Correlation between MRI and and NaF PET/CT in Patients with Pancreatic Kneez Pain”</td>
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<td>Hua Fan-Minogue, MD, PhD</td>
<td>American Association for Cancer Research (AACR)-Merck Scholar-in-Training Award</td>
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<tr>
<td>Fan-Minogue, Hua</td>
<td>Travel Fellowship award from the Helena Anna Hensel Gabe Young Women in Science Fund to attend the American Association for Cancer Research (AACR) 101st Annual Meeting 2010</td>
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<tr>
<td>Alex Grant, MS</td>
<td>Stanford Bio-X Graduate Student Fellowship to support his research in molecular imaging</td>
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<td>Yi Gu, PhD</td>
<td>Trainee Award: Attend the 2009 IEEE Medical Imaging Conference, Orlando FL, October 25-31</td>
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<tr>
<td>Benjamin Hackel, PhD</td>
<td>American Cancer Society/Curu Foundation Early Detection of Cancer Postdoctoral Fellowship: “Novel High Affinity Protein Scaffolds for Molecular Imaging of Tumors”</td>
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<td>Albert Hsiao, MD, PhD</td>
<td>Society of Computed Body Tomography and Magnetic Resonance Carm Lusk Award: “Quantitative assessment of pediatric pulmonary arterial flow dynamics with time-resolved volumetric phase-contrast”</td>
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<td>Albert Hsiao, MD, PhD</td>
<td>John Kirkpatrick Young Investigator Award: “Volumetric Flow Assessment in Congenital Heart Disease with 4D Flow MRI”</td>
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<td>Shijun Hu, PhD</td>
<td>American Heart Association Postdoctoral Fellowship Award: “Transplantation and imaging of Novel Cardiac Stem Cell Therapy”</td>
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<tr>
<td>Ealpyo Kim, PhD</td>
<td>Trainee Award: 2-year Postdoctoral Scholarship from TLL, Inc., Seoul, South Korea</td>
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<tr>
<td>Frances Lau, PhD</td>
<td>California Breast Cancer Research Program (CBCRP) Award: “Electronics for High Resolution Breast-Dedicated PET”</td>
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<td>Andrew Lze</td>
<td>RSNA Research &amp; Education Foundation's Research Medical Student Grant, “Noninvasive Imaging of Cardiac Stem Cells in a Large Animal Model”</td>
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<td>Andrew Lze</td>
<td>Bio-X Graduate Student Fellowship Award</td>
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<td>Anderson Neuwahl</td>
<td>1st Place Best Poster award: “High Resolution Breast MRI” at the 2nd annual Center for Biomedical Imaging at Stanford (CBSIS) Symposium</td>
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<tr>
<td>Peter Okkot</td>
<td>2009 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC) Best Student Paper Award: “Cross-strip capacitive multiplexing and electro-optical coupling for silicon photomultiplier arrays for PET detectors”</td>
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<tr>
<td>Peter Okkot</td>
<td>Trainee Travel Award: 2009 Society of Nuclear Medicine Meeting</td>
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<tr>
<td>Peter Okkot</td>
<td>2009 Bio-X Stanford Interdisciplinary Graduate Fellowship</td>
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<tr>
<td>Hao Peng, PhD</td>
<td>Trainee Travel Award: 2009 IEEE Medical Imaging Conference, Trainee Travel Award: 2009 World Molecular Imaging Conference</td>
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<tr>
<td>Guillem Prats, PhD</td>
<td>American Association of Physicians in Medicine (AAPM) Research Seed Grant: “Using X-ray activatable nanophosphors for anatomical and molecular imaging”</td>
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<tr>
<td>Guillem Prats, PhD</td>
<td>Trainee Travel Award: 2009 Society of Nuclear Medicine Meeting</td>
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<tr>
<td>Guillem Prats, PhD</td>
<td>Dean’s Postdoctoral Fellowship at Stanford University School of Medicine: “X-ray Luminencecence Computed Tomography”</td>
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<tr>
<td>Rebecca Rakower-Penner, MD, PhD</td>
<td>2010 Norman Blank Award for the outstanding medical student in radiology</td>
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<tr>
<td>Rebecca Rakower-Penner, MD, PhD</td>
<td>Finalist for the Young Investigators’ W.S. Moore Award in clinical sciences</td>
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<tr>
<td>Gang Ren, PhD</td>
<td>“Journal of Nuclear Medicine’s Top 3 Basic Science Papers of 2010: “A 2-Helix Small Protein Labeled with 64Ga for PET Imaging of HER2 Expression”</td>
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<tr>
<td>Ying Ren, PhD</td>
<td>2010 Stanford Dean’s Fellowship Award: “Evaluation of Activity and Remission of Inflammatory Bowel Disease by Molecular Targeted Microbubble-Enhanced Ultrasound in a Mouse Colitis Model”</td>
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<tr>
<td>Virginia Spannuzuki, PhD</td>
<td>Axa Group Postdoctoral Fellowship: “1mm Resolution Position Emission Tomography for Enhanced Molecular Breast Cancer Imaging”</td>
</tr>
<tr>
<td>Virginia Spannuzuki, PhD</td>
<td>Trainee Travel Award: 2009 IEEE Medical Imaging Conference</td>
</tr>
<tr>
<td>Virginia Spannuzuki, PhD</td>
<td>Trainee Travel Award: 2009 Society of Nuclear Medicine Meeting</td>
</tr>
<tr>
<td>Stefan T Skare, PhD</td>
<td>John Caffey Award for Best Basic Science Research Paper at the 2010 Society for Pediatric Radiology (SPR) “High-Resolution Motion-Corrected Diffusion Tensor Imaging (DTI) in Infants” (Stefan T Skare, PhD, Samantha J Holdsworth, PhD, Kirsten Yeom, MD, Patrick D Barnes, MD, Roland Bammer, PhD)</td>
</tr>
<tr>
<td>Daniel Sze, MD, PhD</td>
<td>Featured abstract, Society of Interventional Radiology Annual Meeting 2010</td>
</tr>
<tr>
<td>Arne Vandenbroeke, PhD</td>
<td>Postdoctoral Fellowship from the DoD Breast Cancer Research Program (BCRP): “Commissioning and characterization of the worlds first 1 mm 3 resolution clinical PET camera”</td>
</tr>
<tr>
<td>Arne Vandenbroeke, PhD</td>
<td>Trainee Award: 2009 IEEE Medical Imaging Conference</td>
</tr>
<tr>
<td>David Wang, MD</td>
<td>Travel Award: Radiological Sciences of North America (RSNA) Young Investigators in Molecular Imaging, Travel Award: World Molecular Imaging Conference</td>
</tr>
<tr>
<td>Andrew Quon, MD</td>
<td>Awarded the SSRM 2010 Walter Wolf Young Investigator Award</td>
</tr>
<tr>
<td>Maurice Zisman, MD</td>
<td>Awarded a Medical Scholars Scholarship for “Monitoring Anti-VEGF Therapy Using [18F]F-Fluorouracil PET/CT Imaging”</td>
</tr>
</tbody>
</table>
The Department of Radiology at Stanford University offers qualified individuals a unique research opportunity through our Advanced Techniques for Cancer Imaging and Detection Program, which began its 18th year of training on March 1, 2010. The goal of our program is to provide MD and PhD research fellows training in cancer-related imaging research. Fellows have the opportunity to work with our world-renowned faculty who are committed to sharing their knowledge and mentoring future leaders in radiology. Our program allows basic scientists in medical imaging (PhD) and clinical scientists (MD post-residency) to collaborate in an unparalleled environment that combines medical imaging sciences, clinical sciences, a strong cancer focus, and an institutional commitment to training academic radiologists and basic scientists in imaging science. We are currently advertising in major radiology venues to fill two open positions before February 28, 2011.

A specific aim of our training program is to position our trainees for a career in academic radiology. To date, we have graduated 30 trainees from our program. Our trainees continue to be extremely productive. We often collaborate with them in their new positions both locally and throughout the country. We are grateful to the National Institutes of Health for its recognition of the strength and success of our training program.

The Department of Radiology at Stanford University offers qualified individuals a unique research opportunity through our Advanced Techniques for Cancer Imaging and Detection Program, which began its 18th year of training on March 1, 2010. The goal of our program is to provide MD and PhD research fellows training in cancer-related imaging research. Fellows have the opportunity to work with our world-renowned faculty who are committed to sharing their knowledge and mentoring future leaders in radiology. Our program allows basic scientists in medical imaging (PhD) and clinical scientists (MD post-residency) to collaborate in an unparalleled environment that combines medical imaging sciences, clinical sciences, a strong cancer focus, and an institutional commitment to training academic radiologists and basic scientists in imaging science. We are currently advertising in major radiology venues to fill two open positions before February 28, 2011.

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Rachel Bitton, PhD, joined the Radiological Sciences Lab as an NCI fellow in March, 2008. Her research interests include photoacoustic imaging of microvasculature using high frequency ultrasound transducers, MR temperature guidance for interventional high intensity focused ultrasound therapy (HIFU), and targeted contrast agents for photoacoustic imaging and therapy. In March, Rachel was reappointed as a postdoctoral fellow working with Dr. Kim Buatta-Pauly and her focused ultrasound project. Dr. Bitton was recently awarded a two year breast cancer research award from the University of California. Her award "MRI Guided Focused Ultrasound in Breast Cancer Treatment” began on July 1, 2010 through June 30, 2011.

Moses Darpolor, PhD, joined the RSL group as an NCI fellow June, 2008. He is interested in applying multi-parametric MR and multi-modality imaging in oncology. His previous and ongoing projects include DSC-MRI in conjunction with micro-CT imaging of vascular function and morphology of brain tumor with antiangiogenic treatment; H1 decoupled 31P CSI of tumor bioenergetics to detect early response of subsequent CPT11 and flavopiridol treatment; and hyperpolarized 13C imaging to detect early tumor response to radiation therapy. Moses’ two-year appointment ended on May 31, 2010. He is now working with Professors Daniel Spidman and Lei Xing in the Department of Radiation Oncology.

Dragos Constantin, PhD, joined RSL as an NCI fellow in 2009. His research interests involve theoretical and experimental investigation of the magnetic resonance imaging integration with a medical linear accelerator to provide real-time image guidance to target temporally changing tumor anatomy, particularly for cancers in the thorax and abdomen. Dr. Constantin began his second year of training with Dr. Rachel Fahrig in February, 2010, and is working closely with faculty in the Department of Radiation Oncology.

Grace Tye, MD, joined the RSL group in July, 2009. Grace has been very active working on several cancer-related projects with faculty in the Radiological Sciences Laboratories (RLS) Molecular Imaging Program (MIPS) and the newly formed Information Sciences in Imaging at Stanford (ISI) and has attended several conferences and workshops designed to further her academic radiology career interests.

Pojman Ghanousi, MD, PhD, joined the NCI program on July 1, 2010 after graduating from the Stanford Radiology Residency Program. Pojman has a keen interest in research and has submitted a project entitled “In Vivo MRI-Guided High Intensity Focused Ultrasound Thermal Ablation of Porcine Liver” to the Radiological Society of North America Research Resident/Fellow Program. We are waiting to hear from the sponsor regarding his proposal. His mentor for this project is Dr. F. Graham Sommer who has received several NIH awards to study pancreatic and prostate cancers.

NIH/NCI T32 CA 09695
Advanced Techniques for Cancer Imaging and Detection - T32
PI: Gary M. Glazer, MD
Program Manager: Lanzie Rivera

<table>
<thead>
<tr>
<th>NCI Fellow</th>
<th>Completed</th>
<th>Current Position</th>
<th>Current Institution</th>
<th>Primary Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Strong, MD</td>
<td>1995</td>
<td>Assistant Professor</td>
<td>University of Rochester, Rochester, NY</td>
<td>Herfkens</td>
</tr>
<tr>
<td>Susan Lomineux, PhD</td>
<td>1996</td>
<td>Assistant Professor</td>
<td>Diagnostic Imaging Western Virginia Univ., Morgantown, WV</td>
<td>Glazer</td>
</tr>
<tr>
<td>Ian Chen, MD</td>
<td>1996</td>
<td>Radiologist</td>
<td>Southestern Washington Medical Center, Vancouver, WA</td>
<td>Li</td>
</tr>
<tr>
<td>Yi-Fen Yen, PhD</td>
<td>1997</td>
<td>Research Scientist</td>
<td>GE Advanced Health Care</td>
<td>Li</td>
</tr>
<tr>
<td>Gary Gold, MD</td>
<td>1997</td>
<td>Associate Professor</td>
<td>Radiology, Stanford University, Stanford, CA</td>
<td>Macovski</td>
</tr>
<tr>
<td>Bruce Daniel, MD</td>
<td>1997</td>
<td>Associate Professor</td>
<td>Radiology, Stanford University, Stanford, CA</td>
<td>Herfkens</td>
</tr>
<tr>
<td>Roger Shiffin, MD</td>
<td>1998</td>
<td>Assistant Professor</td>
<td>University of Florida, FL</td>
<td>Pelc &amp; Herfkens</td>
</tr>
<tr>
<td>Esther Yeh, PhD</td>
<td>1998</td>
<td>Clinical Fellow</td>
<td>Radiology (Neuroradiology), UCSC, CA</td>
<td>Li &amp; Napel</td>
</tr>
<tr>
<td>Steven Hato, MD</td>
<td>1999</td>
<td>Radiologist</td>
<td>Radiology Imaging Associates, Denver, CO</td>
<td>Li</td>
</tr>
<tr>
<td>Martin Blum, MD</td>
<td>2000</td>
<td>Researcher</td>
<td>PET/Nuclear Medicine, Palo Alto VA, CA</td>
<td>Jeffrey</td>
</tr>
<tr>
<td>Curtis Coulam, MD</td>
<td>2001</td>
<td>Radiologist</td>
<td>Germ Radiation Group, Boise, ID</td>
<td>Sommer</td>
</tr>
<tr>
<td>Lawrence Chow, MD</td>
<td>2002</td>
<td>Assistant Professor</td>
<td>University of Oregon, Eugene, OR</td>
<td>Sommer</td>
</tr>
<tr>
<td>Yishan Yang, PhD</td>
<td>2002</td>
<td>Research Associate</td>
<td>Radiology, Stanford University, Stanford, CA</td>
<td>Buchb Varis</td>
</tr>
<tr>
<td>Samra Giacciou, PhD</td>
<td>2002</td>
<td>Assistant Professor</td>
<td>Radiology, Stanford University, Stanford, CA</td>
<td>Buchb Varis</td>
</tr>
<tr>
<td>Charles Liu, MD</td>
<td>2003</td>
<td>Radiologist</td>
<td>La Jolla Radiology, La Jolla, CA</td>
<td>Herfkens &amp; Sommer</td>
</tr>
<tr>
<td>Susan Hobbs, MD, PhD</td>
<td>2003</td>
<td>Radiologist</td>
<td>CT Section Chief, Kaiser Permanente, Walnut Creek, CA</td>
<td>Buchb Varis</td>
</tr>
<tr>
<td>Karl Vogen, PhD</td>
<td>2003</td>
<td>Research Scientist</td>
<td>University of Wisconsin-Madison, Madison, WI</td>
<td>Buatta-Pauly</td>
</tr>
<tr>
<td>Leann Poirier, PhD</td>
<td>2004</td>
<td>Postdoctoral Fellow</td>
<td>Radiology, Stanford University, Stanford, CA</td>
<td>Glazer</td>
</tr>
<tr>
<td>John Levin, MD</td>
<td>2004</td>
<td>Radiologist</td>
<td>St. Luke’s Medical Center &amp; Clinic, Minneapolis, MN</td>
<td>Herfkens &amp; Sommer</td>
</tr>
<tr>
<td>Daniel Mangolis, MD</td>
<td>2005</td>
<td>Assistant Professor</td>
<td>Dept. of Radiology, UCLA, Los Angeles, CA</td>
<td>Jeffrey</td>
</tr>
<tr>
<td>Daniel Enzi, PhD</td>
<td>2005</td>
<td>Postdoctoral Fellow</td>
<td>University of Washington, Seattle, WA</td>
<td>Peck</td>
</tr>
<tr>
<td>Michael McDonald, PhD</td>
<td>2007</td>
<td>Research Scientist</td>
<td>NIH, Washington, DC</td>
<td>Guccione</td>
</tr>
<tr>
<td>Anthony Farahani, PhD</td>
<td>2007</td>
<td>Research Scientist</td>
<td>NIH, Washington, DC</td>
<td>Peck &amp; Hargreaves</td>
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<tr>
<td>Lewis Shin, MD</td>
<td>2007</td>
<td>Assistant Professor</td>
<td>Radiology, Stanford University, Stanford, CA</td>
<td>Herfkens</td>
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<tr>
<td>John Park, MD, PhD</td>
<td>2008</td>
<td>Assistant Professor</td>
<td>University of Southern California, Los Angeles, CA</td>
<td>Gambril</td>
</tr>
<tr>
<td>Byand Edwards, MD, PhD</td>
<td>2008</td>
<td>Scientific Researcher</td>
<td>Vanderbilt University</td>
<td>Jeffrey</td>
</tr>
<tr>
<td>Cristina Zavaleta, PhD</td>
<td>2008</td>
<td>Scientific Researcher</td>
<td>MIPS, Radiology, Stanford University, Stanford, CA</td>
<td>Gambril</td>
</tr>
<tr>
<td>Stephanie Bailey, PhD</td>
<td>2009</td>
<td>Scientific Researcher</td>
<td>Comprehensive San Diego State University/UCSD Cancer Center Partnership</td>
<td>Pelc &amp; Rivas</td>
</tr>
<tr>
<td>Rachel Bitton, PhD</td>
<td>2010</td>
<td>Postdoctoral Fellow</td>
<td>RSL, Stanford University, Stanford, CA</td>
<td>Buatta-Pauly</td>
</tr>
<tr>
<td>Moses Darpolor, PhD</td>
<td>2010</td>
<td>Postdoctoral Fellow</td>
<td>Radiation Oncology, Stanford University, Stanford, CA</td>
<td>Spidman</td>
</tr>
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</table>
The Stanford Molecular Imaging Scholars (SMIS) program is a cross-disciplinary post-doctoral training program at Stanford University that brings together 45 faculty mentors from 15 departments in the Schools of Medicine, Engineering, and Humanities and Sciences. Faculty mentors provide a diverse training environment spanning biology, physics, mathematics/biocomputation/biomedical informatics, engineering, chemistry, biochemistry, cancer biology, imaging, and medical sciences. The centerpiece of the SMIS program is the opportunity for trainees (PhD or MD with an emphasis on PhD) to conduct innovative molecular imaging research that is co-mentored by faculty in complementary disciplines. SMIS trainees also engage in specialized coursework, seminars, national conferences, clinical rounds, ethics training, and the responsible conduct of research. The three-year program culminates with the preparation and review of a mock grant in support of trainee transition to an independent career in cancer molecular imaging with the ultimate goal of training them to become leaders in the field. Thus far, 14 trainees have entered the SMIS program and 8 have completed the program.

SMIS Trainee Research Interests

Benjamin Cosgrove, PhD, joined SMIS in 2008 and is interested in developing novel molecular imaging technologies to investigate stem cell signaling-phenotype relationships. These molecular imaging technologies will be employed to generate multivariate dynamic stem cell signaling-response data collected under a wide variety of micro environmental stimuli, including tethered and soluble growth factors, in a multi-well three-dimensional hydrogel system, which will then be used to identify key intracellular signaling activities that govern specific stem cell differentiation programs. This work will be conducted under the joint supervision of Drs. Juergen Willmann and Helen Blue.

Sharon Hori, PhD, began her appointment in September 2008. Her research interests include: 1) data-driven mechanistic modeling in relation to cancer and other diseases; 2) math modeling, and parameter estimation methods; 3) the development of imaging probes and optimization of their delivery to molecular targets via an integrative imaging/kinetic and molecular modeling approach. She is working with Drs. Fritzsche, Park, and Gambhir.

Marybeth Pysz, PhD, joined Dr. Juegen Willmann’s lab in October 2008. She is interested in multi-modality imaging of pancreatic cancer and identifying new molecular targets for early detection using molecular ultrasound or PET-CT imaging. She also investigates other methods for sensitive quantification of vascular map profiles of microbubble contrast agent signals with real-time ultrasound imaging in mice using a clinical ultrasound scanner and a high-resolution ultrasound scanner for small animals. Mentors for Dr. Pysz include Drs. Willmann and Cochran.

Nicholas Conley, PhD, joined the SMIS program in 2009 after completing his PhD in Chemistry at Stanford. He is working with Drs. Matthew Scott and Jennifer Cochran on projects related to the Hedgehog signaling pathway. Hedgehog (Hh) signaling is responsible for controlling cell fates in most developing tissues and organs, as well as during many regeneration events. Unregulated activation of the Hh signaling pathway leads to birth defects and cancer.

Eric Gonzalez, PhD, joined the SMIS program in 2009 after completing his PhD in Chemistry at Stanford. He is working with Drs. Craig Levin as his primary mentor to develop a methodology of detecting and processing multiple-photon events that are typically discarded in standard PET imaging.

Jesse Jokert, PhD, who also joined the SMIS program in 2009 after completing his PhD in chemistry at University of Texas at Austin. With a background in graduate school that emphasized Raman fluorescent nanoparticles for biomarker measurement in vitro, Dr. Jokert has found the SMIS program and opportunity to expand his experience in nanotechnology a perfect fit. His primary mentor in the program is Dr. Juonghoo Rau.

R25 Program Graduates

<table>
<thead>
<tr>
<th>SMIS Fellow</th>
<th>Completed</th>
<th>Current Position</th>
<th>Institution</th>
<th>Primary Mentor</th>
</tr>
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<tr>
<td>Jill Lin, PhD</td>
<td>2009</td>
<td>Consultant</td>
<td>Begun Consulting, Emeryville, CA</td>
<td>Gambhir</td>
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<tr>
<td>Keith Hartman, PhD</td>
<td>2009</td>
<td>Senior Analyst</td>
<td>Boston Consulting Group, Washington, DC</td>
<td>Gambhir</td>
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<tr>
<td>Henry Hauber, PhD</td>
<td>2010</td>
<td>Sr. Scientific Officer</td>
<td>Univ. of New South Wales, Australia</td>
<td>Contag</td>
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<tr>
<td>Jennifer Preacher, PhD</td>
<td>2010</td>
<td>Assistant Professor, Chemistry</td>
<td>UC Irvine</td>
<td>Contag</td>
</tr>
<tr>
<td>Richard Komori, PhD</td>
<td>2010</td>
<td>Sr. Research Scientist</td>
<td>The Canary Center, Palo Alto, CA</td>
<td>Cochran</td>
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<tr>
<td>Bryan Smith, PhD</td>
<td>2010</td>
<td>Post Doctoral Scholar</td>
<td>Stanford University (MIPS)</td>
<td>Gambhir</td>
</tr>
<tr>
<td>Hua Fan Minogac, MD, PhD</td>
<td>2010</td>
<td>Post Doctoral Scholar</td>
<td>Stanford University (MIPS)</td>
<td>Felder</td>
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</table>

This is a new multidisciplinary pre-doctoral training program at Stanford University in biomedical imaging technologies. Our mission is to train the next generation of researchers in and inventors of biomedical imaging technology. Imaging technology continues to evolve at a rapid pace generating new techniques in research today that will become the standard of care for tomorrow. There is a high need for trained researchers in this field to fill positions in academia, industry, and government. Stanford University has a unique multidisciplinary research effort in biomedical imaging, spanning magnetic resonance, computed tomography and radiography, radiocelldie and optical methods for molecular imaging, ultrasound, and hybrid imaging such as Xray/ MR and PET/MR, as well as image processing and analysis for diagnostic radiation therapy, and science.

Our new training program will draw and fund students from six different degree granting programs to train in biomedical imaging technology with faculty from 8 different departments and Interdepartmental Programs. Two students would be recruited the first year and three new students would be recruited in each subsequent year. Each trainee will be funded for the initial two years of their considerably longer PhD programs, therefore, two students would be funded in the first year, five in the second year, and six in each subsequent year of the program. We are currently recruiting students to our program.
Over the past 19 years, Stanford University, Department of Radiology has constructed a world class CME program targeted to practicing physicians, academic scientists, radiology technologists, and industry-based engineers and scientists. Stanford Radiology is distinguished by an international reputation for excellence and innovation in postgraduate medical education. The Department was motivated to create such a program to fulfill the educational mission and to disseminate radiological advances. Further the benefits of the effort included an increase in reputation for the Department overall and for the individual faculty, as well as an opportunity to foster relationships globally with academic institutions and societies. The program was especially important to building the reputation and careers of our junior faculty.

The fostering of international relationships has been critical to our educational efforts. We have held biennial courses in Europe in collaboration with Universities of Munich and Erasmus, which again bring together faculty from all participating institutions. In 2007 and 2009, Stanford presented symposia in China with the Chinese Society of Radiologic Technology. Our goal is to continue to build upon these important relationships, which have already led to vital scientific collaborations.

In 2008, the Stanford School of Medicine instituted new policies regarding CME. It was determined that Stanford Radiology’s vision to conduct large, off-site and global CME courses was no longer financially or strategically viable under the new policies. Our CME program’s ability to conduct large, off-site and global CME courses was no longer financially or strategically viable under the new policies. Our CME program’s ability to conduct large, off-site and global CME courses was no longer financially or strategically viable under the new policies. Our CME program’s ability to conduct large, off-site and global CME courses was no longer financially or strategically viable under the new policies.

The research environment generates many new yet prototype designs in RF imaging coils, imaging equipment, monitoring and response devices such as button boxes, eye trackers, and electroencephalogram (EEG) recorders, and sensory devices. Evaluation of these new devices is ongoing to ensure that neither the image data, the safety of the human subject, nor the integrity of the MR system is compromised by the presence of these devices in the magnet room, in the bore of the magnet, or in the presence of an RF coil.
Inverse Geometry CT and Conventional CT

Our research efforts concentrate on the development of technology and applications of computed tomography (CT). The long-term aim of this work is to push the limits of CT performance and to aid in the development of new applications. Intrinsically in this aim is the need to understand the basic limitations in current systems and, when physically possible, to develop solutions to effectively address them.

For many years, we have been working on a project to develop a system that can image an arbitrarily thick section of anatomy (e.g., an entire organ) in a single fast rotation while producing uncompromised image quality and outstanding dose efficiency using an inverted geometry (therefore the term Inverse Geometry CT). Recently we saw the culmination of 4 years of NIH-funded work with the initial testing of a first-ever gantry-based IGCT (Inverse Geometry CT and Conventional CT). The distributed source provides the IGCT work with the initial testing of a first-ever, gantry-based IGCT CT). Recently we saw the culmination of 4 years of NIH-funded using an inverted geometry (therefore the term Inverse Geometry CT and Conventional CT).

We are also working on a number of problems relevant to all CT configurations. Continuing his work on “spectral” CT, Adam Wang developed a technique that can use dual energy CT data from a patient, acquired with two specific spectra, to simulate single and dual energy protocols at arbitrary kVp and filtration. Subject to certain constraints, the method can be used to demonstrate the image quality that would be obtained at a particular technique and dose (Wang abstract). Jangduk Baek continued his work on noise power spectra (NPS) and their eventual use for system evaluation. We derived and evaluated the impact of detector lag on the NPS (Baek abstract). We also continued our work on algorithms to mitigate the artifacts caused by metal implants in the patient (e.g. dental work or artificial joints). Caroline Golden, a visiting undergraduate student from Ireland, conducted a comparison of four correction methods and showed that the technique developed by one of our residents outperformed the other techniques (Golden abstract).

Finally, Sam Mazin, a postdoctoral fellow funded by the Kauffman technique developed by one of our residents outperformed the other techniques (Golden abstract). We conducted an initial demonstration of a concept for PET guided radiation therapy (Mazin abstract). See pages 62-65 for these abstracts.

X-Ray Guidance of Interventional Procedures

Our group conducts research with the broad goal of improving the x-ray guidance of minimally invasive procedures, including guidance of radiation therapy. The Axiom Lab (C-arm CT system) is used for in vivo investigations and the Advanced X-Ray Imaging Lab is used for hardware and software development (table-top digital x-ray imaging, cone beam CT, new detector development and X-ray/MR system development).

Software investigations have the primary goal of improving the image quality of C-arm CT reconstructions. Our modulator approach for scatter correction (abstract by Gao, NIH R21 Scatter) is now moving into clinical testing. A new lag correction approach for amorphous silicon flat-panel detectors provides close-to-CT image quality (abstract by Starman, collaboration with Varian GTC). We are also building a flexible, open-source JAVA-based framework for C-arm CT reconstruction including CUDA-accelerated forward and back-projection that provides the ability to test our new algorithms against industry standards for the first time (abstract by Maier and Keil and by Schwemmer, NIH R01 Cardiac ARRA, collaboration with University of Erlangen- Nuremberg).

In hardware developments, design and optimization of an MR-compatible rotating anode x-ray tube continues (abstracts by Lillaney and Shin, NIH R01 X-ray Tube, as does our simulations of new designs for an MR-compatible linear accelerator (abstract by Constantin, NIH NCI fellow). We also have now two projects on x-ray detector development. The first project is optimizing a new CMOS detector with direct converter HgCdTe for faster high-resolution fluoroscopic imaging (abstract by Ganguly, NIH R99 CMOS, collaboration with RTR Inc.). The second project is a newly-funded NIH R01 academic-industry collaboration with Varian GTC to develop a combined kV-MV detector for CT imaging around dense metal objects such as hip implants or fillings.

We continue to develop new clinical imaging protocols using ECG-gated C-arm CT, and are now looking at the ability to image fresh myocardial infarct in the cardiac interventional suite (abstract by Girard-Hughes, collaboration with Siemens AX). We have also completed our study demonstrating the ability to make quantitative measures of brain perfusion using the C-arm system (abstract by Ganguly and Fieselman, collaboration with Siemens AX). The next area for C-arm CT development is imaging in a weight-bearing geometry, which we hope to use for patellar motion tracking and perhaps spinal imaging (abstract by Choi). Finally, we recently received funding to optimize the inverse geometry scanning beam digital x-ray system for use during magnetically-guided lung nodule biopsy (abstract by Yoon, NIH R21 Lung Biopsy). See pages 65-71 for these abstracts.
Our research group uses computational methods to leverage the information in images to enable biomedical discovery and to guide physicians in personalized care. Just as biology has been revolutionized by online genetic data, our goal is to advance radiology by developing computational methods to extract quantitative and semantic content from images (“image biomarkers”) and to electronically correlate images with other clinical data such as pathology and molecular data to discover image-based predictors of disease and treatment response. Our work develops and translates basic biomedical informatics methods to improve radiology practice and decision making in several areas: tools to efficiently and thoroughly capture the semantic terms radiologists use to describe lesions (structured reporting, ontologies, and next-generation PACS); standardized terminologies to enable radiologists to describe lesions comprehensively and consistently; image processing methods to extract quantitative features from images that are informative of the underlying biology of lesions; content-based image retrieval; quantitative image—methods to enable physicians to objectively and reproducibly assess lesions in images and to more effectively monitor the response to treatment; natural language techniques to enable uniform indexing, searching, and retrieval of radiology information resources such as radiology reports; and decision support applications that relate radiology findings to diagnoses to improve diagnostic accuracy.

This year our laboratory become one of the sites in the Quantitative Imaging Network (QIN), a newly established national research consortium by NCI who will advance the science of quantitative methods of imaging to understand cancer. We are developing a national informatics infrastructure to define a new paradigm for acquiring, mining, and using a broad range of quantitative imaging data in cancer research, and to provide decision support to oncologists based on quantitative imaging assessments of patients with cancer. We are also establishing a large database of annotated quantitative imaging cancer studies as a resource for discovering new biomarkers that will improve the sensitivity of detecting cancer treatment response.

We collaborate with a variety of investigators at Stanford both in Radiology and Oncology as well as with investigators outside Stanford. We also participate in a national working group that is developing imaging informatics infrastructure for the cancer Biomedical Informatics Grid program at NCI. Our ultimate goal is to bridge the divide between radiological knowledge and practice - for all radiological knowledge and research data to be structured, accessed, and processed by computers so that we can create and deploy decision support applications in image workstations to improve radiologist clinical effectiveness.

The Cancer Systems Biology Lab (CSBL) views cancer as a complex system whose components can be reverse-engineered for the purposes of understanding the underlying mechanisms of cancer progression and identifying approaches for more effective cancer control strategies. Currently, our laboratory infers complex features of cancer progression through a variety of approaches that include: (1) reconstructing molecular networks of cancer, (2) integrating a diversity of molecular, pathological, imaging and clinical cancer data, and (3) mathematically modeling the progression of primary disease to metastatic stages in patients. Ultimately, our goal is to develop a comprehensive, multiscale view of cancer progression that merges these various approaches.

(1) Reconstructing molecular networks: We apply a wide range of computational and statistical techniques to infer molecular networks underlying cancer using genomic, transcriptomic and proteomic data. These networks often represent interactions between genes or sets of genes, mediated by a diversity of transcriptional regulators. Typically, we use these networks to generate new hypotheses about the stem-cell-like and self-renewing properties of cancer progression. Recently, we have been funded by the NCT Integrative Cancer Biology Program as a national Center for Cancer Systems Biology to promote this research with a grant entitled “Modeling the Role of Differentiation in Cancer Progression,” focusing on hematologic malignancies with a multi-disciplinary team across the Stanford campus. In addition, we have established a “wet-lab” in LUCAS P169 to experimentally validate our computationally-derived findings. With the new “wet-lab” we are now expanding our molecular-network-based research to the analysis of solid tumors, specifically breast cancer.

(2) Integrating a diversity of molecular, imaging and clinical data: We have embarked on numerous projects that involve the integration of multi-platform cancer datasets through probabilistic modeling. In a recent collaborative effort through ISIS, with investigators from the Stanford Departments of Radiology and Surgery, we are creating an association map between CT and PET image features and gene expression microarrays of human non-small cell lung carcinoma. This map should provide a molecular characterization of imaging features of lung cancer. It should also enable us to infer the prognostic significance of CT lung imaging features by leveraging on a vast amount of clinically annotated, publicly available lung cancer gene expression microarray. This effort has pilot funds from GE Medical Systems.

(3) Mathematically modeling the progression of primary disease to metastatic stages in cancer patients: We develop multi-scale models of the natural history of cancer that describe the stochastic behavior of tumor growth and metastatic spread. We have used these models to address important health policy questions related to early detection, such as: how does screening mammography and MR1 impact breast cancer mortality? and how would CT screening for lung cancer impact lung cancer mortality rates? This effort has been funded for over 10 years and has been renewed for an additional 5 years of funding through the NCI Cancer Intervention and Surveillance Network (CISNET). In CSBL, computational and biomathematical scientists and engineers work side-by-side with biological experimentalists and clinical researchers to ensure the biological and clinical relevance and translation of our work. By developing new computational methods to integrate complex experimental cancer data, we aim to contribute to a more comprehensive, multi-scale understanding of cancer progression that will identify new approaches to eliminate deadly aspects of this disease.
Image Analysis, Bioinformatics, and Computational Modeling

Our group is primarily interested in how biological information is extracted and quantified from both anatomic and molecular imaging, how it is represented, how it is modeled and how it is disseminated with an outlook toward combining imaging-derived information with other sources of biological and clinical information. We are particularly interested in applying computational techniques toward a better understanding of cancer. While most computational models and analyses focus on a single source or modality of data, it is becoming increasingly clear that models must integrate across a wide variety of data types as well as spatial and temporal scales. Our focus is on developing these types of models.

Beginning with information extraction, we are working to investigate how radiologists visually interpret images in collaboration with Geoff Rubin, Sandy Napel and Justus Roos. We are continuing work on computational methods to maximize the multiplexing capabilities of hyperspectral imaging with Raman-labeled nanoparticles. In the area of modeling, we have an ongoing collaboration with Dean Felmser’s laboratory in mathematically modeling oncogene addiction through quantitative imaging. This has led to new areas of investigation including using rate kinetics equations of the apoptosis cascade cascade in order to better predict the effect on overall tumor growth kinetics. In the area of knowledge representation and dissemination, we have several related projects in nanoparticle agent knowledgebases in collaboration with the NCI’s CcDB Program, the National Center for Biomedical Ontology and the NCI’s cBIB initiative.

Our long-term goal is to enable and simplify the problem of information extraction and information flow from medical/molecular imaging to be on par with that of genomic and proteomic profiling technologies so that these very different types of information may be treated as siblings computationally. Our philosophy is that for an integrative approach to imaging and non-imaging information to come to fruition, a major pre-requisite is to be able to maximally extract and represent information from imaging, with emphasis on the specificity of molecular imaging.

Interventional and Open MRI

This year, our group focused primarily on MR-guided focused ultrasound for the treatment of diseases in the liver, prostate, breast, heart, and brain.

Ultrasound energy can be focused to a point deep within the body without damage to overlying tissues. MRI provides a means to target the treatment, monitor the treatment in real-time, and evaluate the tissue after the treatment.

In body applications, our major project includes the development of an MR-guided focused ultrasound treatment for the liver. This includes developing the MRI temperature imaging during free breathing, as well as developing therapeutic capacitive micro-microwave applicators. We also have a project for MR-guided high intensity ultrasound ablation in the prostate with transurethral ultrasound applicators. This year, we have been developing feedback and control of the treatment. Our cardiac project has been focused on generating good quality temperature images in the heart based on a hybrid multibaseline-ref-ereenceless processing approach. In the breast, we have looked at the effect of focused ultrasound on the appearance of the tissue, its visibility and stiffness.

In the brain, we have been developing a method for MR-guided focusing in the presence of phase aberrations. This depends on imaging the focus with acoustic radiation force imaging. We are analyzing the effect of nearby calcifications on tissue heating. We have also been investigating neuremodulation with focused ultrasound. Lastly, we have investigated the opening of the blood brain barrier with ultrasound. You should all see this in the following abstracts.
The Body MR Imaging group addresses applications of MRI to clinical body imaging, including abdominal imaging, musculoskeletal imaging, breast imaging and cardiovascular imaging. We collaborate with clinicians as well as scientists at GE Healthcare and in Electrical Engineering. More information is available at http://bmr.group.stanford.edu.

This year the group welcomes Dr. Manoj Saranathan as a senior research associate, most recently from GE Healthcare’s Applied Science Lab. Manoj is working on breast MRI and vascular imaging, as well as 7T technology with Brian Rutt’s group. Dr. Catherine (Kitty) Moran has also joined us as a post-doctoral fellow, following her PhD at University of Wisconsin. Kitty is primarily working on breast MRI. This year Minh Hung successfully defended her thesis, entitled “Dynamic Contrast-Enhanced Breast MRI” and will soon begin a post-doctoral fellowship at UCSF. Ernesto Stanzione and Kristin Granlund are exploring a new 3D diffusion and T2-measurement method in the knee and breast, and Marc Alley has enabled this method for routine clinical use. Anderson Nnewihe continues to work on high-resolution breast imaging, and completed his 4-channel breast receive coil, which offers some of the highest resolution MR images of the whole breast seen to date. Caroline Jordan successfully completed her Bioengineering qualifying examination, and has begun working on non-contrast vascular imaging, as well as modeling susceptibility effects. Kyung Sung has developed a new method based on Compressed Sensing to exploit the varying information content at different sharpness levels in images. Pauline Wurters has made significant contributions to vascular imaging, and more recently to imaging near metallic implants. Both Pauline and Kyung were recently promoted to research associate positions. Marcus Alley continues to support new applications in the clinic, including vascular, musculoskeletal and breast imaging, and has made substantial improvements to imaging abdominal blood flow in collaboration with Dr. Shreyas Vasanawala. Our group continues strong collaborations with numerous radiologists including Bruce Daniel, Bob Herfkens, Garry Gold, and Shreyas Vasanawala.

The long-term objective of the High Field MR Group is to develop a next-generation 7 Tesla whole-body magnetic resonance imaging (MRI) facility at Stanford, to serve as a platform for cutting-edge imaging research and development, as well as for radiological and neuroscience research. The scientific scope of the projects that will use this new facility will span the range from fundamental biology to patient-based clinical imaging research. The group approach will be interdisciplinary, bringing together researchers from the specialties of physics, engineering, bioengineering, biology, physiology, radiology, neurology, psychiatry, and psychology. The 7T MR facility will act as a catalyst and common platform for these broad groups to create, refine, implement, validate and utilize the most advanced forms of magnetic resonance imaging. Major patient-based imaging research applications of this next-generation 7T MRI platform include development of brain development, psychopathology, drug dependence, alcohol-induced brain damage and its functional consequences, neurodegenerative processes, brain injury, musculoskeletal disorders, and therapeutic interventions associated with some or all of the above.

Brian A. Hargreaves, PhD

The Functional MRI Group continues to develop and optimize methods for the acquisition of functional MRI imaging data. Projects include the development of qMRI methods that reduce signal dropout and improve efficiency, real-time biofeedback for training brains and reduction of physiological noise in fMRI signals and investigation of brain network dynamics. In addition, we continue to play an active role in the NIBR-funded FIRST BBIN schizophrenia test bed project, with Gary Glover as the chair of the calibration working group. The following are only a few of the highlights of scientific progress, see abstracts for further details.

Graduate/PGY-4 MD student Rebecca Rakows-Penner defended her PhD thesis in Biophysics and is finalizing the writeup on the use of BOLD contrast for detecting and characterizing breast tumors. She was nominated as a finalist in the prestigious ISMRM’s Moore Young Investigator Award competition. She was honored with the Norman Blank Award from the Radiology Department, and received her hood at graduation this June, with family from near and far in attendance. She is in final stages of publishing her work on artifact reduction in breast imaging using an innovative saturation method that reduces confounding signal from the heart.

Gary Glover, PhD

Postdoc Moriah Thomson Caires has continued work on genetic influences on brain development in children and is now considering choices for several faculty appointments.

Grad student Catie Chang discovered that the brain’s resting state networks are highly variable in their inter-region activity, and has published her methods of investigation of this unexpected phenomenon. She collaborates with my investigators at Stanford on real-time fMRI, and internationally with scientists who use her denoising algorithms and her dynamic network methods.

Anesthesia Faculty and group member Sean Mackey was featured in a 3-page article in Nature (Vol 461:T194, 29 October 2009), discussing his research studies on mitigation of pain using the real-time biofeedback methods developed by our group. Dr. Mackey cautioned that the techniques are still in research phase but show promising results in training patients to reduce their chronic and episodic pain.
Clinical Center for Advanced Neuroimaging (CFAN)

Advances in magnetic resonance imaging (MRI) continue to revolutionize neuroimaging. We now routinely map and measure brain tissue water movement, blood flow, and the brain’s ability to develop and maintain functional-structural integrity in adult and pediatric patients. To apply our clinical excellence in advanced neuroimaging, the Clinical Center for Advanced Neuroimaging (CFAN) has been built upon the large framework of a number of funded NIH grants from the RSL, Lucassen Center, Stanford Stroke Center, and the Pediatric Radiology faculty dedicated to providing the best MRI techniques to help clinicians do their job more effectively.

The research program behind CFAN brings over $2.2M per year to Stanford, which has been augmented in part by stimulus grants. These grants focus exclusively on clinical neuroimaging using the tools of MD and PhD clinicians and researchers across several departments in the Stanford School of Medicine and the Lucille Packard Children’s Hospital. CFAN brings a wide and growing array of funded efforts together and is disease as well as method oriented.

We continue to make significant progress in developing advanced imaging technologies in several key adult and pediatric clinical areas. These include diffusion and perfusion techniques to image acute stroke and to image white matter structure and integrity. We are now funded to use the whole body 7 Tesla MRI scanner and research parallel RF transmit systems to improve higher-resolution tools of high-field and high-speed MRI, focusing on disease processes in “brain attacks” (cerebral stroke) in both adults and in children, cerebral pulse, and pediatric tumors using diffusion MRI (DWI), tumor perfusion mapping (PWI), as well as the new field of mapping the brain connectivit, DTI, and susceptibility-weighted MRI (SWI). Clinical imaging of the moyamoya and transient ischemic attacks (TIA) of the brain have also been recently added.

CFAN also maps high-resolution diffusion images to explore and map hippocampus structure and function in active mental tasking, which will reveal new key findings in aging brain function to separate short-term from long-term structural changes in the brain. Similar high resolution methods are also used in cholesteatomatosis to isolate current residual abnormalities to assess nerve viability. Recently, we have expanded our portfolio of sequences to include rapid 3D relaxometry, which accurately measures T1, T2, proton-density, and transmit and transmit fields simultaneously without the use of a prohibitively (especially important in children) high RF energy deposition. These tools offer great potential for pre-clinical contrast agent studies and in an advanced assessment of patients suffering from demyelinating diseases, such as MS.

CFAN also focuses on improving angiographic methods by inventing innovative MR pulse sequences and optimizing the timing and amount of contrast delivery. Efforts are also underway to improve analysis and mapping of complex flow patterns by blood flow streamline analysis and comparing those results to computational fluid dynamic models.

CFAN is also interested in reducing image blur and artifacts by developing both hardware and software for real-time motion correction of MRI scans with a special focus on children. This prospective approach is a major paradigm change and promises to reduce sedation needed to image children.

Roland Bammer was recently promoted to Associate Professor of Radiology and Neurology, and Neurological Sciences (by courtesy), and is the key imaging physiologist for Pediatric Radiology. He is also a visiting professor at Bosphorus University, Istanbul, a university Docent at the Medical University of Graz, Austria, and a Senior Fellow of the Freiburg Institute for Advanced Studies (FRIAS). Roland also serves as a reviewer on NIH study sections; is a full member of the editorial board of Magnetic Resonance in Medicine and the Journal of Magnetic Resonance Imaging; and was recently elected to Chair of the ISMRM publication committee. He also directs the year-long Physics course for Radiology residents. This year Roland also received the prestigious CAfey research award from the Society of Pediatric Radiology (SPR).

Greg Zaharchuk is an Associate Professor in Neuroradiology. He has several funded projects and works with Neurology and Neurosurgery to clinically evaluate CFAN methods in patients with altered CNS blood flow in MS, Moyamoya, TIA, stroke, and cerebral vascular diseases of the aging brain. Dr. Zaharchuk is our expert on diffus- trace to study brain perfusion and has revamped the research in arterial spin labeling (ASL) and dynamic X-enhanced CT. For his work on ASL, he received the ASNR award. His mentees, Albert Hsiao, received the SPR poster award. Greg’s research has also helped optimize our CT perfusion methods, bringing them to a competitive level. His efforts also directly benefit patients. This year, Greg also received his first NIH R01, which supports him and his team to study blood flow in Moyamoya patients. He also leads a Tiger-team neuro project, part of a multi-disciplinary joint effort with GE Healthcare to advance MR neuroimaging.

Mike Moseley is a past President and Gold Medal winner of the International Society of Magnetic Resonance in Medicine (ISMRM) and was elected as a Lifetime Member of the Society of Magnetic Resonance Technologists (SMRT). As a leading expert and pioneer of stroke imaging, he also sits on many NIH study sections and jour- nal editorial boards. This year Mike was successful in receiving a highly competitive NIH SIU award, which allows for a major hardware upgrade for the TT animal system, the work horse for preclinical studies in the small animal imaging suite.

One of CFAN’s goals is to actively engage and collaborate with new faculty, such as Dr. Kristen Yeom at Stanford and Lucille Packard to develop new key approaches to imaging children. Kristen recently received a research grant from the LPHC research council to study pediatric tumors- an on-going assessment CFAN methods. Another example is the key imaging team consisting of the CFAN guidance involves Dr. Michael Zeineh, with whom the support and mentorship of Scott Atlas and working with Samantha Holdsworth, has developed a high-resolution MRI sequence to image white matter fiber tracts in the hippocampus, an anatomical structure that could not be visualized before.

Thomas Christen, Ryan Spilker, and Greg Zaharchuk have developed a battery of clinical imaging methods mapping brain oxygenation uti- lization and reserve for patients with compromised vascular systems. This work is being added to the clinical stroke workup protocol in an effort to predict whether acute stroke therapy can be extended to patients receiving early MRI scans.

Roland Bammer, PhD, Greg Zaharchuk, PhD, MD, Michael Moseley, PhD

Research Group Updates

Magnetic Resonance Research

Roland Schmiedekamp, a Bioengineering graduate student, is adapting his novel imaging sequences for imaging blood flow and functional changes in stroke. Daniel Kopeinigk, a graduate stu- dent in Electrical Engineering, works with Roland, Marcus Alley, and Dominik Fleischmann on con- trast-enhanced angiography with a special focus on improving contrast injection profiles to achieve desired enhancement profiles in the arte- rial system. Raphaël O’Halloran, a new research associate, uses novel 3D volume diffusion spiral methods for clinical imaging. Eyun Soo Choi and Shangping Feng are both second year graduate students in Electrical Engineering. Eun Soo has already made major strides in writing soft- ware to perform coherence path analysis and Bloch simulations for complex MR sequences.

Thomas Brosnan, who is a senior research scientist, directs the RSL and Lucas IT infrastructure. His work is key in adapting the new MR sequences to the clinics where imaging data is fed in real-time to the RSL servers for rapid process- ing and feedback to the clinicians. Where companies employ a whole battalion of computer engineers, the RSL has a team of computer scientists. Roland Bammer, PhD, Greg Zaharchuk, PhD, MD, Michael Moseley, PhD

Lucassen Center, Stanford Stroke Center, and the Pediatric Radiology fac

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Multimodality Molecular Imaging Lab (MMIL)

Sanjiv Sam Gambhir, MD, PhD

We are developing imaging assays to monitor fundamental cellular events in living subjects. We are actively investigating technologies such as micro-positron emission tomography (micro-PET); bioluminescence optical imaging with a charge coupled-device (CCD) camera; fluorescence optical imaging; micro-computerized axial tomography (microCAT); ultrasound; photoacoustics; intravital microscopy; and Raman spectroscopy in small animal models. Our goals are to marry fundamental advances in molecular/cell biology with those in biomedical imaging to advance the field of molecular imaging. We have a particular focus on cancer biology. We have developed several reporter genes/reporter probes compatible with all of the above imaging modalities. These reporter genes and reporter probes are being used in cell trafficking models, gene therapy models, as well as in transgenic models for studying cancer biology. Assays to interrogate cells for mRNA levels, cell surface antigens, protein-protein interactions, protein phosphorylation, and intracellular folding are also under active development. We are also extending many of these approaches for human clinical applications. New patient trials for PET imaging of T-cell trafficking in patients are being performed with our reporter gene strategies. We are also developing several new PET agents for cell surface targets based on new protein scaffolds.

Cancer Molecular Imaging Chemistry Lab (CMICL)

Zhen Cheng, PhD

The main research of our group is to develop novel multimodality imaging probes and techniques for cancer early detection. Our multidisciplinary team is composed of members with expertise in organic chemistry, radiochemistry, biotechnology, biochemistry, molecular and cellular biology, radiological science, medicine, and molecular imaging. Currently, we are actively studying several important problems in the molecular imaging field. First, we are investigating a variety of novel platform molecules (peptides, proteins, nanoparticles) as universal strategies for cancer imaging. Second, we are establishing new methodologies for site-specific labeling these platform molecules for multimodality imaging. Third, by applying the knowledge obtained from the above research, we are optimizing PET and optical imaging probes for imaging of melanoma, breast cancer, prostate cancer, and ovarian cancer. We hope to quickly translate two molecular probes into clinical PET imaging in the very near future.

Our research is supported by National Institute of Health, Department of Defense, the Melanoma Research Alliance and the Radiology Department at Stanford.

Cellular and Molecular Imaging Lab (CML)

Jiangrong Rao, PhD

The general research interest in the Rao lab is to develop novel molecular probes and imaging strategies for in vivo imaging by combining chemical synthesis and macromolecular engineering with imaging technologies. Current projects are broadly defined in three areas: 1) Imaging enzyme activity in vivo. Our established class of protein molecules, enzymes catalyze biochemical transformations and are widely implicated in biological processes and diseases. We are developing “smart” activatable probes for both small molecule probes and nanoparticles-based nanosensors to in vivo detection and in vivo imaging of the activity of proteases such as matrix metalloproteinase-2 (MMP-2) and furin in cancer cells. Toward imaging these enzyme targets, different imaging modalities have been employed from optical imaging, to magnetic resonance imaging, to positron emission tomography. 2) A second major area of interest is developing general strategies to label proteins and RNAs in living cells for in vivo imaging. Our approach is to design small organic dye molecules that are not fluorescent initially but that become fluorescent after binding to a receptor or tag fused to either a protein or RNA molecule of interest. We are combining rational design and library selection methods, such as SELEX and phage display, to discover novel molecular tags for super high resolution single-molecule imaging in living cells. 3) The third research focus is to develop novel sensing and imaging technologies. We mimicked the naturally occurring bioluminescence energy transfer (BRET) system in the sea pansy, Renilla reniformis, and developed a QD-BRET technology widely applicable for in vitro biosensing and in vivo imaging. We are applying both protein engineering and nano engineering to create novel nanoparticles for imaging and sensing applications.

Molecular Imaging Instrumentation Laboratory (MIIL)

Our research interests are to advance instrumentation and algorithms for the non-invasive imaging of basic molecular and molecular signatures associated with disease. These new “cameras” – image photon emissions from molecular probes designed to target specific molecules associated with disease in cells located deep within the tissues of living subjects. The technical goals of the instrumentation projects are to advance the photon detection efficiency and spatial, spectral, and temporal resolutions. The algorithmic goals are to understand the physical system comprising the subject tissues, photon transport, and camera, and to realize the best available reconstructed image quality and data acquisition efficiency; computer modeling; computer graphics; tomographic image reconstruction algorithms; signal/image processing algorithms; and data/image analysis. Key goals of our research are to incorporate these innovations into practical imaging devices and introduce new in vivo imaging tools to advance studies of molecular mechanisms and aid discovery of novel treatments of disease in the clinic as well as in preclinical research. If successful, these novel system will substantially enhance the visualization and quantification of subtle molecular signatures associated with disease with the hope that molecular imaging can play a role in earlier disease management. The research is supported by grants from the National Cancer Institute, National Institute of Biomedical Imaging and Bioengineering, Department of Energy, GE Healthcare and Philips Healthcare. Trainee fellowships are supported by Stanford’s Bio-X Program, School of Medicine Deans Fellowship Program, Stanford Molecular Imaging Scholars Program, Stanford REU Program, US Department of Defense, Society of Nuclear Medicine, Swedish Research Council, National Science and Engineering Research Council of Canada, China Scholarship Council, AXA Research Fund, and TLI Inc.
Cardiovascular and Molecular Imaging Lab (CMLI)

Ischemic heart disease is the number one cause of morbidity and mortality in the United States. The repetitive nature of ischemic insults can lead to congestive heart failure, which is the leading cause of hospital admissions for people aged 65 years and over. In the next decade, cardiovascular diseases will likely be targeted at the basic cellular and molecular levels. The Cardiovascular & Molecular Imaging Lab (http://wulab.stanford.edu) combines expertise in molecular and cell biology, cardiovascular physiology, and molecular imaging. We work on the biological mechanisms of adult stem cells, embryonic stem cells, and induced pluripotent stem cells. We use a combination of geno profiling, tissue engineering, physiological testing, and molecular imaging technologies to better understand stem cell biology in vitro and in vivo. For adult stem cells, we are interested in monitoring stem cell survival, proliferation, and differentiation. For ESC, we are currently studying their tumorigenicity, immunogenicity, and differentiation. For iPS, we are working on novel derivation techniques. We also work on development of novel vectors and therapeutic genes for cardiovascular gene therapy applications. The eventual goal is to establish molecular imaging techniques in translational research in cancer and gene therapeutics for ischemic heart disease in the 21st century.

Molecular Imaging of Nociception and Inflammation Lab (MINIL)

Chronic pain sufferers are unfortunately limited by poor diagnostic tests and therapies. The lab is interested in using multi-modality molecular imaging techniques to study nociception and neuronal inflammation as a means of improving objective, image-guided diagnosis and treatment of chronic pain generators. The past couple of years welcomed a number of exciting members and collaborations to the group. Justin Du Bois, PhD, William Parsons, BS, Frederick Chin, PhD, Aileen Hoehne, PhD, David Yeomans, PhD and the Biswal BS, Frederick Chin, PhD, Aileen Hoehne, PhD. The lab projects and to initiate collaboration with Dr. Kathleen Jacobs, Vijay Rao. In subjects suffering from neuropathic pain. In subjects with neuropathic pain but treated with minocycline, an agent known to ‘deactivate’ macrophages, not only would the macrophages be inhibited from trafficking to the site of nerve injury, but also the subjects would experience less pain, suggesting an important relationship between macrophages, neurons and the pain experience. This work was won Dr. Ghanouni a 2009 RSNA Research Scholar Award. Vijay Rao MD, a Radiology Resident from SCVMS, used his spare time to determine that [18F]FDG PET-CT could more accurately determine painful metastatic bone lesions than [18F]FDG PET-CT. This work won him a 2009 RSNA Research Scholar Award. Subrat Behera, MBBS, joined the lab recently to help with the lab projects and to initiate collaboration with Dr. Jyotsna Rao, a nuclear medicine physician in Hyderabad, India. Drs. Archana Prabhakar and Sumit Singh have also recently joined the lab projects and to initiate collaboration with Dr. Kathleen Jacobs, Vijay Rao. Our mission is to translate these novel molecular and functional imaging techniques for early detection and treatment monitoring of abdominal and pelvic cancer.

Cellular Pathway Imaging Laboratory (CPIL)

Breast cancer is a highly heterogeneous disease, and there is a growing body of evidence that this heterogeneity arises at both genetic and phenotypic levels. The heterogeneous nature of breast cancer complicates the issue of developing a general therapeutic strategy that can target breast cancer at different subtypes. Although breast cancer researchers have improved the efficacy of therapies, especially for a sub-type of breast cancer that is estrogen receptor positive (endocrine therapy), the increase in the incidence of receptor negative phenotype, and the presence of receptor positive anti-estrogen non-responsive (tamoxifen resistant) phenotype, have contributed to the increase in the mortality rate of breast cancer. Our lab focuses on developing new therapeutic strategies for treating receptor negative and tamoxifen resistant breast cancers as well as imaging estrogen receptor (α and β) ligand interactions to elucidate the basic mechanisms involved in the development of tamoxifen resistance by the receptor positive sub-type. Endocrine therapy is mainly designed to target ERα and is considered to be negative in receptor negative breast cancers. The discovery of ERβ thus raises the concern of its status in receptor negative breast cancers, but also opens the option to use ERβ specific ligands for endocrine therapy. Specifically, we are interested in developing a combinatorial therapeutic approach in which we will use ERβ specific ligands in combination with the down-regulation of some specific microRNAs (miR23a, miR250, miR353, miR355, miR373 and miR200c) that are over-expressed in receptor negative breast cancers. As ERβ currently is not explored in these sub-types of breast cancer, this strategy, if successful, has enormous potential as a new anti-estrogen therapy (β-specific) for receptor negative breast cancers. The anti-sense microRNAs will be explored to block the functions of microRNAs that are over-expressed. In addition, our lab is also developing new in vivo imaging assays for monitoring different epigenetic processes (DNA-methylation, histone methylation, and histone acetylation) that are critical for maintaining cellular homeostasis, and are considered to be a potential therapeutic target for treating many diseases arising from altered cellular homeostasis such as different types of cancers.

Translational Molecular Imaging Lab (TML)

In the United States, cancer continues to be the leading cause of death in patients between 25 and 64 years of age, and the second leading cause of death in patients both above 65 years and between 1 and 14 years. Prognosis and survival of patients with cancer very much depends on what tumor stage the cancer is at the time of diagnosis, and therefore early cancer detection is showing great promise in prolonging survival and improving quality of life for cancer patients. Consequently, novel imaging strategies that allow detection of cancer at early stages are highly desirable. With the advent of novel therapeutic options for cancer patients, there is an increasing demand for non-invasive imaging biomarkers to identify those patients early on who benefit most from a given treatment or to modify/terminate treatment for those patients not responding to treatment.

In our lab, we focus on the development and clinical translation of novel molecular and functional imaging biomarkers. We have a special focus on imaging abdominal and pelvic cancer including pancreatic, liver, renal, ovarian, and prostate cancers. We further advance clinically available radiological imaging modalities such as ultrasound, magnetic resonance imaging (MRI), and positron emission tomography (PET) as promising imaging tools for early detection and treatment monitoring of abdominal and pelvic cancer.

Our mission is to translate these novel molecular and functional imaging strategies into clinical protocols for improved patient care in the shortest possible time frame.
Clinical Imaging Facilities

- Medical School Campus
- Stanford University Hospital
- Lucile Packard Children’s Hospital
- The Stanford Cancer Center
- Blake Wilbur Imaging
- Diagnostic Imaging Center, VA Palo Alto
- Stanford Medicine Outpatient Center: Redwood City
- Stanford Medicine Imaging Center, Sherman Avenue, Palo Alto

Research Facilities

- The Richard M. Lucas Center for Imaging
- The James H. Clark Center
- Edwards Building
- Grant Building
- Alway Building
- 1501 California Avenue, Palo Alto
- 480 California, Palo Alto

The Stanford 3D Medical Imaging Laboratory

Geoffrey Rubin, MD
Sandy Napel, PhD
Laura Pierce, MPA, RT(CT), Lab Manager

The Stanford 3D Medical Imaging Laboratory is guided by the mission of developing and applying innovative techniques for efficient analysis and display of medical imaging data through interdisciplinary collaboration. Since 1996, our clinical goal has been to deliver 3D imaging advances as rapidly as possible for the swift and accurate diagnosis and treatment of disease; our educational goal is to disseminate knowledge and duplicate our 3D services at other institutions; and we continue to facilitate cutting edge research through our collaborations with faculty in Radiology and other Departments. To facilitate the bridge between innovation and other clinical use of technology, we also offer services as an imaging core lab for medical device developers.

Progress

Clinical: Over the past year, the 3D Laboratory has continued its operations simultaneously in the Lucas Center as well as the James H. Clark Center, a building dedicated to interdisciplinary science. Our average monthly 3D volume has increased to approximately 950 examinations, and we have processed over 78,000 examinations overall since our inception. The majority of our referrals continue to come from vascular surgery, cardiology, orthopedics, hematology, radiology, reconstructive surgery, ophthalmology, neurosurgery. 3D clinical procedures now offered by the Lab include CT Virtual Colonoscopy for both diagnostic and screening evaluation of polyps (fig 1), CT Temporal Bones for visualization of tiny structures in the inner ear (fig 2), and MR Heart for quantification of muscle mass, ejection fractions, and flow velocity (fig 3).

Education: This year the 3D Laboratory has been attended by international visiting scholars from Japan, as well as Stanford Radiology fellows, residents, and medical students who acquire skills in 3D interpretation as part of their medical training. Stanford researchers from engineering and medical departments have also been trained in acquiring 3D images and data for research projects, including measurements of craniofacial deformities for reconstructive surgery, pulmonary vasculature volumes for 3D model fluid flow simulations for vascular surgery, and 3D modeling for multimodality small animal imagers. The 3D Laboratory has also hosted several visiting radiology managers and technologists from domestic and international medical centers through our 3D clinical fellowship program.

Infrastructure

3D imaging specialists include: Laura Pierce, 3D Laboratory manager; senior 3D technologists Marc Sofilos and Linda Novello; 3D technologists Keshni Kumar, William Johns, Nancy Ware and Shannon Walters. Technologists John William Weidinger and Kristen Hogart provide per diem 3D services to maintain up-to-date workflow (image 1). Our technologists offer not only expertise in 3D imaging, but also experience in CT and MRI scanning techniques as well. Support staff includes administrative assistant Lakesha Winston and Debra Frank, and database administrator, Kala Ramani. The research arm of the lab retains an annual average of 12 engineering graduate students and post-doctoral scholars as well as 2 clinical MD researchers. In the Clark Center, a central area table invites professional collaboration, and student desks with moveable workspaces provide areas for independent research. The Lucas Center 3D Laboratory also houses equipment on a central table, surrounded by student carrels. The lab equipment comprises a total of 13 advanced 3D workstations, three TeraRecon servers, which also provide remote 3D rendering to the Stanford medical community, and two research and development servers for image and data storage. Three remote PACS workstations allow access to all Stanford medical imaging and reporting.

We continue our excellent relationships with corporate developers of 3D workstations (e.g., GE Healthcare, TeraRecon, and Vital Images) who site their hardware and software in the 3D lab in anticipation of our feedback. These relationships ensure that we maintain the most advanced multidimensional analytical technologies available. To expedite workflow and allow for flexible workspaces, we are upgrading the infrastructure of the 3D Laboratory to access all 3D software applications on centrally located vendor-supplied servers, to allow for processing and sharing of image data throughout our enterprise on generic PC workstations. We have already begun this transition by utilizing the TeraRecon Intrusion® server from multiple locations for real-time interactive 3D rendering, and the MEDIS QMash® and GQForm® analysis software which allows for enterprise collaboration when measuring cardiac output and analyzing muscle mass.

Conclusion

The 3D Medical Imaging Laboratory continues to function as an international leader in clinical care, teaching, and research in medical imaging analysis. The confluence of talented, medical and engineering expertise as well as the most up-to-date equipment has been a consistent source of innovative developments in diagnostic and treatment planning approaches.
In our continuing efforts to provide support to the Radiology investigative staff, we are entrusted with the responsibility of overseeing all animal model protocols within our department and all other departments carrying on research studies at the Lucas Center. Two experienced California Licensed Veterinary Nurses (RVTV) are available to serve as a resource for all animal studies at the Lucas Center. Accordingly, we ensure that proper respect for life is a part of all research studies. Research conducted at the Lucas Center improves and develops new invasive and non-invasive procedures that utilize magnetic resonance imaging (MRI), high intensity focused ultrasound (HIFU), computed tomography (CT), CT fluoroscopy, and positron emission tomography (PET) to guide them. Clinical studies currently conducted include the study of cancer and liver radio frequency (RF) ablation, myocardial infarction, liver and prostate cancers, neuromodulation with ultrasound, and structural neuroimaging of the brain. The techniques currently being explored at the Lucas Center contribute to more efficient and effective medical treatment for human illness and disease.

All personnel working with animal models under approved Institutional Animal Care and Use Committee (IACUC) protocols have completed required training from Stanford University Department of Comparative Medicine. In addition, specifically tailored “on one” training for more advanced techniques are taught by the veterinary technicians at the Lucas Center. We realize that living subjects are needed to advance our knowledge, and to that end we ensure that proper respect for life is a part of all research studies. Research conducted at the Lucas Center improves and develops new invasive and non-invasive procedures that utilize magnetic resonance imaging (MRI), high intensity focused ultrasound (HIFU), computed tomography (CT), CT fluoroscopy, and positron emission tomography (PET) to guide them. Clinical studies currently conducted include the study of cancer and liver radio frequency (RF) ablation, myocardial infarction, liver and prostate cancers, neuromodulation with ultrasound, and structural neuroimaging of the brain. The techniques currently being explored at the Lucas Center contribute to more efficient and effective medical treatment for human illness and disease.

Small Animal Imaging Center - SCi3
Tim Doyle, PhD, Head, Small Animal Imaging Facility, MIPS

The Stanford Center for Innovation in Vivo Imaging (SCi3) has seen another successful year as a shared core facility, both in terms of instruments available and time used on the equipment. Demand for instrument time has increased by about ten percent, and we have purchased new research instruments which are now available to the research community at Stanford. Oversight of the core has been transferred from Stanford University Department of Comparative Medicine. The Dean of the SoM, along with the University President and the Department of Radiation Oncology, generously provided unrestricted funds to the core, thanks to the efforts of Professor Gambhir. These were used earlier in the year to purchase a second small animal ultrasound scanner, which provides improved functionality as well as increasing the capacity to image animals with this popular modality. We will use the remainder of these funds to replace the gradient coil with a pair of “nested” coils, along with other upgrades that will hopefully provide greater utility of the MRI. Dr. Brian Rutt also secured funds from the Department of Neurosciences, with matching funds from the Bio-X program to help with these upgrades, and we hope that the hardware will be installed before the end of the year.

Finally, the planning of a second Small Animal Imaging Facility to be located in the basement of the new Lorry I. Lokey Stem Cell Research Building (lokey.stanford.edu) were finalized this year, and will be occupied in September. This new core will serve animals housed in a clean “barrier” facility, which is also located in the basement of this building. The new core will run in parallel with the current facility, serving the two populations of mice housed at Stanford (those in the new barrier, as well as those in current housing facilities). The core will initially be equipped with an Invivo MicroPET-CT scanner, funded by the CIRM, as well as an IVIS Optical Imaging system that was purchased by Prof. Irving Weissman, and has space to expand to the other modalities already in place in the SCi3, such as SPECT, ultrasound, MRI and MicroCT. This extra imaging capacity will ensure that Stanford remains a leader in Molecular Imaging.

Lucas Center MR Systems
Anne Marie Sawyer, BS, RT (R)(MR), FSMRT
Sandra Rodriguez, BS, RT (R)(MR)

1.5T, 3T1, 3T2 AND 7T Whole Body Magnets

Research Support 2009 - 2010
The 1.5 Tesla (Figures 1 and 2) and 3.0 Tesla GE Healthcare MR systems are currently operating at 15x systems revision; the 3.0 Tesla GE “750” (Figure 3) at 20x software; and the 7.0 Tesla (Figure 4) at 12.4. The systems operate at a maximum slew rate of 150 Tesla per meter per second and maximum gradient amplitudes of 50 milliTesla per meter (1.5T and 3T2) and 40 milliTesla per meter (3T1 and 7T). The hardware currently allows the use of 8-channel phased array coils at 1.5T, 16 channels at 3T1 and 7T, and 32 channels at 3T2.

Daily support in MR system operation and screening and safety is provided to all researchers including faculty, post-doctoral fellows, graduate students, and visiting scholars in the Lucas Center and Department of Radiology; researchers from other University departments such as Psychology, Psychiatry, Neurology, Neurosurgery, and Nephrology; and service center users from outside of the University.
The Radiochemistry Facility (RF) develops and offers radiotracers for early detection and therapeutic monitoring of disease in both preclinical and clinical imaging settings. Radiochemistry personnel (faculty, staff, and postdocs) numbers around 30 people. New instruments that were recently installed include an Eckert & Ziegler Radiosynthesis Modular Lab with autosyringe and two high-pressure liquid chromatography systems with autosamplers. The facility is expanding to include radiochemistry space for making clinical-grade radiopharmaceuticals in the new Molecular Imaging Clinic that is scheduled to open in October. The additional space will meet essential clinical radiochemistry demands as well as comply with current regulatory policies. The existing radiochemistry labs continue to provide tracers for pre-clinical investigations and maintains our [C-11]carbon dioxide and [F-18]fluorine gas radiochemistries for all our research needs.

Cyclotron Suite Update
Frederick Chin, PhD
David Dick, PhD

Our staff provides routine clinical tracers for use at the Stanford Hospital. Fluorine-18 labeled fluorodeoxyglucose (FDG) is still produced daily (now 6-days/week) and can also be made using the new FASTlab FDG system with much higher yields relative to the current MX-FDG module. Nitrogen-13 ammonia (myocardial perfusion assessment) and Fluorine-18 sodium fluoride (bone imaging) are also synthesized for the clinic as needed.

GE TRACERlab modules are the workhorses in the lab and perform the syntheses of our F-18 and C-11 labeled radiotracers for collaborative researchers at Stanford and pharma. These modules have enabled us to perform new radiochemistries, providing [18F]EF-5 (imaging tumor hypoxia) and [18F]FPPRGD2 (imaging tumor angiogenesis) for human studies. Additional PET radiotracers that study the mechanisms and treatment of cancer as well as neurological disorders will soon become available to meet the increasing needs for performing preclinical ([11C]raclopride, [18F]saxitoxin, [18F]FBR, [18F]FTC-146) and clinical ([11C]tamoxifen, [18F]Avastin/Bayer compounds) research studies with PET.

Frederick Chin, PhD
David Dick, PhD

Radiolabeled Compounds

The following table summarizes an updated list of requested radiolabeled compounds that are made in the research radiochemistry lab, excluding research compounds protected under confidentiality agreements (Bolded tracers = preclinical and clinical use).

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Use</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11C]Raclopride</td>
<td>Imaging dopamine-2 receptors (D2R)</td>
<td>Monitoring D2R-related neurological disorders (e.g., Parkinson’s Disease)</td>
</tr>
<tr>
<td>[11C]PIB</td>
<td>Hypoxia imaging agent</td>
<td>Evaluating clinical-relevant hypoxia-directed cancer therapies</td>
</tr>
<tr>
<td>[11C]PIB</td>
<td>Hypoxia imaging agent</td>
<td>Evaluating clinical-relevant hypoxia-directed cancer therapies</td>
</tr>
<tr>
<td>[18F]EF-5</td>
<td>Hypoxia imaging agent</td>
<td>Evaluating clinical-relevant hypoxia-directed cancer therapies</td>
</tr>
<tr>
<td>[18F]Fluorodeoxyglucose</td>
<td>Tumor imaging agent</td>
<td>Evaluating clinical-relevant cancer therapies</td>
</tr>
<tr>
<td>[18F]Choline</td>
<td>Prosthetic labeling group</td>
<td>Radiolabeling peptides with specific cysteine moiety</td>
</tr>
<tr>
<td>[18F]Fluorobenzaldehyde</td>
<td>Prosthetic labeling group</td>
<td>1) Radiolabeling peptides for potential clinical use 2) Radiolabeled antibody for imaging of NCR2mex</td>
</tr>
<tr>
<td>[18F]Fluorobenzaldehyde</td>
<td>Prosthetic labeling group</td>
<td>Radiolabeling peptides for potential clinical use</td>
</tr>
<tr>
<td>[18F]Fluoropropionic Acid</td>
<td>Prosthetic labeling group</td>
<td>Radiolabeling peptides for potential clinical use</td>
</tr>
<tr>
<td>[18F]Fluorobenzylmercaptoacetic acid</td>
<td>Prosthetic labeling group</td>
<td>Radiolabeling peptides for potential clinical use</td>
</tr>
<tr>
<td>[18F]Fluorobenzylmercaptoacetic acid</td>
<td>Prosthetic labeling group</td>
<td>Radiolabeling peptides for potential clinical use</td>
</tr>
<tr>
<td>[18F]FBA</td>
<td>Prosthetic labeling group</td>
<td>Radiolabeling peptides for clinical use</td>
</tr>
<tr>
<td>[18F]FBG</td>
<td>Imaging agent for HSV1 receptors (formerly known as herpes simplex virus receptors)</td>
<td>Monitoring neuroinflammation induced by stroke or radiation therapy</td>
</tr>
<tr>
<td>[18F]FAU</td>
<td>Imaging substrate expressing mutant HSV1-u39k</td>
<td>1) Monitoring gene therapies targeting cancer 2) Monitoring cell therapies</td>
</tr>
<tr>
<td>[18F]FBG</td>
<td>Imaging agent for tumors expressing HSV1-u39k</td>
<td>Monitoring various cancer therapies</td>
</tr>
<tr>
<td>[18F]FET</td>
<td>Imaging agent for tumor cell proliferation</td>
<td>Monitoring various cancer therapies</td>
</tr>
<tr>
<td>[18F]FPPRGD2</td>
<td>Imaging agent for integrin expression</td>
<td>Imaging tumor integrin expression</td>
</tr>
<tr>
<td>[18F]FPPRGD2</td>
<td>Imaging agent for sigma-1 receptor</td>
<td>Imaging agent for studying depression, Schizophrenia, Alzheimer’s Disease, drug addiction, and certain cancers (e.g., prostatic, breast)</td>
</tr>
<tr>
<td>[18F]Saxitoxin</td>
<td>Imaging agent for sodium currents</td>
<td>Imaging agent for sodium channels linked to pain</td>
</tr>
<tr>
<td>Other [18F]-labeled RGD peptides</td>
<td>Integri IV imaging agent</td>
<td>Imaging tumor integrin expression</td>
</tr>
</tbody>
</table>
Abstracts in this section describe research that is conducted using sophisticated x-ray and Computed Tomography (CT) techniques to improve image quality, decrease the amount of radiation exposure, or reduce the amount of time required to complete an exam. The overall goal of these projects is to improve our ability to detect and monitor disease using these x-ray-based methods.

Synthetic CT: Simulating arbitrary low dose single and dual energy protocols

AS Wang, 1,2, NJ Pelc 1,2,3
Departments of Electrical Engineering, 1Radiology, 3Bioengineering, Stanford University, CA; 3Radiology, Stanford University, CA

While imaging protocol is a critical determinant of radiation dose and image quality, it is difficult to find the protocol (kVp, mAs, filtration) that offers the lowest dose for images of appropriate diagnostic quality. Therefore, we developed a method for retrospectively synthesizing CT scans of arbitrary kVp and filtration for low dose single and dual energy protocols using a previously acquired dual energy scan.

Axial scans of a phantom were acquired on a GE CT750 HD system at 80 kVp and separately at 140 kVp. Additional scans at 100 and 120 kVp and at different exposures were made to compare with synthesized results. Material decomposition is performed in projection space, and the desired spectrum is transmitted through the material decomposition. However, to synthesize realistic single energy scans and dual energy decompositions, the noise must have the correct statistics. The original data has an inherent noise that can be found from the covariance of the decomposition. Noise is inherent noise that can be found from the statistics. The original data has an inherent noise that can be found from the covariance of the decomposition. Noise is then added so that the total noise matches the expected noise of the simulated protocol.

The resulting synthesized 100 kVp scans are indistinguishable from the actual 100 kVp scan. Similarly, a synthesized 100/120 kVp dual energy decomposition is equivalent to the actual decomposition. In conclusion, synthetic CT enables users to see the impact of protocol changes on the contrast and noise of single and dual energy scans by providing realistic feedback that can be used to develop lower dose protocols for future scans by demonstrating dose/noise/protocol trade-offs and source filtration effects.

References/Funding Source

Advanced X-Ray and Computed Tomography (CT) Techniques

Effect of Image Lag on Noise Power Spectrum

J Baek1, NJ Pelc1,2,3
Departments of Radiology, RSL, Bioengineering, Electrical Engineering, Stanford University, CA

Purpose: We examined the effect of detector lag on CT image noise and quantified it with noise power spectrum (NPS). Methods: We first derived an analytical expression of the NPS with image lag, and then verified it using computer simulations. The dependence of the NPS on image lag coefficients (i.e., “High lag” and “Nominal lag”), location and size of the ROI, and the number of views used in the reconstruction (i.e., 500 and 1000 views) was investigated with uniform and view dependent non-uniform noise profile. For image reconstruction, we chose a parallel beam geometry since it otherwise would have stationary noise behavior, to show the effect of image lag most clearly. Results: The NPS with “High lag” coefficients showed more noise correlation in the azimuthal direction and reduced the amplitude of the NPS. The azimuthal blurring increased with increasing radial distance, and therefore the local ROI images centered at the larger radial distance had lower noise power. In addition, the NPS of a smaller ROI image showed lower noise power due to increased noise correlation. With constant lag per sample, compared to a noise image reconstructed with 1000 views, a noise image reconstructed with 500 views showed more noise correlation which decreased the amplitude of the NPS. Conclusions: The shape of the NPS showed the dependence on image lag coefficients, location and size of the ROI, and the number of views used in the reconstruction. In general, the noise correlation caused by image lag decreased the amplitude of the NPS.

References/Funding Source GE Healthcare, Lucas Foundation, and NIH grant EB006837

An Inverse Geometry CT System with Scanned Stationary Source Arrays

SS Hash, NJ Pelc
Department of Radiology and Electrical Engineering, Stanford University, CA

Traditional CT systems face a tradeoff between temporal resolution, volumetric coverage and cone beam artifacts. Inverse geometry CT (IGCT) enhances volumetric coverage while suppressing cone-beam artifacts by placing a small, possibly fragile x-ray source opposite a large, rotating scanned source array. However, like traditional CT systems, its temporal resolution is ultimately limited by the gantry rotation speed, which in turn is limited by mechanical constraints introduced by the heavy, and possibly fragile x-ray source. By replacing this rotating source with a series of stationary scanned sources we can greatly accelerate gantry rotation speeds and hence temporal resolution. We investigate the feasibility of this design. We anticipate that it will be necessary to have a physical separation between the separate source arrays, gaps in the sinogram will appear which in most cases prohibit reconstruction with standard techniques. However, in the case that these source arrays, a triangular field of view emerges when the gaps can be filled in using symmetry. A timing and collimation scheme was developed that efficiently uses the source array and small detector to virtually build up fan-beam sources with large detector except within the gaps. In simulations, the two-dimensional MTF and noise characteristics are comparable to a parallel-beam scan. We anticipate that under this scheme, a complete volumetric scan can be completed within 100 milliseconds.

References/Funding Source National Defense Science and Engineering Graduate Fellowship, NIH grant R01EB006837

Multi-spot Inverse Geometry CT (IGCT) System

NJ Pelc1,2,3, J Baek, RJ Helferica, D Fleischmann1,2
Departments of Radiology, RSL, Bioengineering, Electrical Engineering, Stanford University, CA

Purpose: The aim of this NIH-funded collaboration with GE Healthcare Research Center is to build the first scanner gantry-mounted IGCT system. Methods: In contrast to conventional CT scanners which have one or perhaps two x-ray sources, the IGCT architecture uses a wide distributed source array and a detector set opposite a large, rotating scanned source array. Results: The sources demonstrated operation with switching that is narrower in the lateral direction. Each source only illuminates a portion of the field which decreases the amplitude of the NPS. Conclusions: The shape of the NPS with 500 views. (b) NPS with 1000 views. (c) NPS dependence on ROI size. (d) NPS with view dependent nonuniform noise.

Real-Time Scanning Beam Digital X-ray Image Guidance System for Transbronchial Needle Biopsy

S Youn1, BP Wilfley2, PJ Jasper2,1, D Krishna1, R Fahrig1
Department of Radiology, Stanford University, CA; Triple Ring Technologies, Inc., Newark, CA; SuperDimension, Inc., Minneapolis, MN; Palo Alto Medical Foundation, Palo Alto, CA

We investigate a real-time digital tomosynthesis (DTS) imaging modality that provides improved image guidance for transbronchial needle biopsy (TBx) because of its multi-planar imaging, cone beam artifacts, and minimal invasiveness. Specifically, we investigate an alternative DTS approach based on the scanning beam digital x-ray (SBDX) hardware used in conjunction with an electro-magnetic navigaton (ENB) system. Improved lung nodule (<20mm) visualization when using the SBDX system versus the currently SBDX system configuration. There exist a well-defined interference-free region, where the volume-of-interest (VOI) is at least 50mm away from the SBDX system source and detector. Inside this region, tomographic angle ranges from 3° to 10° depending on the VOI location. Improved lung module (20mm) contrast is achieved by imaging the VOI near the SBDX system detector, where the tomographic angle is maximized. The combination of the SBDX and ENB imaging guidance with an ENB system would enable a real-time visualization with improved localization of the target and needle/biopsy instrument, thereby increasing the accuracy and lowering the variance of the yield for TBx.

References/Funding Source NIH R01 HL083503-01 and the Lucas Foundation

Lucas Annual Report 2010
64
65
Advanced X-Ray and Computed Tomography (CT) Techniques

Simultaneous Segmentation and Reconstruction for Limited View Computed Tomography

S Yoon, AR Pineda, R Fahrig
Departments of Radiology, Stanford University, CA; Mathematics, California State University, CA

An iterative tomographic reconstruction algorithm that simultaneously segments and reconstructs the reconstruction domain is proposed and is applied to tomographic reconstructions from a sparse number of projection images. The proposed algorithm uses a 2-phase level set method segmentation in conjunction with an iterative tomographic reconstruction to achieve simultaneous segmentation and reconstruction. The simultaneous segmentation and reconstruction is achieved by alternating between level set function evolution and per-region intensity value updates. To deal with the limited number of projections, a priori information about the reconstruction is enforced via penalized likelihood function. Specifically, smooth function within each region (preserves-smooth function) and bounded function intensity values for each region are assumed. Such a priori information is formulated into a quadratic objective function with linear bound constraints. The level set function evolution equations are acquired by artificially time-evolving the level set function in the negative gradient direction; the intensity value updates are achieved by using the gradient projection conjugate gradient algorithm.

References/Funding Source

A New Method for Lag Reduction in Flat-Panel X-ray Detectors

J Starman1,2, R Fahrig1
Departments of Radiology, Biengineering, Electrical Engineering, Stanford University, CA; Varian Medical Systems, Mountain View, CA

Detector lag, or residual signal, in a-Si flat-panel (FP) detectors can cause significant shading artifacts in cone-beam CT reconstructions. Most correction models have assumed a linear time-invariant (LTI) model and correct lag by deconvolution with an impulse response function (IRF). However, many ways deconvolution exist. Specifically, the IRF become functions of exposure and the noise within each region. The proposed algorithm framework has the flexibility to be adapted to different a priori constraints while maintaining the benefits achieved by the simultaneous segmentation and reconstruction.

References/Funding Source

Mechanical Modal Analysis of an MR Compatible X-ray Tube

M Shi1
Departments of Radiology, RSL, and Mechanical Engineering, Stanford University, CA

We are developing a new x-ray tube for an MR compatible x-ray system. One of the design constraints is that the source cannot operate continuously at or near the mechanical resonant frequency of any x-ray tube assembly. It is important to determine the resonant frequency in order to avoid passing through it during the spin-up of the tube. Mechanical modal analysis of the x-ray tube has been done by means of both a finite element software program and an analytical approach. Based on a 3-D finite element simulation using the commercial software COSMOL, and a simplified x-ray tube model, the first modal frequency is 85.3 Hz (5100 rpm). Since this frequency is higher than the expected rotational frequency of 60 Hz (3600 rpm), our tube design satisfies our constraint.

References/Funding Source
NIHR01 EB 037627 and the Lucas Foundation

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References/Funding Source
NIHR01 EB 037627 and the Lucas Foundation
A challenge in the development of hybrid X-ray/MRI imaging systems is the close proximity of the X-ray source to the MR magnet. The fringe field of the magnet affects the electronic/optical X-ray source causing focal.dataset filtering and deflection. Previous work from our group focused on correcting for these effects using an active magnetic shielding approach [2]. However, problems with heating of the active shield arose when correcting for magnetic field strengths on the order of 0.1 T. It is proposed that the focal spot deflection can be corrected by applying a static electric field (Estatic) in the direction parallel to the deflection (fig. 1a).

The analytical solution for the electron trajectories in this combined electric and magnetic field environment can be solved for using the approximate coordinate transformation, and subsequent Lorentz boost to an inertial frame K, which moves with velocity c in the Estatic + Bdirection with respect to the laboratory frame K (here B is the vector addition of Estatic and the electric field of the X-ray tube, Estatic, B). In the boosted inertial frame K, the Lorentz factor γ must be applied to all other electric fields (assuming Estatic >> Emagnetic, c = speed of light), yielding a simple solution to the relativistic equations of motion [3]. Trajectories in the laboratory frame K are found by applying an inverse Lorentz transformation followed by an inverse coordinate transform.

The method described above was solved and plotted for a tube potential of 70 kVp and anode-cathode spacing of ± 1.5 cm, Estatic = 4 MV/m (120 kVp corresponded to 20.6 cm). The electron trajectory with no Estatic applied curved drastically and the electron never reached the anode (fig. 1b). However, with Estatic applied, the electron reaches the anode with an insignificant amount of deflection (fig. 1c).

Using the ICUDA interface, the reconstruction time is reduced from 87 seconds (Manufacturer’s Re-Construction time) to 15 seconds using our parallel implementation (speed-up factor 5.8). Hence, recon- struction is sped up considerably with an off-the-shelf CUDA-compatible graphics card.

Furthermore, computationally highly expensive adaptive noise filters can be computed within the inter- ventional time constraints. With a complete implementation of an adaptive noise filter in CUDA, we can re- ducethe computation time further from 1,156 seconds on the CPU to 168 seconds on the graphics card. This corresponds to an 8.9-fold speed-up.
Recently, a promising scatter measurement and correction method for x-ray computed tomography (CT) has been developed and experimentally verified. The method uses a primary modulator, a checkerboard pattern of attenuating blockers, placed between the x-ray source and the object. We have studied the effects of the system parameters on the accuracy of the x-ray scatter correction. An optimization of the modulator design is presented. The blocker size, d, and the blocker transmission factor, a, are critical to the performance of the method. In this work, an error caused by the primary aliasing (whose magnitude depends on the choices of d and a, and the scanned object) is set as the object function to be minimized. The constraints include the x-ray focal spot, the physical size of the detector element, and the noise level. The optimization is carried out by two steps. In the first step, d is chosen as small as possible subject to a lower-bound condition. In the second step, a is selected to balance the error level in the scatter estimation and the noise level in the reconstructed image. The lower bound of d on our tabletop CT system is 0.83 mm. Numerical simulations suggest 0.6 < a < 0.8 is appropriate. Using a Copper modulator, a photon modulator (d = 0.49 mm, a = 0.70) has a significant advantage over an aluminum modulator (d = 2.83 mm, a = 0.90), reducing the error of CT number from 371.4 to 21.9 Hounsfield units, and increasing the contrast to noise ratio from 10.9 to 19.2.

References/Funding Source

Optimization of Modulator Parameters for X-ray Scatter Correction Using Primary Modulation
H Gao1, L Zhu2, R Fahrig1
Department of Radiology, Stanford University, CA; Nuclear and Radiological Engineering and Medical Physics Programs, The George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA

Perfusion CT (PCT) imaging is commonly used in identifying salvageable tissue in cases of ischemic stroke. Based on a CT diagnosis, a stroke patient may be a candidate for endo-vascular treatment. Such procedures are guided by angiographic/flouroscopic systems on a C-arm. However delays between the CT diagnosis and the start of the interventions have a major value of 5 h. Enabling C-arm systems to perform perfusion CT could alleviate this problem and permit intra and post procedural PCT. However, rotation speeds of C-arms are slow compared to CT. We have developed a PCT protocol for C-arm cone-beam CT (C-arm CBCT) that overcomes this problem and has evaluated it in an animal study.

Free unseeded pigs (34 ± 4 kg) were imaged using a C-arm CBCT system (Axiom Artis dTA and DynaCt Siemens AG) and a conventional CT scanner (Somatom 64 Siemens AG). The C-arm rotates in 4.3 s with 1.25 s for turnaround, vs. 0.5 s on a clinical CT. One C-arm scan consists of 6 continuous bi-directional sweeps. Multiple scans with different delays between starts of scans and intra-arterial injection of iodine were used to increase temporal resolution. Scan combinations (6 scans, 3 scans or 2 scans) and different injection protocols (1mls at 100%, 1mls at 67% and 1mls at 50% contrast concentration) were studied. Cerebral blood flow (CBF) maps from C-arm CBCT and CT were calculated in 2 slices and compared. A linear fit correction to the CBF data resulted in the field’s 50% contrast injection having the best intra-modality match and highest concordance correlation coefficient (CC) (mean difference 0.006.88 ml/100g/min of tissue, CCB=0.894). Some of the more clinically relevant 3- and 2-scan sets have performance similar to the 6-scan dataset. This animal study demonstrates that C-arm CBCT can produce accurate cerebral blood flow perfusion maps.

References/Funding Source
National Institute of Health (NIH, grant R01HL087917), by Siemens Health Care, and by the Lucas Foundation.
In this section, you will read about innovations in display and interaction, feature extraction, and computer simulation and modeling techniques. These projects aim to improve the accuracy and efficiency of human interpretation of medical imagery, as well as predict patient prognosis, the molecular subtypes of their disease, and their response to treatment options in a way that is highly personalized for each patient. These efforts share the common goal of developing decision-making tools that assist with patient diagnosis, treatment, and disease monitoring.

References/Funding Source

D Rubin1, V Kleper2, A Flanders3, D Channin2
Department of Radiology, Stanford University, CA; 2Northwestern University, Evanston, IL; 3Thomas Jefferson University, Philadelphia PA

Background: Capturing quantitative and qualitative aspects of images is an essential activity of radiology research. One goal was to develop a tool to capture this information as the radiologist records observations about images. Our tool can be customized and applied to any particular study, making all quantitative and qualitative image content explicit as part of the radiology report.

Evaluation: We previously developed a tool called ClearCapture that captures quantitative and semantic information in images, and stores this in the Annotation and Image Markup format for interoperability. We developed an application providing a menu-driven interface permitting users to define the data capture fields and templates created for the studies. These templates were used and evaluated by three users for sufficiency and efficiency in conducting the respective studies. Discussion: The template editor application provides a menu-driven interface permitting users to define the data capture fields and templates. Whether or not an item is required, and nesting of items. Templates can then be imported into iPAD and used for structured reporting of quantitative and semantic aspects of studies. Users reported that the templates created for the three studies were sufficient for the data collection tasks and that the workflow in using the templates in the research studies was more efficient than it would have been without the tool because data collection is integrated with image viewing.

Reinventing Radiology Reporting: Combining Structured Capture and Radiology Image Annotation

D Rubin1, C Beaulieu1, C Rodriguez1, C Baldassano2, S Napel1
Departments of Radiology and Computer Sciences, Stanford University, CA

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References/Funding Source
callbI Imaging Workpackage, NCI: Dl Rubin, V. Kleper, AS Flanders, DS Channin, P Mongkolwat;

D Rubin1, C Beaulieu1, C Rodriguez1, C Baldassano2, S Napel1
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References/Funding Source
callbI Imaging Workpackage, NCI: Dl Rubin, V. Kleper, AS Flanders, DS Channin, P Mongkolwat;
**Semantic Annotation and Image Mark-up in a Commercial PACS Workstation**

D Rubin1, D Korenblum2, V Yeluri1, P Frederick3, R Herbens2
Departments of 1Radiology, Stanford University, CA; 2Biomedical Informatics, Vanderbilt University, TN

**Abstract**

**Background:** The NCIBIG project recently developed a commercial PACS workstation that included a semantically-aware image annotation tool called iPAD, an open source plug-in to the Osirix image viewing workstation. iPAD extracts and saves quantitative and qualitative information about particular image features. We developed an analytic routine to process each annotated lesion, including performing response category assessments that generate target lesion measurements from the image annotations. Annotated images in the workation, an AIM document is produced simultaneously, without interfering with the speed of image annotation or workflow. AIM objects are stored in a database separate from the images to facilitate image query and to reduce any performance impact on the operational PACS database. We evaluated our implementation by annotating images containing cancer lesions in serial CT studies and by validating the results against medical records. This software module to analyze AIM annotations to produce automatically quantifiable summaries of lesion measurements for tracking tumor burden.

**Discussion:** Our implementation is transparent to the user, while annotating images in the workstation, an AIM document is produced simultaneously, without interfering with the speed of image annotation or workflow. AIM objects are stored in a database separate from the images to facilitate image query and to reduce any performance impact on the operational PACS database. We evaluated our implementation by annotating images containing cancer lesions in serial CT studies and by validating the results against medical records. This software module to analyze AIM annotations to produce automatically quantifiable summaries of lesion measurements for tracking tumor burden.

**References/Funding Source**


**Semantic Reasoning with Image Annotations for Tumor Assessment**

M Levy1, D Rubin2
Departments of 1Biomedical Informatics, Vanderbilt University, TN; 2Radiology, Stanford University, CA

**Abstract**

**Background:** The Annotated Breast Map (ABM) is a semantically aware tool to automate asessment of tumor burden. ABM integrates information from clinical records, radiology information systems, and web-based breast imaging studies. ABM integrates automatically generated target lesion measurements from the image annotations. Our tool is that all the information needed to assess response category assessments that identify (with linear or circularlesions) is directly derived from image annotation; all the user need is to delineate the lesions.

**References/Funding Source**

cabiG Imaging Workshop, Nashville, TN

**Automated Computational Assessment of Tumor Burden**

D Rubin1, C Babaladoma2, C Rodrigue2, M Levy3
Departments of 1Radiology, Stanford University; 2Biomedical Informatics, Vanderbilt University

**Abstract**

**Background:** Radiological imaging provides rich information for evaluating the response of cancer patients to treatment. A challenge, however, is that there are many images, many studies, and no system to automatically identify the tumor burden. We developed an analytic tool to perform response category assessments that identify (with linear or circular lesions) is directly derived from image annotation; all the user need is to delineate the lesions.

**References/Funding Source**

cabiG Imaging Workshop, Nashville, TN
Biomedical Image Metadata Management for Similar Image Retrieval

D Korentzum, D Rubin, S Napel, C Rodriguez, C Beaudou
Department of Radiology, Stanford University, CA

Metadata, such as imaging observations ("semantic metadata") describing radiology images, are usually described in text reports that are not directly linked to the images; this disconnect hinders basic research and the development of new medical systems and educational training tools. We developed a system, the Biomedical Image Metadata Manager (BIMM), (1) to address the problem of managing large volumes of images in less than 1 day. For comparison, the commercial, web-based teaching file, MyPACS, contains ~21,000 cases contributed from 8,952 hospitals.

Conclusion: BIMM combines a compact representation of the teaching-relevant content in reports and a versatile search engine with the scale of the entire RIS/PACS collection of case material. NL-Panels more precise semantic-based search capabilities for radiology images, are usually descriptive and unstructured, teaching-related content is not captured. We developed RADTF using a PHP-configured MySQL database server running on Apache Linux. The RIS/PACS collection of case material, containing 750,000 images, was accessed through a relational database. Our system permits continuous monitoring of our CT equipment and is crucial to our patient safety program. We thus computed Mean Normalized Discounted Cumulative Gain (NDCG) for several metrics.

References/Funding Source: 1Computer Science, 2Radiology, 3Electrical Engineering, Stanford University, CA

Automatic Quantification of Margin Sharpness of Liver Lesions at CT: Application to CBIR

N Agrawal1, J xu, D Rubin2
Dept of Computer Science, Radiology, Electrical Engineering, Stanford University, CA

Purpose: Margin sharpness of liver lesions is related to accuracy; thus we sought to develop a method to characterize margin sharpness, and evaluate it for similar liver image retrieval.

Method: We defined 2 attributes to characterize margin sharpness: difference in intensities between the lesion and its surrounding tissue, and abruptness of transition across the lesion boundary. We automatically predicted the sharpness of a lesion by fitting sigmoid functions along radial lines automatically drawn across the lesion and observing characteristics obtained for each fitted curve. We represent each lesion by a histogram of these parameters. We then computed the Mean Normalized Discounted Cumulative Gain (NDCG) for several metrics.

Results: The correlation coefficients for blue and intensity difference attributes in simulated images were 0.983 and 0.998 respectively. The mean, standard deviation, worst NDCG score for clinical images for the retrieval of 5 images, 8, 10, 20 and 30, were 0.84, 0.07, 0.63, 0.85 and 0.06, 0.63, respectively. Discussion: Our method is highly correlated with known margin attributes and accurately predicts reference standard rankings in clinical CT images of liver lesions.
Evaluati on of ROI Methods for High Throughput Molecular Image Quantification
F Habs v 1, S Budhapr a, T Dej py 2, C Lavi n 3, D Pak 4 1 Department of Radiology, 2 Department of Pediatrics, Stanford University, CA

Purpose: Previous studies showed that there is a significant variability on molecular image quantification depending heavily on the definition of region of interest (ROI). To address this issue, several semi-automatic segmentation tools have been developed. For molecular images, these tools usually perform poorly due to lack of clear boundaries of a specific region of interest. This is especially a challenge in high throughput image quantification, typically performed in in-vivo clinical imaging. The goal of this study is to evaluate and compare the performance of different ROI definition methods.

Materials and Methods: For this study, we used five dynamic datasets obtained from microPET/CT, which was acquired as a phantom study. In the first part of our study, we used a large volumetric ellipsoidal ROI to completely define region of interest. The normalized and adjusted ROI mean statistic value at each time point of the dynamic data is computed and compared with different threshold level, which is applied to remove low-level pixels from considering on the computation of ROI statistics. In subsequent study, we compared mean ROI statistics of most commonly

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References/Funding Source
Purpose: Surface-enhanced Raman scattering (SERS) microscopy is a light scattering technique of vibrational microspectroscopy for the selective detection of specific biomolecules. This technology combines the advantages of Raman imaging and biological visualization and is useful in early quantifying biological processes and in early prediction of disease. The goal of this work was to develop an ontology for Raman spectra unmixing in living subjects thereby enabling capture of meaningful features of a biomarker, including imaging data acquisition and analysis as well as biological application. In addition, we create a differential, biological process and experimental subject that are associated with each biomarker. Materials and Methods: We identified imaging biomarkers from 19 primary research projects that have shown that many of the similarities in Raman spectra unmixing can be applied to the data where the relatively lower signal-to-noise-ratio in vivo presents an even greater challenge. We are currently working toward optimizing the performance of this quantitative technique for Raman spectra unmixing in living subjects thereby resulting in significant potential for application of Raman spectroscopy in the analysis of nanoparticles.

References/Funding Source

Department of Radiology and Microbiology and Immunology, Stanford University, CA.

Purpose: With the advancement of pre-clinical molecular imaging techniques, a wide array of novel imaging biomarkers have been developed and demonstrated effectiveness in quantifying biological processes and in early prediction of therapeutic outcomes. However, integration and re-use of imaging biomarker data and knowledge is incomplete because most of the quantitative measurements are only available in the text-based literature that requires expertise and time to synthesize. The goal of this work was to develop an ontology of imaging biomarkers to enable storage and retrieval of detailed imaging biomarker measurements, mining new information from the expanding imaging biomarker literature, and translation of novel imaging biomarkers to laboratory and clinical research.

Method: We have begun a bottom-up approach to constructing the ontology by conducting a literature review of the Journal of Molecular Imaging and Biology (2006-present) to identify and catalog imaging biomarkers. To resolve ambiguities, we decompose a quantitative imaging biomarker into three components: quantitative measurement and combination of data (single point, serial, etc.), measurement modality and contrast agent/tracer, and biological target. This approach enables capture of meaningful features of a biomarker, including imaging data acquisition and analysis as well as biological application. In addition, we create a differential, biological process and experimental subject that are associated with each biomarker.

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References/Funding Source

Department of Radiology and Microbiology and Immunology, Stanford University, CA.
A Quantitative Shape Descriptor for Content-Based Retrieval of Similar Appearing Lesions in Medical Images

J Xu1, CF Beaulieu2, DL Rubin2, S Napel1

Departments of "Electrical Engineering and Radiology, Stanford University, CA"

Purpose: To develop a quantitative descriptor of shape for use in content-based image retrieval of similar appearing lesions in medical images.

Materials and Methods: We used three distinct contour-based shape features: compactness, centroid distance signal, and multi-scale local area integral (LAII). Compactness gives a rough measure of circularity. Centroid distance signal is obtained by sampling the shape boundary in a polar coordinate system centered at the centroid of the shape. LAII entails the notion of curvature in a scale-space. Together these features comprise a 14-element feature vector invariant to translation, rotation, and scale. We defined the similarity between two images as the inverse of a weighted sum of the absolute difference between each element. We tested our feature with simulated images using several reference standards, and with clinical images (lesions from 79 portal-venous-phase liver CT scans) using a reference standard for similarity derived from five readers who rated the smoothness of each lesion boundary on a 5 point scale. We used a leave one out analysis and Normalized Discounted Cumulative Gain (NDCG) to compare rankings of similarity to each query image with the expected ranking based on the reference standard, and averaged over all query images.

Results: In simulated images, the feature combining weights were trained to exhibit excellent results for all reference standards, with average NDCG >90% for all queries. Quite good results were also obtained with clinical images.

Conclusions: Experiments in a simulated lesion database show that our computational shape descriptor is trainable to a wide variation of notions of similarity and, in each case, ranks similarity in close agreement with the reference standard. Results in clinical images were visually excellent, but mean NDCG scores were not as favorable owing to difficulties in setting the reference standard.

Abstracts: Image Analysis, Bioinformatics, and Computational Modeling

Prototype Software for Content-based Image Retrieval of Similar Appearing Lesions in Medical Images

J Xu1, CF Beaulieu2, DL Rubin2, S Napel1

Departments of "Electrical Engineering, Radiology, Stanford University, CA"

Purpose: To develop a software platform for retrieving medical images containing similar appearing lesions.

Materials and Methods: We included a combination of semantic features described by radiologists (using iPAD — see separate report), and pixel-based features derived by computer algorithms, to create rich feature vectors describing each image in our database. Similarity between any pair of images was computed as the negative of a weighted sum of differences between corresponding elements of two feature vectors. Weights were derived using a machine-learning method that maximizes the retrieval performance, as measured by Normalized Discounted Cumulative Gain (NDCG). The software was tested using a database of 79 portal-venous liver CT images containing various types of lesions and several reference standards created by radiologists. Performance was evaluated using NDCG and Precision-Recall Metrics.

Results: The system performed well, ranking images in the database appropriately with respect to the query and the reference standard. See Figure for details.

Conclusions: Content-based retrieval of lesions seen in radiological images is feasible. This warranted continued development of a larger and more comprehensive database, and extension to other diseases and modalities.

Abstracts: Image Analysis, Bioinformatics, and Computational Modeling
Lung Nodule Detection in the Peripheral Visual Field: Impact of Size, Distance and Local Lung Complexity

M Tall, D Lu, K Roychoudhury, J Ross, D Paik, S Napel, G Rubin
Department of Radiology, Stanford University, CA

Purpose: To determine the factors that attract or distract observer attention when searching for lung nodules in volumetric CT data.

Method: A 3x3x5 cm lung mass was simulated and imbedded into 5-mm-thick subvolumes (SV) extracted from 3 unenhanced lung MDCT scans (4mm, 1.25 mm, 0.7 mm thickness, 0.7 mm increment). The mass was visible on all transverse sections in the SV. Two collections of 30 and secondary nodules were simulated with 4-6 mm and 7-8 mm diameters, respectively. A total of 207 SVs were created containing one secondary nodule imbedmed at a random depth and distance from the edge of the mass of 2.5, 3.7, 5, or 10 cm, and along rays cast every 45° from the center of the mass. For each SV, we created a movie of the transaxial slices from superior to inferior at 3 sections. Six radiologists observed each movie and filled out a confidence rating form. A computer algorithm was used to track the confidence ratings and calculate statistics for each feature.

Findings: Upon completion of each viewing the radiologist assigned a confidence rating (0-5) to the detection of a secondary nodule and indicated on the screen the slice containing the second CT and PET datasets

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Cancer screening programs are currently recommended for only certain types of cancer, such as breast cancer, but not for others, such as lung cancer. The goal of this project is to develop progress models for lung cancer and breast cancer in order to address two critical issues in cancer screening: how early we need to detect cancer (i.e., the ideal detection threshold) and whether we need to screen asymptomatic individuals, so that we can capture the tumor before it progresses beyond cure (i.e., the ideal screening threshold).

We develop a stochastic model for cancer progression, which enables us to estimate the cure fraction from cancer and the tumor volume doubling time. The estimate about cure fraction allows us to address the ideal detection threshold of a screening technology whereas the doubling time allows us to estimate the ideal screening interval. The model is applied to data on lung cancer and breast cancer separately. The study population was identified from the Surveillance, Epidemiology, and End Results (SEER) cancer registry and included patients diagnosed with non-small cell lung carcinoma from 1980 to 2003 and patients diagnosed with invasive ductal carcinoma from 1975 to 1979. Model parameters were estimated based on the SEER data using the maximum likelihood estimates. The model reproduces SEER, validates against two external clinical trials and produces estimates of tumor volume doubling times that are consistent with empirical data. Our results demonstrate that breast cancer has a much higher cure fraction than lung cancer if the tumors are detected at the same size. In the absence of screening, we predict that the likelihood of cure due to clinical detection is 44% for breast cancer whereas 6% for lung cancer. In order to achieve a cure fraction of 30% by screening, breast cancer needs to be detected and treated when it is 1.9 cm in size whereas lung cancer needs to be detected and treated when it is 0.7 cm. Our estimates also show that lung cancer grows more rapidly than breast cancer: the estimated median tumor volume doubling time is 134 days for lung cancer versus 252 days for breast cancer. These findings suggest that when compared to breast cancer screening, an effective screening program for lung cancer needs to use a technology with smaller detection threshold and a shorter screening interval.

References/Funding Source U01CA88248 and Canary Foundation

Quantifying and Comparing the Disease Progression Characteristics of Lung Cancer and Breast Cancer
R.S. Lin1 and S.K. Plevritis2
Departments of Biomedical Informatics and Radiology, Stanford University, CA

Breast cancer is the leading cancer for women in the United States. Patients’ outcomes have been improved since the 1980’s due to cancer interventions, such as mammography screening and adjuvant therapy. The goal of this study is to quantify the effects of mammography screening and adjuvant therapy on likelihood of cure from breast cancer.

We developed a mathematical model of the natural history of cancer to estimate the relationship between the size of the primary tumor and the likelihood of cure. The model is applied to breast cancer, separately for patients who were diagnosed from 1975 to 1979 and those diagnosed from 1991 to 1993. Model parameters were estimated using data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry. The model reproduces SEER, validates against an external clinical trial and produces estimates of tumor volume doubling times that are consistent with empirical data. Our results suggest that the likelihood of cure from breast cancer has been substantially improved (from 44% to 67%) from 1975 to 1979 due to advances in adjuvant therapies and screening mammography. The median tumor size at which the disease progresses to non-curable state has increased from 2 cm to 3.6 cm, primarily due to advances in adjuvant therapy. Consequently, the median time for screening mammography (threshold 1.5 cm) to detect a tumor while the disease is curable increased from 0.8 years to 2.8 years, indicating screening has become more effective due to the advances in treatment. Our results suggest that given the efficacy of current medical history and values pushes the burden of information regarding the complex interplay of mammography screening benefits and harms to clinicians.

We plan to further develop natural history model for breast cancer patients with different hormone receptor statuses and use the model to understand the cancer progression patterns of those cancer.

References/Funding Source U01CA88248 and Canary Foundation

Breast cancer screening programs are currently recommended for only certain types of cancer, such as breast cancer, but not for others, such as lung cancer. The goal of this project is to develop progress models for lung cancer and breast cancer in order to address two critical issues in cancer screening: how early we need to detect cancer (i.e., the ideal detection threshold) and how often we need to screen asymptomatic individuals, so that we can capture the tumor before it progresses beyond cure (i.e., the ideal screening threshold).

We develop a stochastic model for cancer progression, which enables us to estimate the cure fraction from cancer and the tumor volume doubling time. The estimate about cure fraction allows us to address the ideal detection threshold of a screening technology whereas the doubling time allows us to estimate the ideal screening interval. The model is applied to data on lung cancer and breast cancer separately. The study population was identified from the Surveillance, Epidemiology, and End Results (SEER) cancer registry and included patients diagnosed with non-small cell lung carcinoma from 1980 to 2003 and patients diagnosed with invasive ductal carcinoma from 1975 to 1979. Model parameters were estimated based on the SEER data using the maximum likelihood estimates. The model reproduces SEER, validates against two external clinical trials and produces estimates of tumor volume doubling times that are consistent with empirical data. Our results demonstrate that breast cancer has a much higher cure fraction than lung cancer if the tumors are detected at the same size. In the absence of screening, we predict that the likelihood of cure due to clinical detection is 44% for breast cancer whereas 6% for lung cancer. In order to achieve a cure fraction of 30% by screening, breast cancer needs to be detected and treated when it is 1.9 cm in size whereas lung cancer needs to be detected and treated when it is 0.7 cm. Our estimates also show that lung cancer grows more rapidly than breast cancer: the estimated median tumor volume doubling time is 134 days for lung cancer versus 252 days for breast cancer. These findings suggest that when compared to breast cancer screening, an effective screening program for lung cancer needs to use a technology with smaller detection threshold and a shorter screening interval.

References/Funding Source U01CA88248 and Canary Foundation

References/Funding Source U01CA88248, Dean’s Postdoctoral Fellowship School of Medicine, Stanford University (2010-2011). S.E. Geneser, S.L. Rutledge, S.K. Plevritis.

The Effect of Mammography Screening Schedules on Age-Specific Mortality and Survival
S. Ganesan1, S. Plevritis2
Departments of Radiology, RSI, Stanford University, CA

Background: The recent changes in U.S. Preventive Services Task Force (USPSTF) breast cancer screening recommendations have generated significant confusion and controversy. Indeed, the suggestion that women from 40-49 years of age make individualized decisions to screen based on their own medical history and values pushes the burden of information regarding the complex interplay of mammography screening benefits and harms to clinicians.

Objective: Our goal is to simulate and examine the benefits of mammography screening schedules among various age groups and provide additional metrics to better elucidate the impact of screening.

Methods: We simulated screening and treatment among a large population of women to determine the effect of regular annual screening at age 49 on age-specific breast cancer survival, morbidity, and life years saved.

Results: Though there is little relative difference between the overall population mortality levels, there is a significant improvement in mortality rates among women who die in their 40s and 50s when the population is regularly screened from 40-74 as opposed to 50-74. Moreover, our preliminary analysis indicates that regular screening among women aged 40-74 with no screening after age 47 to be the most efficient screening schedule in terms of life years saved per woman screened.

Conclusion: An age-based analysis of mammography screening schedules provides additional information about the benefits of screening that may be useful in deliberations regarding the benefit of screening women between the ages of 40 and 50.
In Vivo Metabolic Imaging of Hyperpolarized [1-13C]-Pyruvate in Orthotopic Hepatocellular Carcinoma

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A primary liver cancer, hepatocellular carcinoma (HCC), is a highly malignant tumor type with average survival rates that are currently less than a year following diagnosis. Most patients with HCC are diagnosed at an advanced stage, and no efficient marker exists for determining prognosis and/or predicting response(s) to therapy. In the present study, we implemented a three-dimensional double-echo chicken spectroscopic imaging (3D DSE-EPSI) pulse sequence to investigate potential hallmarks of cellular carbon metabolism in rat liver bearing orthotopic HCC. In addition, gene expression analysis was performed for lactate dehydrogenase-alpha (LDH-a), NADH quinone oxidoreductase-1 (NOQ1), and alanine aminotransferase (ALT) using quantitative real-time PCR. We show that differentially expressed genes and proteins in pyruvate metabolism could be exploited to distinguish HCC tissues from normal liver tissues. A total of 7 buffalo rats were surgically implanted with hepatocellular carcinomas cells into the medial lobe of the liver. A 3 ml bolus injection of hyperpolarized [1-13C]-pyruvate was administered via the tail vein, resulting in a peak blood concentration of approximately 8 mmol/L. Acquisition of MRSI data began 20 s after the start of bolus injection. Computed sets of metabolic maps are displayed along with a T1-weighted proton image from a representative 3D volume of a rat liver (Fig 1, top). Spectra from tumor voxel and normal liver voxel displayed elevated Lac and Ala (Fig 2a-b), with corresponding gene expressions for LDH and ALT shown in Fig 2c. The data herein suggest that the conversion of exogenous [1-13C]-pyruvate to [1-13C]-lactate and [1-13C]-alanine is a characteristic marker of HCC in vivo. Such molecules of significant HCC should serve as an impetus to developing novel enzyme inhibitors as therapeutic agents with hyperpolarized 13C MRSI serving as a diagnostic tool for early detection a surrogate marker or endpoint for drug activity targeting these specific enzymatic pathways.

References/Funding Source

GE Healthcare

Distortion Reduction of Metal Artifacts in MRI using Shear Correction

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Imaging around metal in MRI is known to be challenging due to susceptibility effects [1]. Susceptibility differences give rise to arbitrary frequency shifts which is the primary reason for distortion and image artifacts. Our method Slice Encoding for Metal Artifact Correction (SEMAC) [3] correct for slice distortion by using slice angle tilting (SAT) [3].

VAT is a simple modification that compares using the same slice gradient used for excitation during the readout window. This essentially tilts the voxels in such a way that off-resonance spins appear to be located in the correct position with respect to on-resonance spins.

There are, however, limitations associated with this method: (a) the readout window is limited to the length of the slice gradient, which leads to restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency; (b) the readout k-space is effectively modulated by the slice gradient, resulting in restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency; (b) the readout k-space is effectively modulated by the slice gradient, leading to restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency; (b) the readout k-space is effectively modulated by the slice gradient, leading to restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency; (b) the readout k-space is effectively modulated by the slice gradient, leading to restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency; (b) the readout k-space is effectively modulated by the slice gradient, leading to restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency; (b) the readout k-space is effectively modulated by the slice gradient, leading to restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency; (b) the readout k-space is effectively modulated by the slice gradient, leading to restrictions of the readout duty cycle and thus signal-to-noise (SNR) efficiency.

Butts-Pauly has shown that this blurring can be mitigated with the use of a quadratic phase RF pulse and/or restricting the readout window to the main lobe of the RF pulse [4].

This work proposes the use of a processing method, called shear correction, to resolve readout distortion instead of using VAT. In SEMAC, slice distortion is resolved by performing extra phase-encoding in the slice direction. Therefore, the exact amount of off-resonance is known as is linear with distance from the center on-resonance slice. Instead of using VAT, slice distortion can be corrected by shifting the slices in the readout direction. Thus, the readout window is no longer limited to the length of the RF pulse width, allowing longer readout windows (e.g., lower receive bandwidth), increased SNR and/or higher spatial resolution images.

References/Funding Source

GE Healthcare

Parallel Transmit Enabled Pulse Sequence Development for High Field MRI

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We are developing multi-channel RF transmit systems hardware and methods for full transmit capability for 7-T MRI human MR imaging. Due to the RF wavelength becoming comparable to human body dimensions at 7 T, image quality can be seriously degraded as a result of propagation delays through conductive/dielectric tissue, leading to destructive interference of the transmitted signal and across inhomogeneity. By implementing multiple transmit sources and coil elements, we will create the ability to transmit independently to each coil element. A major application of this new technology will be to improve B1 uniformity. Two specific methods will be investigated. The first is referred to as “B1 shimming”, and is a scalable method which replaces a single large RF power amplifier with an array of smaller amplifiers, permitting independent control of the phase and amplitude of the RF pulse transmitted from each coil element. A second method known as “parallel transmit”, will allow the transmission of multiple RF waveforms simultaneously, one from each coil element, which enables the acceleration of 2D and 3D RF sequences, thereby geometrically tailored excitation volumes. In addition we are developing hardware and methods to explore the use of multiple spatial modes associated with volumetric transmit array coils and variations of the Butler Matrix beam forming networks. This will allow us to control many field patterns with only one or two transmit waveform sources and RF power amplifiers. By interleaving multiple RF field distributions we have the potential to improve overall RF transmit uniformity and image quality over larger fields of view.

References/Funding Source

GE Healthcare
High-Frequency Subband Compressed Sensing MRI

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Compressed sensing (CS) is an acquisition and reconstruction technique that can dramatically reduce the measurement size [1-2]. Its promise to improve imaging speed of magnetic resonance imaging (MRI) has been successfully demonstrated with the wavelet transform [3]. CS MRI assumes that MR images are sparse (or compressively) typically in the wavelet domain, meaning many wavelet coefficients are close to or equal to zero. Conventionally CS MRI, however, is limited by computational complexity with existing acquisition methods as well as by possible reconstruction failure, which manifests as residual incoherent artifacts.

We present a novel method, called Hi-Sub CS (High-Frequency Subband Compressed Sensing), to better exploit the increased sparsity of the high frequency information in images compared with that of the lower frequency information. The idea of this method is to undersample the outer k-space region (high-frequency subbands) much more than the central k-space region. Wavelet subbands typically contain different wavelets due to the wavelet-tree structure; high-frequency subbands contain outer area that is highly undersampled with randomized sample positions. A demonstration of Hi-Sub CS in a GE resolution phantom is shown in the figure. Despite a net acceleration of 16 (R = 4 and R CS = 20), the high-resolution features in the phantom are very well depicted due to a better sparsifying transform for CS.

The Hi-Sub CS is a resolution phantom. Beginning with a 128 X 128 X 128 full-sampled image (LEFT), the corresponding image created with Hi-Sub CS (MIDDLE). In Hi-Sub CS, the use of parallel imaging (AC) combined with the randomization and outer k-space reduction at control of the size of the outer k-space region made very little loss of high-resolution detail. This is highlighted in the central-sliced image.

B1 inhomogeneity. Conventional fat suppression pulses. A slab-selective SSFP pulse sequence with a robust two-echo implementation of the SSFP SE state, causing ghosting artifacts. We propose GUINNESS (Group-encoded Unilateral Inversion Nailing for Non-contrast Enhancement in the Steady State) with a balanced SSFP-Dixon technique with a novel group-encoded k-space segmentation scheme for breath-hold non-contrast MRA. A new group-encoded view ordering scheme was developed to a minimize ceddy currents b) retain sequential and centric view ordering properties for contrast manipulation and immunity to breath-hold loss c) enable use of non-separable sampling patterns such as 2D self-calibrated parallel imaging as well as k-space corner removal. The new flexible ordering helped restrict scan times to breath-holding limits. A 3D dual-echo bipolar readout balanced SSFP pulse sequence with a robust two-echo Dixon reconstruction algorithm with 130ms at 3T. This enabled us to acquire the 3D volume in a single breath-hold, eliminating the need for respiratory triggering which could be unreliable or prolong scan times, especially in sick and elderly patients. Additionally, free-breathing scans were acquired to assess the motion robustness of the group-encoded k-space segmentation scheme.

T2 Maps and Diffusion-Weighted Imaging of Knee Cartilage with a DESS Sequence at 3T

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INTRODUCTION: In order to follow the changes related to early osteoarthritis and cartilage repair, we require the capability to show the morphological and biochemical properties of cartilage. Two promising techniques are T2 mapping and diffusion-weighted imaging (DWI).

The Dual-Echo Steady-State (DESS) sequence has been used for morphological and cartilage characterization. However, we require an algorithm in a clinical setting.

METHODS AND RESULTS: We obtained T2-maps at 3T using EPI sequences with excitations as follows: one with a gradient amplitude of 4.0 G/cm and an 18° flip angle, and a second with a gradient amplitude of 0.46 G/cm and a 35° flip angle. From the four acquired images, we calculated T2 and ADC maps. The T2 values were compared to those generated with the gold standard sequence (a spin-echo sequence of acquisitions with varying echo times). In all cases, the T2 values estimated simultaneously with ADC were closer to the gold standard than when estimating T2 independently of these effects.

Variable Voxel-Size Intensity Correction

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High-density surface coil arrays have been used for achieving highly-accelerated, high resolution images for brain, breast and cardiac MRI studies [1-5]. Due to the low SNR of the coil elements, these arrays usually exhibit sensitivity variations across the field of view. Several intensity correction algorithms have been investigated in literature, and many of these algorithms significantly change the intensity in the data due to the post-processing, which is undesirable [3,4]. In this study, we present a variable-voxel-size intensity correction method that maintains the original noise profile while reducing intensity variations across the image.

The principle idea consists of averaging voxels in regions of low sensitivity and properly scal- ing the result, thereby boosting the SNR in these regions. We present the results of this variable voxel-size algorithm for an ultrasound resolution 3D breast phantom scan using a 6-channel surface coil array. We assumed that the coil intensity profile is a slowly varying spatial function and approximated this bias field using a low pass filter on the original data. We normalized this bias-field and created a "volumetric voxel map" where larger voxel sizes correspond to regions of low intensity of the bias field. We passed the original dataset individually through scaled low pass filters of varying bandwidths to achieve the desired resolution in the voxel volume map. In the final corrected dataset, we chose the appropriate dataset for each voxel based on the voxel volume map. This results in better visualization of the glandular tissue near the chest wall using the variable voxel correction. Additionally, the correction algorithm is conservative in terms of increase in voxel volume, so there is no noticeable loss of detail in breast images. Further studies need to be performed to evaluate the utility of this algo- rithm in a clinical setting.
In this work, BI maps of phantoms were obtained using the standard gradient echo double angle method (DAM) and using the SEMAC DAM [4,5] on a 1.5T whole-body MR scanner. A comparison of these maps shows an insignificant difference of 0.85% between these techniques, validating the accuracy of the SEMAC DAM technique. We have applied the SEMAC DAM technique to a shoulder implant phantom as shown in the figure. We had validated the use of the SEMAC double angle echo method for B1 mapping around metal. Further experiments need to be carried out on different metallic implants, in different orientations. The results obtained will help determine locations that may suffer from increased local SAR.

Body MR Imaging

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Power or specific absorption rate (SAR) estimations are important when testing the MR compatibility of implanted metallic objects. B1 mapping through the flip angle maps is a tool often used to estimate SAR experimentally. As the number of metallic implants used during orthopaedic procedures increases [1], there is a need for an accurate and safe imaging technique. Recent developments in pulse sequences such as SEMAC [2], has enabled MRI near metallic implants by correcting image artifacts present and allows for improved image quality. Despite these advancements, more experiments need to be carried out in order to make sure that the new sequences comply with SAR limits [4] and do not cause osteoclasticity of tissues.

Reference/Funding Source


Comparison of Non-Contrast-Enhanced IFIR bSSFP for Renal and Mesenteric MRA at 1.5T and 3T

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Patients with kidney disease are most likely to need renal imaging, yet the standard technique of contrast-enhanced MR angiography with gadolinium may be contraindicated in these patients. This and other disadvantages demonstrate a need to explore non-contrast-enhanced MRA methods. Albeit, the 3T HASTE MRI sequence was developed with one non-contrast-enhanced MRA technique, which has shown promising results in respiratory-gated In-Flow Inversion Recovery (IR) MRA. The IR sequence has potential in a wide range of applications, especially in the clinical adoption of this approach for routine clinical use in patients where contrast agents are contraindicated or for the detection of aneurysms.

Reference/Funding Source


High-resolution T2 and Diffusion-weighted Breast Imaging using FADE

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Dynamic contrast-enhanced MRI is commonly used to detect breast tumors. However, its use is limited by the fact that it is expensive and requires a physician to be present during the study. Invasive and noninvasive breast MRI improve the feasibility of using MRI for breast cancer screening.

We are using a fast acquisition double contrast technique (FADE) [3] to image breast lesions without injecting contrast. The FADE sequence is a steady-state imaging sequence that acquires two images with spiral gradients played between the two acquisitions. The first echo, the time-2 echo, and the second echo has strong T2 weighting. We are able to modify the image contrast by changing the flip angle, echo times, and the gradient ordering for our gradient source; for our current studies, we are modifying the diffusion weighting by changing the spiral gradient areas.

We have scanned 7 patients with suspected lesions using the standard clinical breast MRI protocol and the FADE sequence.

References/Funding Source


Reducing the Scan Time of Time-Resolved, 3D Phase Contrast Imaging with 2D Autocalibrated Parallel Imaging

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Time-resolved 3-dimensional phase-contrast MRI (3D PCM) has developed as an active area of research in vascular imaging because of its ability to acquire directional flow information along an entire vascular structure. When the motionless protons in an object are imaged as a function of time, parallel imaging can accelerate data acquisition in one dimension. In this work, we demonstrate the ability to perform parallel imaging of the entire body to accelerate data acquisition in one dimension. This work in progress also demonstrates the ability to perform parallel imaging at different flip angles to improve image quality.

All imaging was performed using Sigma scanners (GE Healthcare, Milwaukie, WI, USA). The sequence used for the time-resolved flow measurements was a 3D spoiled gradient-echo (SGE) phase contrast sequence modified to collect k-space data for an auto-calibrated parallel imaging reconstruction.

Reference/Funding Source

NIH Grant RR009784 and NSF Healthcare, MT Alley, PW Worters, A Hissaw, S Vasanawala, Accepted for the Scan Time of Time-Resolved, 3D Phase Contrast Imaging with 2D Autocalibrated Parallel Imaging, in Proc., ISMRM, 10th Annual Meeting, Stockholm, Sweden, June 14-19, 2010.
Adaptive Slice Encoding for Metal Artifact Correction

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Metallic implants are routinely used for joint replacements, bone reconstructions, spinal fusions, and dental fillings. In MRI, metallic implants cause severe susceptibility variations that result in static magnetic field variations on the order of ~10-100 kHz at 1.5T. These cause severe artifacts in normal imaging, often rendering MRI non-diagnostic. However, by acquiring a limited 3D (z,y,x) space, where f-frequency, image distortions can be dramatically reduced at a cost of increased scan time. We recently developed a method called slice-encoding for metal artifact correction (SEMAC), which is a useful routine at Stanford Hospital [1]. The main limitation of SEMAC is the increased scan times, which is around 11-10 minutes. Because the pattern of magnetic field distortion varies considerably based on the metallic device shape, composition, size and orientation, it is desirable to tailor the scan to the specific device, often enabling reduced scan times.

For each slice, a “spectral localizer” scan is obtained by turning off the readout gradients in a standard 2D multislice scan (about 30 seconds), to detect the frequency range for each slice. A modified SEMAC acquisition and reconstruction uses a variable flip angle on the imaging slab for each slice, and the slice thickness is modified to efficiently saturate the metallic implant.

Partial saturation of an outer slab can reduce inflow enhancement and pulsatile ghost artifacts by preparing flow at a steady state before entering the imaging slab, while decreasing their signal [2]. However, partial saturation requires an additional RF pulse and spoilers, increasing TR. Here, we present a short RF pulse that simultaneously excites the imaging slab while partially saturating the outer slab [2].

The new RF pulse combined a maximum-phase RF pulse for the partial saturation slab and a minimum-phase RF pulse for the imaging slab. By using the maximum-phase RF pulse for the partial saturation slab, gradient spoiling for this slab can be achieved by the slab-select gradient [3]. By using the maximum-phase RF pulse for the par-

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Parallel Transmit Enabled Pulse Sequence Development for High-Field MRI

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High-field MRI systems have the potential to enable ultra-high spatial resolution imaging, provide enhanced susceptibility contrast and improved chemical species discrimination in spectroscopy. However, high-field MRI also poses challenges in the form of decreased radio frequency (RF) excitation homogeneity. This manifests as shading artifacts in the images, making quantitative imaging challenging. Recent developments in multi-transmit radiofrequency pulse design offer a possibility of combating this by using multiple parallel transmitters to excite a complex pattern in k-space using RF and gradient pulses in multiple channels that results in combating this by using multiple parallel transmitters to excite a complex pattern in k-space using RF and gradient pulses in multiple channels that results in a net uniform excitation field across the region of interest. One of the key inputs to excitation k-space using RF and gradient pulses in multiple channels that results in a net uniform excitation field across the region of interest is the initial phase variation, we can perform multiple low flip-angle excitations with FSE readouts without waiting for the longitudinal signal to recover via T1 relaxation, a condition ideal for spectroscopic imaging of hydrated, highly mobile water, which is promising for T2 mapping. Its feasibility in hyperpolarized 13C applications will be explored in the future.

We report a new MR spectroscopic imaging sequence that utilizes non-CPMG FSE echo trains with quadratic phase modulation of the refocusing pulses to catalyze the stability of longitudinal magnetization while keeping the transverse magnetization refocused during the echo train. Other alternative phase modulation schemes (XY, MLEV etc.) are useful only over a very restricted range, close to 90°, of the refocusing pulse rotation angle (latitude). The non-CPMG phase scheme performs well for rotations as low as 160° and with a proper design of RF pulses of wide bandwidth, this technique can be quite suitable for fast spectroscopic imaging. Because non-CPMG allows us to obtain a full magnitude signal even in the presence of initial phase variation, we can perform multiple low flip-angle excitations with FSE readouts without waiting for the longitudinal signal to recover via T1 relaxation, a condition ideal for spectroscopic imaging of hyperpolarized nuclei. As a result, we show proof of concept results of multi-excitation non-CPMG with low flip angles (MENLO) and one of its potential applications for mapping T1 relaxation time. The technique was performed on a 3T MRI platform with a 13C enriched phantom, with imaging parameters suitable for future hyperpolarized 13C applications. Consistent and stable FSE signals were obtained for a range of 7000 Hz chemical shift frequencies (Fig 1) and the longitudinal signal sustained for multiple excitations. Figure 2 shows the comparison of 13C CEST images acquired with the CESTACCE and the CESTACMSE techniques, with the CESTACMSE technique showing more prominent metabolite suppression with less signal loss. This technique is promising for mapping T1 relaxation time and is currently being evaluated in vivo by the Menlo Park team at GE with the aim to develop a novel technique for water suppression and quantification.
Magnetic Resonance Spectroscopy

Adiabatic Magnetization Preparation Pulse for T2-contrast at 7-Tesla

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High-resolution MRI at 7T has the potential to provide tremendous improvement in the diagnosis and treatment of a wide range of neurological diseases. High-resolution T2-weighted sequences are sensitive for assessing subtle structural abnormalities associated with many of these diseases [1]. Unfortunately, conventional T2-weighted sequences, such as Fast Spin Echo (FSE), utilize a train of high flip-angle Shinnar-Le Roux (SLR) pulses that are very susceptible to the severe B1 inhomogeneity and SAR limitations observed at 7T. To explore the potential of adiabatic magnetization preparation (AMP) technique to obtain B1-sensitive T2-contrast at 7T, a BIR-pulse [3,4] with a flip-angle tailored to separate each B1-sensing interval is used to initiate T2-decay. An AMP pulse was designed for use at 7T and validated with phantom and in vivo experiments.

Figure 1A: Proton and (B) AMP pulse applied. The spectral profile of AMP pulse followed by a 90° excitation pulse plotted for the AMP pulse scaled to range of B1 sensitivity factors.

Glutamate and Glutamine Changes with Ethanol Treatment in the Rat Brain Detectable using 3T CT-PRESS

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A variety of psychiatric disorders are associated with brain elevations in the combined resonances of glutamate (Glu)-glutamine (Gln) (Glu/Gln) (GS) (i.e., Glu) [1]. However, Glu measurements, based on the complex relationship between Gln and Glu. The current analysis was conducted to determine whether the signal from Glu could be quantified separately from that of Gln.

The study group comprised 10 pairs of healthy Wistar rats. After the pre-EOH baseline scanning session (MRS), one rat from each sibling pair was exposed to a mixture of EOH and air, and the other to air using a solvent alcohol inhalation system. Animals received intraperitoneal injection to vaporize EOH (14 at night) for 24 weeks. MRS was performed at week 16. Blood ethanol concentrations (BECs) averaged ~445 mg/100ml in the EtOH group. MRS spectra were acquired with CT-PRESS from a 16×16 mm voxel in the basal ganglia. The novel finding presented here is the observation of higher levels of Glu in the EtOH group compared with the control group after 16 weeks of EOH exposure (MRS2, Figure 1).

In increases in brain Glu are reported in patients with hepatic encephalopathy upon postmortem examination [2]. Evidence for mild liver damage in the EtOH group [3] and for elevations in N-acetyl aspartate with EOH exposure [6] suggests an explanation for elevated Glu. The mechanism of brain amonia detoxification is the formation of Gln from Glu by the enzyme glutamine synthase [7]. With prolonged EOH exposure, however, the levels of Glu synthetase may be compromised [8], leading instead to a buildup in the levels of Glu as observed after 24 weeks of EOH exposure. Given the decline in NAA, the current results may imply that elevated Glu levels mediate brain EOH toxicity (p < 0.05).

Dynamic and High-Resolution Metabolic Imaging of Hyperpolarized [1-13C]-Pyruvate in the Rat Brain

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Fast chemical shift imaging strategies are advantageous in metabolic imaging of hyperpolarized compounds due to the limited duration of the signal amplification. At the same time, reducing the acquisition time in hyperpolarized imaging does not necessarily lead to the conventional penalty in signal-to-noise ratio that occurs in imaging at thermal equilibrium polarization levels. Here a high-performance gradient insert was used in combination with undersampled spiral chemical shift imaging to utilize the imaging speed and spatial resolution of hyperpolarized C1 metabolic imaging on a clinical 3T MRI scanner. Both a single-shot sequence with a total acquisition time of 123 ms and a k-space sequence with a nominal in-plane resolution of 1.5 mm were implemented. The 8-space trajectory was used in the clinical experiment.

Quantification of Glutamate and Glutamine using CT-PRESS at 3T

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Glutamate (Glu) and glutamine (Gln) are two major neurotransmitters in the central nervous system. Quantifying Glu and Gln in vivo using magnetic resonance spectroscopy (MRS) has been of particular interest to basic science for understanding the Glu/Gln component of the Krebs cycle and its alteration by neuropsychiatric disorders such as schizophrenia, bipolar and alcoholism. However, quantification of Glu and Gln using conventional in vivo MRS techniques is difficult because it is unclear how the metabolite structure of the measured signal and metabolite model are validated in vivo. Constant-time point resolved spectroscopy (CT-PRESS) [1] has been developed to reduce signal overlap by applying effective homonuclear decoupling, and the method has been optimized to detect the Glu C4-resonance at 2.35 ppm [2]. However, the Glu C4-resonance is not well resolved as it overlaps with the resonance from the acetate moiety of NAA at 2.35 ppm. Because the described CT-PRESS spectra are generated by integrating the 2D spectra along the diagonal in magnitude mode for the purpose of SNR, linear least square fitting techniques with prior knowledge [3], are not directly applicable. In this study, we developed a method that achieves quantification of both Glu and Gln using CT-PRESS validated in phantom experiments, and applied it to data from in vivo studies on the effects of ethanol (EOH) on rat brain chemistry.

References/Funding Source
A cross-sectional study was designed to assess metabolic response of prostate cancer to transrectal mouse model of prostate adenocarcinoma (TRAMP), a model that closely resembles human carcinoma.

References/Funding Source
To be presented at ASTRO 2010 Annual Meeting

Dynamic and High-Resolution Metabolic Imaging of Hyperpolarized [1-13C]-Pyruvate in the Rat Brain

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Rapid chemical shift imaging (CSI) techniques are of considerable interest for dynamic metabolic imaging in vivo with hyperpolarized 13C-labeled substrates. Undersampled spiral CSI (pSPI) with free induction decay (FID) acquisition subverts metabolic imaging of hyperpolarized 13C [1]. Phase correction of the FID acquisition is challenging, especially with contributions from aliased-out-of-phase peaks. This work extends the pSPI to a single double spin-echo sequence capable of acquiring dynamic metabolic images in vivo with hyperpolarized 13C-labeled substrate.[2] The DSE-optCSI sequence was compared to FID-pSPI in single time-point and dynamic imaging of hyperpolarized 13C-pyruvate and its metabolic products lactate, alanine and bicarbonate.

References/Funding Source
Cerebral Dynamics and Metabolism of Hyperpolarized [1-13C] Pyruvate using Time Resolved Spiral-MRSI

RE Hunt, D Mayer1,2, KF Vel, J Tropp, A Pfefferbaum, DM Spielman, D Mayer. Cerebral dynamics and metabolism of hyperpolarized [1-(13)C]pyruvate using time-resolved MR study, fast 125 msec dynamic imaging (10) is used to better characterize the bolus, Hyperpolarized pyruvate, delivered as an 80 mM bolus, was reported to result in along with lactate and bicarbonate labeling in normal anesthetized rat brain (9). Hyperpolarized pyruvate, delivered as an 80 mM bolus, was reported to result in along with lactate and bicarbonate labeling in normal anesthetized rat brain (9).

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Objective: In recent years there has been increased interest in using cardiac interventional techniques such as EP ablation under MR-guidance. Directly monitoring the temperature rise during these procedures and in real-time could be helpful to verify successful ablation and predict treatment outcome. Here, we investigate the feasibility of monitoring temperature changes in the left ventricular myocardium in real-time. Temperature images based on the proton resonance frequency (PRF) shift are reconstructed using a hybrid method that combines multi-baseline subtraction and referenceless thermometry. Materials and Methods: Short-axis free-breathing cardiac images were acquired in the volunteers (no heat applied) in real-time using spiral gradient echo acquisitions with 4-5 interleavings on a 3T scanner using echo times of 3, 5, and 7 ms. Hybrid temperature image reconstruction was performed off-line in Matlab. The hybrid imaging model assumes that three sources contribute to image phase during thermal treatment: Background anatomical phase, spatially smooth phase shifts, and focal, heat-induced phase shifts.

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In breast conservation surgery, the current method to locate non-palpable tumor perimeter. Ablation sonications were prescribed along the non-palpable tumor perimeter. Ablation sonications were prescribed along the non-palpable tumor perimeter. The temperature uncertainty was reduced given the same mechanical force.

For the referencess portion of the processing, six-hundred background polynomials were used and the multi-backbone libraries were comprised of 150 images (sliding window re- construction) acquired during fast breathing, representing approximately three cardiac cycles. Temperature reconstruction was performed over circular regions of interest containing the entire left ventricle (Fig. 1). Temperature uncertainty was measured in the septum and the free wall using a 12 mm diameter circular ROI (Figs. 2, 3).

RR Bitton1, E Kaye1,2, BL Daniel1, K Butts-Pauly1 Departments of Radiology, RSL, and Electrical Engineering, Stanford University, CA

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In breast conservation surgery, the current method to locate non-palpable tumor perimeter. Ablation sonications were prescribed along the non-palpable tumor perimeter. Ablation sonications were prescribed along the non-palpable tumor perimeter. The temperature uncertainty was reduced given the same mechanical force.
Fabrication of CMUT Cells with Gold Center Mass for Higher Output Pressure

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Capacitive micromachined ultrasonic transducer (CMUT) technology is a promising candidate for high intensity focused ultrasound (HIFU) therapy as it allows the fabrication of arbitrary array geometries and is inherently magnetic resonance (MR) compatible. In this study, we investigate a way to improve the output pressure of a single CMUT cell by modification to the basic CMUT cell structure. Adding a mass 700 mm in diameter and 5 mm thick centered on the center of the top CMUT plate. Using the direct wafer bonding fabrication process we realized 1D linear CMUT arrays. On top of the 0.8 mm thick silicon plate, a 200-μm thick aluminum layer and a 10-μm thick titanium layer were deposited. A lift-off technique was used to deposit a gold mass on top of the adhesion layer, at the center of each cell. The 1-μm-thick gold layer was deposited in multiple steps with improving cooldown periods to ensure low thermal-induced stress between the gold and the metallized CMUT plates. Electrical impedance measurements of the devices revealed improved performance due to the gold mass, and the average resonance frequency in air for the elements in the 2D array decreased from 7 MHz to 3.6 MHz with a standard deviation of 0.12 MHz and 1.57 MHz, respectively. A direct comparison of cells with and without the gold mass in terms of measured output pressure at the surface of a single cell demonstrated a 23% improvement. When biased with a DC voltage equal to 70% of the pull-in voltage, the device with the gold mass delivered a 1.875 MPa-peak to-peak surface pressure at a frequency of 2.6 MHz. The results indicate that adding a center-mass to regular CMUT cells improves device performance in terms of acoustic output pressure.

References/Funding Source

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Introduction: During the planning stage of MRI-guided focused ultrasound treatments in breast, the actual location of the focus is verified by visualization of a low temperature spots using proton resonance frequency (PRF) thermometry. However, in air PRF becomes unreliable. The alternative approaches are based on T1-weighted imaging with fast spin-echo (FSE) [1] and on displacement imaging with MB-ARFI. The goal of this study was to evaluate both methods in human ex vivo breast tissue.

Methods: For six localizations, imaging was performed with ultrasound, using MB-ARFI and FSE. For FSE, repetition time (TR) was varied. Imaging was performed on a 3T MRI scanner equipped with a HIU system, and timed such that the excitations and the scans occurred at the same time. SNR of the signal at the focus was analyzed using MB-ARFI displacement maps and FSE magnitude difference images.

Results: The focal spot was apparent in the unprocessed MR-ARFI phase images, as shown in Figure 1. For FSE, the focal spot was visible only on the difference images, but not on the unprocessed magnitude images. The displacement maps the mean SNR was 4, and for the optimal TR of 50 ms the FSE difference image the SNR was 11.5.

Conclusion: The results of this study show that T1-weighted imaging and MB-ARFI allow visualization of the ultrasound focal spot. MR-ARFI provided greater SNR at the focal spot and deposited 10 times more ultrasonic energy than needed during FSE acquisition. Current MR-ARFI sequences require a longer scan time than FSE, but could be mitigated in the future.

References/Funding Source

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MR Tools for Focal Spot Visualization during FUS Breast Treatment

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Introduction: The purpose of this work was to improve targeted prostate ablation with transurethral multicore ultrasound applicators. To do this, an integrated imaging and treatment platform was developed to monitor and adjust the treatment, and also provide real-time temperature feedback. We incorporated integrated device localization, prostate-specific algorithms, adaptive control, and a reduced FOV for a single patient. Our system was developed specifically for prostate ablation and the additional features are based on ultrasound displacement and temperature control, which is achieved using a fully integrated real-time ultrasound and MR-ARFI system. Our system is capable of providing real-time displacement and temperature monitoring, and it is designed to support a variety of prostate ablation treatments.

Materials and Methods: The system is a fully integrated ultrasound and MR-ARFI system, which provides real-time displacement and temperature monitoring, and it is designed to support a variety of prostate ablation treatments.

Results: The focal spot was apparent in the unprocessed MR-ARFI phase images, as shown in Figure 1. For FSE, the focal spot was visible only on the difference images, but not on the unprocessed magnitude images. The displacement maps the mean SNR was 4, and for the optimal TR of 50 ms the FSE difference image the SNR was 11.5.

Conclusion: The results of this study show that T1-weighted imaging and MB-ARFI allow visualization of the ultrasound focal spot. MR-ARFI provided greater SNR at the focal spot and deposited 10 times more ultrasonic energy than needed during FSE acquisition. Current MR-ARFI sequences require a longer scan time than FSE, but could be mitigated in the future.

References/Funding Source

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High Intensity Focused Ultrasound (HIFU) of the Liver for the Treatment of Metastatic Colorectal Cancer

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Abstract: Magnetic Resonance Research

Intensive MR and HIFU Control System: Towards Real Time Treatment of the Liver

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High Intensity Focused Ultrasound (HIFU) of the Liver: From In-vitro to In-vivo

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Abstract: Magnetic Resonance Research
Neural and Behavioral Responses to Threatening Emotion Faces in Children as a Function of the Short Allele of the Serotonin Transporter Gene

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Recent evidence suggests that a genetic polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter gene (SLC6A4) mediates stress reactivity in adults. Little is known, however, about this gene-brain association in childhood and adolescence, generally conceptualized as a time of heightened stress reactivity. The present study examines the association between 5-HTTLPR allele variation and responses to fearful and angry faces presented both sub- and supraliminally in participants, ages 9-17. Behaviorally, carriers of the 5-HTTLPR short (s)-allele exhibited significantly greater attention bias to subliminally presented fear faces than did their long (l)-allele homozygous counterparts. Moreover, s-allele carriers showed greater neural activations to fearful and angry faces than did l-allele homoygotes in various regions of association cortex previously linked to attention control in adults. These results indicate that in children and adolescents, s-allele carriers can be distinguished from l-allele homoygotes on the basis of hypervigilant behavioral and neural processing of negative material.

References/Funding Source
National Institute of Mental Health; NIH#5151083 to MET, and MRG#65943 to INS; NASA X Young Investigator Award to MET; NIH Intramural Research Program; ME Thomson, MR Harvy, JP Hamilton, J Joormann, DS Pine, M Ernst, D Goldman, K Moggi, BP Bradley, JC Britton, KM Lindstrom, CS Monki, KS Sanki, HMK Louriu, IH Gotlib. (In Press) Neuroimaging & fMRI

Variable Density Spiral-In/Out fMRI

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A variable-density spiral k-space trajectory is introduced for brain functional magnetic resonance imaging (fMRI). The proposed spiral trajectory consists of an Archimedean spiral from the k-space origin to an arbitrary fraction r of the maximum k-space radius, extending beyond this point with a variable-density spiral in which the sampling density decreases as the k-space radius increases. It therefore permits a reduction in readout time at the expense of undersampling only the high spatial frequencies, in which the energy in T2*-weighted brain images is typically low. The trajectory was implemented in a 2D spiral-in/out sequence, and single-shot high-resolution (1.71 x 1.71 x 3.0 mm3 in-plane) fMRI data were acquired from human volunteers. Compared to a two-shot uniform-density spiral sequence with the same spatial coverage and total scan time, the variable-density sequence yielded greater activation magnitudes with improved temporal efficiency and minimal artifacts.

References/Funding Source

Selective Reduction of Cardiac Artifact in Breast MRI

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Purpose: Cardiac motion causes significant artifact in breast MRI. Conventional slab saturation pulses cannot be applied to the heart without obscuring portions of the axillary breast tissue. We have implemented a 2D cylindrical saturation pulse that selectively saturates the heart and diaphragm.

Methods: We collected data on six healthy volunteers at 1.5T (GE Healthcare, Waukegan, WI). A 2D excitation was applied with gradient pulses in both x and z for an elliptical cylindrical superior-inferior prescription encompassing the heart. Gradient crushers followed the cylindrical excitation, then dephasing and reducing the signal from the selected area. The heart saturation pulse was followed by a dual-echo spiral spatial RF pulse for bilateral breast excitation, and a 3D variable-density stack of spirals for acquisition. The TR for the saturation pulse is 12 ms, in addition to the 32 ms bilateral spatial pulse.

For analysis, three ROIs were drawn in each image: one in the heart, one in the glandular breast tissue, and one in the image background. To calculate the signal emanating from the outer area, the standard deviation of the outer ROI was normalized by dividing by the mean signal from the breast ROI.

Results: In spiral imaging, the ghosting artifact from the heart motion manifests as a confounding artifact (compared to ghosting in the phase encode direction present with Cartesian imaging). The artifact signal without heart saturation was on average 3.5 times the artifact signal with heart saturation (p<0.001). On average, 58% of the heart signal was eliminated with heart saturation.

Conclusions: Elliptical cylindrical saturation of the heart significantly eliminates artifact from the heart in breast MR imaging without sacrificing important diagnostic information. This saturation pulse can be applied to many breast MR sequences and is particularly promising in spiral imaging.

References/Funding Source

Time-frequency Dynamics of Resting Brain Connectivity Measured with fMRI

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Most studies of resting-state (“intrinsically”) functional connectivity using fMRI employ methods that assume temporal stationarity, such as correlation and data-driven decompositions computed across the duration of the scan. However, evidence from both task-based fMRI studies and animal electrophysiology suggests that intrinsic functional connectivity may exhibit dynamic changes within time scales of seconds to minutes. In the present study, we investigated the dynamic behavior of resting-state connectivity across the course of a single scan, performing a time–frequency coherence analysis based on the wavelet transform. We focused on the connectivity of the posterior cingulate cortex (PCC), a primary node of the default-mode network, and total scan time, the variable-density sequence yielded greater activation magnitudes with improved temporal efficiency and minimal artifacts.

References/Funding Source

Matinees Magnetic Resonance Research
Abstracts: Magnetic Resonance Research

References/Funding Source
Functional Connectivity in Patients with Chronic Neuropathic Pain

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Cognitive behavioral therapy has long been used as a strategy for modulating chronic pain. Functional connectivity is an imaging technique to examine the strength of time-course covariance of two neural networks. To better understand connectivity in the supraspinal modulation of pain, we looked at functional connectivity of the “pain matrix” as chronic pain patients modulated pain intensity with pain (p<0.05, r=0.26, extent = 40). 

Five patients with chronic NP in a limb were instructed and trained on the cognitive-behavioral strategies of attention, distraction, and positive and negative reappraisal. Each subject completed 4 scans using each strategy to modulate their pain, and a resting state scan. After performing resting state fMRI using a 3T MRI, the connectivity for each subject was calculated as the pairwise correlation between average ROI time-courses. Subsequently, the average connectivity was determined by averaging across subjects. Finally, connectivity in different scans was compared using the Fisher’s Z transformation.

The following results were significant at p<0.05. Compared to the resting state, attention decreased connectivity between the primary somatosensory cortex (S1)-insula, S1, thalamus, periaqueductal grey (PAG). Distraction decreased connectivity between the secondary somatosensory cortex (S2)-insula, S1, thalamus. Positive reappraisal decreased connectivity between PFC-CAc, anula, S1, S2. Attention, as compared to distraction, decreased connectivity between the thalamus-S2, and increased connectivity between the thalamus-S1, and between PAG-PFC, thalamus. Negative reappraisal increased connectivity between PFC-ACC, anula, S1, S2. Attention, as compared to distraction, decreased connectivity between the thalamus-S2, and increased connectivity between the thalamus-S1, and between PAG-PFC, thalamus. Negative reappraisal, as compared to positive reappraisal, decreased connectivity between S2-PFC.

This study demonstrates significant differences in the functional connectivity of chronic NP patients using different cognitive strategies. Our goal is to use this information to target areas and strategies to use in real-time MRI, a non-invasive modular tool.

References/Funding Source


Application of Support Vector Machines to the Detection of Chronic Pain

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The subjective nature of pain makes an objective measurement difficult to produce. If such a measurement is possible, then this knowledge would assist in the diagnosis and treatment of patients whose self report of pain is unreliable or called into question. Past studies have demonstrated that chronic pain is associated with abnormalities in GM atrophy by magnetic resonance imaging. We show that this decline in GM density can be used to distinguish between healthy and chronic low back pain (LBP) subjects with greater than chance accuracy. Structural MR scans from 100 subjects were segmented and spatially normalized to the standard MNI template using SPMM. Each image was resampled to 5x5x5 mm, resulting in approximately 1700 voxels. The average age GM density within each voxel was used to generate the feature vectors for a linear support vector machine (SVM) classifier. Performance of the classifier was assessed using a k-fold cross validation scheme and significance was assessed with a Monte Carlo permutation test. The SVM classifier identified the group (LBP vs. healthy) with high sensitivity (85%) and specificity (79%) using MRI alone as the input data. The SVM classification was then validated on an independent test set of 40 subjects and the classifier correctly classified 80% of the test set with a receiver operating characteristic (ROC) curve area of 0.89. Our results show that GM density is a sensitive and specific biomarker for chronic pain, particularly LBP, and could be used to help improve patient diagnosis and treatment.

References/Funding Source


Duloxetine and Placebo Alter Different Gray Matter Regions in Chronic Low Back Pain Patients

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Chronic lower back pain (CLBP) affects millions of people and cost billions of dollars per year in the United States alone. Recent evidence indicates that chronic back pain may cause structural changes in brain grey matter (GM), suggesting that GM changes may be an important metric in evaluating the efficacy of pain treatments. In this double-blind crossover study, we used tensor based morphometry (TBM) to test our hypothesis that treatment with duloxetine (a selective serotonin-norepinephrine uptake inhibitor) would cause GM changes that are distinct from those caused by treatment with placebo.

14 male subjects with CLBP were recruited. They rated pain as at least 4.0/10 on average over the previous 4 months prior to the start of the study and were not on pain medications. Study design was a double blind, placebo control, 12-week crossover study utilizing duloxetine as the active drug. Structural scans were conducted at baseline and at the end of each drug period.

Tensor-based morphometry was used to evaluate structural changes between baseline and follow-up scans in a method similar to that outlined by Kaps (Kaps, J Neurol Neurosurg Psychiatry, 2005). Significant clusters were defined at p<0.05 corrected for multiple comparisons. Both duloxetine and placebo caused changes in local brain GM. These changes were distinct in that duloxetine led to increases in GM in bilateral caudate and decreases in GM in orbital and ventromedial prefrontal cortex, while placebo led to increases in GM in left inferior anterior insula and bilateral caudate. Correlations with behavioral measurements are ongoing. Our study suggests separate brain mechanisms for duloxetine and placebo effects in chronic low back pain patients.

References/Funding Source


Reward Processing in Adolescents with First Episode Mania

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Objective: To evaluate performance and neural activity during reward processing in adolescents with first episode mania (FEM) and healthy controls (HC), hypothesizing that those with FEM would exhibit greater activation than will HC in the ventral striatum (nucleus accumbens) and amygdala in anticipation of gains. These activations will be associated with increased reward sensitivity and increased activity in the ventral striatum in anticipation of gains. Within the HC group, increased activation was associated with increased intracerebral and somatosensory motor area during gain anticipation. Between group comparisons showed significantly increased right nucleus accumbens activation in HC relative to BD participants while anticipating gains (p=0.01, uncorrected, extent = 40). Prior work demonstrated orbital activation in HC but not in BD (p=0.01, extent=20).

Discussion: Altered profiles of network activation were associated with reward processing in adolescent mania. BD adolescents showed activation in predominantly visual cortical and motor preparation regions in response to reward stimuli, whereas healthy adolescents showed increased activation in prefrontal and ventromedial regions. Further studies characterizing reward processing in mania are warranted.
Human Brain Activity Identifies the Presence or Absence of Pain

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Introduction: Currently, the most reliable method of assessing pain is self-report. If however, self-report is unreliable or called into question, pain may be assessed using behavioral or physiological markers. Therefore, a biomarker for pain would help to better inform clinical decisions. Suggesting that patterns of brain activity might provide a biomarker for pain, regions of the human brain are more activated by painful stimuli than by non-painful stimuli. This study aims to use fMRI to determine the degree to which patterns of neural activity can predict the presence or absence of pain.

Methods: The protocol was approved by the Stanford Institutional Review Board, and subjects provided written, informed consent and completed the experiment. Using fMRI, we recorded brain activity during the presentation of both painful and non-painful thermal stimuli. Using maps of brain activity from a heat stimulus was painful, the SVM performed with 87% overall accuracy and with 91% true positive values that exceeded 95%.

Conclusions: FMRl measurement of brain activity provides a clinically relevant biomarker for the presence or absence of pain. We show that the brain activity patterns associated with several individuals’ subjective experiences of pain can be used to objectively identify the experience of pain in a set of different individuals.

References/Funding Source


Structural Brain Differences in Fragile X Syndrome and Idiopathic Developmental Delay

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Previous MRI studies of children and adolescents with fragile X syndrome have shown altered morphology in sub-cortical brain structures including enlargements of the caudate, thalamus and fourth ventricle.Automated anatomical parcellation and segmentation tools such as FreeSurfer have recently been successful in delineating brain structures (including deep-brain structures) in typically developing individuals. We extend the feasibility of using FreeSurfer to segment deep-brain structures in young adults with fragile X syndrome and compare them with typically developing individuals.

We scanned 30 young adults with fragile X syndrome ranging in age from 15 to 25 years (mean 21.84 ± 2.7 years) and 13 with idiopathic developmental delay ranging in age from 16 to 26 years (mean 21.15 ± 2.3 years). Participants were matched for age and IQ.

We obtained T1-weighted structural MRIs on a 3T MRI scanner (GE) at Stanford University. Images were analyzed using FreeSurfer’s automated pipeline. Sub-cortical regions were outlined using FreeSurfer’s volumetric segmentation methods.

Discussion: Enlargements of the caudate, pallidum and thalamus have shown to be present in other disorders such as autism spectrum disorders and schizophrenia. However, these differences have not been examined in fragile X syndrome. We are currently examining the degree to which patterns of neural activity can predict the presence or absence of pain.

References/Funding Source

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Regional Grey Matter Accounts for Individual Differences at Risk for Developing Dyslexia in 5-6 Year Olds

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Objective: We aimed to compare patterns of N-acetyl aspartate, myoinositol, and other metabolites in the cerebral vermis of bipolar and healthy controls to examine whether changes in these neuronal metabolic concentrations occur in bipolar prior to onset of the illness. Methods: 9-17 year old children and adolescents with bipolar I disorder (N=11) or bipolar II disorder (N=10) were recruited. Participants were matched for age and IQ.

We obtained T1-weighted structural MRIs on a 3T MRI scanner (GE) at Stanford University. Images were analyzed using FreeSurfer’s automated pipeline. Sub-cortical regions were outlined using FreeSurfer’s volumetric segmentation methods.

Discussion: Decreased cellular metabolism and interference with second messenger pathways may be present in the cerebral vermis in individuals at risk for BD as evident by decreased myoinositol and choline concentrations in this region. These results may be limited by a cross-sectional design, co-existing diagnoses, and medication exposure. Longitudinal studies are necessary to determine if early neurochemical changes can predict the development of mania. Improved methods for identifying children with certain neurochemical vulnerabilities may inform preventive and early intervention strategies prior to the onset of the illness.

References/Funding Source

National Institute of Health (ROI 5 K08DA0260751-01, P50MH085754-04, and K24MH096919), the National Alliance for Research on Schizophrenia and Depression (NARSAD), and Lucile Packard Children’s Hospital Child Health Research Program. Miss Singh, D Spaulman, A Libby, E Adams, T Acquaye, M Howe, L Kenly, A Reiss, K Chang: Neurochemical Deficit in 5-6 Year Olds at Risk of Developing Bipolar Disorder. Poster to be presented at the 15th Annual International Fragile X Conference, Detroit, Michigan.

Reward Processing in Adolescents with First Episode Mania

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Objective: To evaluate performance and neural activity associated with reward processing in adolescents with first episode mania (BD) and healthy controls (HC), hypothesizing that BD adolescents would show decreased reward processing relative to HC. Methods: Adolescents (ages 13-18 years) with bipolar I disorder (N=21) diagnosed within the previous 9 months were recruited through the local pediatric psychiatry clinic. Participants were predicted to be more robust with an affective prime relative to HC during gain anticipation. Between group comparisons showed significantly increased right nucleus accumbens and amygdala activations in anticipation of gaining more relative to HC.

Results: Within the BD group, increased activation was observed in the ventral striatum and ACC in gain anticipation. Within the BD group, increased activation was seen in the occipital lobe and supplemental motor area during gain anticipation. Between group comparisons showed significantly increased right nucleus accumbens activations in HC relative to BD participants while anticipating gains (p<0.01, uncorrected, extent=40). Printing produced orbitofrontal activations in HC but not in BD (p<0.01, extent=20).

Discussion: Altered profiles of network activation were observed in adolescents with first episode mania. BD adolescents showed increased recruitment of visual and motor prefrontal regions in response to reward stimuli, whereas healthy adolescents showed increased recruitment of ventral and frontal regions. Further studies characterizing reward processing in mania are warranted.

References/Funding Source

Changes in Brain Activation Following Family-Focused Treatment in Youth at Risk for Bipolar Disorder
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Objective: To investigate changes in brain activation associated with family-focused treatment (FFT) in adolescents at high risk for developing bipolar disorder.

Background: Previous studies have found that FFT is effective in stabilizing symptoms of mania and depression in these patients. This treatment may also be associated with changes in the function of brain regions associated with emotional responses.

Methods: Ten subjects with a family history of bipolar disorder and current subclinical symptoms completed scans at baseline and after 12 weeks of treatment (either treatment as usual or FFT). Functional magnetic resonance imaging scans were acquired using a spiral pulse sequence at 3T, while participants performed a classic Go/NoGo task that requires inhibition of a response. Each block consisted of 60 trials in random or sequential order. The Stop Signal Task measures the ability to withhold a response to a ‘go’ signal after a delay period. The performance of each participant was compared to a group of healthy controls.

Results: The whole brain repeated measures analysis showed that, from baseline to follow-up, the following changes occurred: (1) amygdala activation decreased, (2) dorsolateral and orbitofrontal cortices activation increased. Further analyses showed that: (a) higher activation in the right amygdala at baseline, associated with the greater clinical improvement in depressive symptoms at follow-up. (b) lower right DLPFC activation at baseline, associated with greater improvement in depressive and manic symptoms at follow-up (see Figure), and (c) greater increases in right orbitofrontal cortex activation from baseline to follow-up, associated with greater improvement in depressive and manic symptoms.

Conclusions: Clinical improvement is associated with functional changes in specific brain regions that have been implicated in emotion perception and regulation. These changes also suggest that SPMs may help us to predict who will respond best to this treatment.

References/Funding Source NIH 5R01-MH50047 (ALR).

Neuroimaging & fMRI

Evaluating an Intensive Behavioral Intervention for Children and Adolescents with Fragile X Syndrome
SS Hall, J Hammond, MA Hirt, AL Reiss
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This study will attempt to overcome putative specific learning dysfunction in children and adolescents diagnosed with Fragile X syndrome (FXS) using a malleable equivalence (SE) teaching paradigm. Mathematical performance and brain activation prior to and following SE training will be examined. The efficacy of the intervention will be studied in comparison to a control group of male, verbal IQ, age-matched individuals with FXS who were not exposed to the developmental delay (DD) in order to understand the specificity of mathematical dysfunction exhibited by individuals with FXS. Performance in the target domain will be compared to that of the control group.

References/Funding Source National Institute of Mental Health (K08).

Neuroimaging of Dynamic Social Stimuli
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We performed MRI with healthy volunteers to elucidate the brain circuits involved in processing social stimuli. One hundred and twenty volunteers were scanned while performing a two-second video clips of a live actor who performed either a social gesture (e.g. waving, handshake) or a non-social gesture that was matched for amount and direction of movement (e.g. reach, grab). For each half of the clips, the actor either (i) faced the camera, and in the other half of the clips the actor was turned at an angle (i.e. as if they were addressing an unseen individual, just off camera). To tease apart the influence of facial movements and eye gaze on processing, we also created blurred versions of all stimuli.

Our novel design allowed us to tease apart many aspects of social processing. We conducted a whole-brain functional MRI (fMRI) study using these movie stimuli. Participants were instructed to watch the short movie clips for a red dot to appear near the eyes/nose region on half of the clips, and were not given instructions regarding the social/non-social aspect of the stimuli. All contrasts were performed using a whole-brain voxel-level threshold of p<0.001, cluster corrected at p<0.05. A contrast of all Social vs All NonSocial gestures found significantly greater activation in the left occipital cortex (BA 19) and posterior cingulate cortex (BA 23), in comparison to the Go trials, than did the control participants. These significantly activations were also found in the left fusiform gyrus (BA 40), posterior insula (BA 13) and right inferior frontal gyrus (BA 45). NonSocial gestures more strongly activated left parietal regions, including the inferior parietal lobule (BA 7, BA 40) and postcentral gyrus (BA 5). Our analysis provide further support for the role of frontal and temporal cortices in the processing dynamic social stimuli.

References/Funding Source NSF-0514578 (ALR).

Longitudinal MRI Study Exploring Differences in Response Inhibition in Fragile X Syndrome
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Individuals with fragile X syndrome (FXS) have known difficulties with executive function tasks, including the inhibition of inappropriate responses. Simple stop/ go/no-go imaging studies have suggested that this difficulty is related to activation differences, relative to control participants, in regions such as the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). We used MRI in a longitudinal design to explore changes in brain activation related to response inhibition in individuals with FXS, compared to healthy controls.

We scanned 10 individuals with FXS (5 females) and 14 typically developing controls aged 9-19 years at the first timepoint and 17.93±8.43 years at the second timepoint; on average, the scans were separated by 3.91±1.81 years. Participants performed a classic Go/NoGo task that requires inhibition of a prepotent response. For each subject we generated a linear model that included block regressors for “go” and “go/no-go” blocks, with time and 2 scans modeled as separate sessions. We extracted contrast estimates for the “go/no-go” minus “go” block, as a measure of activation related to response inhibition, from our regions of interest (ROI’s) (bilateral VL/PC, insula, and ACC). We used paired t-tests to identify time differences within groups, and repeated measures ANOVA’s to test for time x group interactions, using age and gender as covariates.

FXS participants showed significant decreases in activation from time 1 to time 2 in the bilateral VL/PC, insula, and ACC, whereas the TD participants showed a significant decrease over time in the bilateral insula (p<0.01). When comparing longitudinal changes between groups, we found that the right parieto-occipital region of the inferior frontal gyrus (p<0.001) and bilateral ACC (p<0.005) showed a significant group x time interaction; activation in these regions decreased more over time in the FXS group compared to the TD group.

References/Funding Source 5R01-MH63047-ALR.

Aberrant Brain Activation During a Response Inhibition Task in Adolescent Eating Disorder Subtypes
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Objective: Behavioral and personality characteristics associated with excessive inhibition and disinhibition are observed in patients with eating disorders. This study examined the neural correlates of inhibition control in adolescents with eating disorders. We hypothesized that patients with eating disorders would show aberrant brain activation in the binge eating and purging would show aberrant activation in regions associated with response inhibition, and that this pattern would differ from patients with restricting eating behaviors.

Methods: Thirteen adolescents with binge eating and purging, i.e., bulimia nervosa or anorexia nervosa, binge-purge subtype, 14 with anorexia nervosa, binge-purge subtype, and 13 healthy controls performed a rapid jittered event related Go/NoGo task using a 3T GE scanner and restricted subtype, and 13 healthy controls performed a rapid jittered event related Go/NoGo task using a 3T GE scanner and

Results: The binge-purge group showed significantly greater activation than the healthy control group in the bilateral prefrontal gyrus, anterior cingulate cortex, and middle and superior temporal gyrus, and greater activation compared to both controls and anorexia nervosa restricting type group in the hypothalamus and right dorsolateral prefrontal cortex. Within-group analysis found that only the anorexia nervosa, restricting group showed a positive correlation between percent correct on NoGo trials and activation in posterior visual and anterior insula, and anterior cingulate. Conclusions: The current study provides preliminary evidence that during adolescence, eating disorder subtypes may be distinguishable in terms of neural correlates of inhibitory control. This distinction is consistent with differences in behavioral impulsivity in these patient groups.

References/Funding Source NIH 5R01-MH50047 (ALR).
Bolus Perfusion-Weighted Imaging Measurement Of Quantitative Cerebral Blood Flow Can Be Improved Using An Arterial Spin Label Deriving Scaling Factor: A Comparative Xenon CT Study

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Bolus dynamic susceptibility contrast (DSC)-perfusion-weighted imaging (PWI) and arterial spin labeling (ASL) are two methods of measuring cerebral blood flow (CBF) using MRI. Each has different strengths and weaknesses. ASL CBF levels are reliable in high flow regions, but suffer from corrections of both low and slow SNR in regions with long arterial times. PWI, particularly when using delay-invariant deconvolution, is in theory unaffected by long arrival times. However, absolute quantification is challenging, due to uncertainties in Arf & VOF partial volume and the nonlinear relationship between transverse relaxation and contrast concentration. This study describes a method that uses ASL CBF measurements in regions with short transit delays (as measured by TLAS) to scale PWI CBF measurements. Stable xenon CT was used as a gold standard for CBF. Practically, a single global scaling factor will never improve correlation within an individual patient. Also, the upper limit of the improvement in between-patients correlation is set by the accuracy of ASL. However, PWI results with long TLAS, we found improved CBF correlation for corrected bolus PWI compared to uncorrected PWI or ASL CBF. While we used a 6 min high-resolution ASL sequence as part of our standard imaging, in principle, much lower resolution ASL CBF maps with shorter acquisition times could be obtained, since the scaling factor is determined by a relatively large volume of tissue.

We conclude that the combined ASL-PWI method is superior to either method alone for measuring quantitative CBF with MRI.

References/Funding Source
National Institute of Mental Health (K23)

Diagnostic Accuracy Of High-Resolution Multi-Shot Diffusion-Weighted MRI For The Detection Of Breast Cancer

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Diffusion-weighted imaging (DWI) may provide information - physically to microvascular changes detected by contrast-enhanced MRI - that can improve the specificity of MRI for breast cancer diagnosis. Attempts thus far to benefit from the information content that DWI may offer have been limited by the use of single-shot techniques, with inherent sensitivity to geometric distortions and limitations in detected lesion size. The aim of this HIPAA-compliant, IRB-approved study was to compare the sensitivity and specificity of high-resolution DWI of the breast to 'conventional' dynamic-contrast-enhanced MRI, and to pathology. We performed a retrospective analysis of diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) in 104 patients (mean age 50.3 years, range: 18-81) undergoing 1.5T MRI for the evaluation of breast cancer. Pathological confirmation was obtained for all but one of the lesions marked as 'suspicious' on 3D-MRI. As expected, the sensitivity of DCE-MRI was very high, with a lower specificity. The presence of DWDWI echoes and temporal enhancement (PERMEATE) was developed, in which the temporal enhancement (TE) was determined using the echo with shortest time delay. The purpose of this study was to evaluate the benefits of such advanced acquisition scheme with the PVE and bulk-blood corrections.

We found that the combined ASL-PWI method is superior to either method alone for measuring quantitative CBF with MRI.

References/Funding Source
National Institute of Mental Health (K23)

Estimation of CBF Values Using Multi-Echo DSC-MRI: a Comparison with a Xenon CT

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Spatial distortions in EPI sequences and clipping of vascular signals during bolus passage may cause a scanning sequence for perfusion with multiple echoes and temporal enhancement (PERMEATE) was developed, in which the confounding artifacts should be reduced. Data acquired with first (short) echo should be used to properly recover the vascular signals, whereas the later echoes are used to determine signals in the tissue maintaining better signal-to-noise ratio therein. Such state-of-the-art perfusion acquisition is complemented by a PWI post-processing pipeline, including correction for partial volume effects (PVE) in vascular signals and susceptibility effect of the paramagnetic SNR loss in tracer in large vessels. The purpose of this study was to evaluate the benefits of such advanced acquisition scheme with the PVE and bulk-blood corrections and to quantify the improvement of values in the computed quantitative perfusion maps. In this work, we have demonstrated the acquisition of diffusion-weighted whole brain volumes using a SSFP-DTI sequences. Compared with other diffusion techniques, our approach can achieve much higher SNR with desired diffusion weighting and limited imaging time. The DSI sampling strategy also benefits from reduced sensitivity of subject motion. However, since only the 0th order phase error term can be extracted and corrected, images may still be contaminated by residual motion artifacts, especially for high b-values. A proper 3D navigator should help further improve the image quality. Another advantage of this method is a more robust estimation of the true SNR at high field, which may lead to higher SNR at high field. The approach is compared to a full DFI method in diffusion-tensor imaging DTI of the thoracic spine in one healthy volunteer.

Methods: MRI: Single-shot twice-refocused DTI of the thoracic spine was performed on a healthy volunteer using a 1.5 T MRI scanner with a 4-channel spine coil. Three un-weighted (b=0 s/mm²) images and 60-diffusion-weighted directions (b=500 s/mm²) were collected on 7 slices with 4 mm slice thickness. Both the DFI method and a conventional full DFI method were performed in a scan time of 3.12 min.

References/Funding Source
Comparison Between Readout-Segmented (RS)-EPI and an Improved Distortion Correction Method for Short-Axis Propeller (SAP)-EPI

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Abstract: Short-axis readout (RF) and terminal (TE) readout (TR) echoes are processed between RF pulses. Proceedings of the Joint Annual Meeting of ISMRM/ESMRMB, Stockholm, Sweden. p 2962.

R2/R2* estimation from short-axis images of diffusion-weighted imaging (DWI) in healthy volunteers using two matrix sizes: 252x252 (blade/blind slice) and 384x384 (blades/blindleth slice). Together with noise maps generated from repeated b = 0 scans, the scan time efficiency was calculated from the RS-EPI and RS-EPI corrected images.

In our previous distortion correction implementation for SAP-EPI, the dis
torted blade data underwent two unnecessary sampling steps which now have been removed. Each of these resampling steps caused a slight loss in resolution, which, when added to the additional distortion introduced by the line-sparse to 2D fast Fourier transform (FFT) operation, degrades the overall image quality. Therefore, to improve the image quality, we demonstrate that SAP-EPI results in a similar image resolution to RS-EPI for a given SNR normalized for scan time/slice.

All images were acquired on a 3T whole-body MRI unit using an 8-channel head coil. Scan-time matched SAP-EPI and RS-EPI DWI experiments were first performed on healthy volunteers using two matrix sizes: 252x252 (blade/blindeight slice) or 384x384 (blades/blindleth slice). Together with noise maps generated from repeated b = 0 scans, the scan time efficiency was calculated from the RS-EPI and RS-EPI corrected images.

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All images were acquired on a 3T whole-body MRI unit using an 8-channel head coil. Scan-time matched SAP-EPI and RS-EPI DWI experiments were first performed on healthy volunteers using two matrix sizes: 252x252 (blade/blindeight slice) or 384x384 (blades/blindleth slice). Together with noise maps generated from repeated b = 0 scans, the scan time efficiency was calculated from the RS-EPI and RS-EPI corrected images.
Improving DSC-MRI by Orientation-corrected AIF and VOF

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Quantitative DSC-MRI perfusion imaging requires signals that can be accurately corrected for known contamination by other tissue concentrations. A new approach to measuring vascular concentration (e.g. arterial input function AIF) remains challenging. Susceptibility artifacts induce significant errors in the frequency that is linear with the tracer concentration and does not depend on T1. This change in frequency can be assessed by change in MR signal phase and could potentially deliver better estimates of tracer concentration. The observable phase effect depends however on the orientation of the vessel relative to the sequence (e.g. table 1) and information about vessel orientation is thus required to avoid extra cumbersome measurements. We propose to estimate the vessel orientation from the magnitude data of the dynamic T2* Scan itself.

Intravascular concentration of paramagnetic tracer can be estimated using equation below, where T1 is the tilt angle of the vessel relative to B0.

At low T1 angles, the TE is very low (e.g. AIF in MCA and VOF in SSS). The plots show estimated concentration during bolus passage (using phase signal from early phase (up), and magnitude signal from late echo phase (left)).

Figure shows vascular gadolinium concentration values that were obtained either from phase (first echo) or magnitude data (first and third echo). Moreover, the T2-dependency of short-TE magnitude data at early bolus arrival can be clearly seen.

A new method for improving the estimation of vascular Gd concentration has been proposed. Major advantages of the phase-based approach are its immunity to log-Rician transformed noise (present in perfusion signals when computed in magnitude data) and immunity to T1-artifacts as well as linearity of signal with respect to Gd concentration.

References/Funding Source: NIH (R01NS081758, R01NS081760, R01NS081755, R01NS083760, R01NS084722, R01NS085086, R01NS083025-04A1). Center of Advanced MR Technology at Stanford (HR089502). Lucain Foundation, Oak Foundation and an anonymous philanthropist. Presented at the Conference of International Society for Magnetic Resonance in Medicine, Stockholm, Sweden (May 1-7, 2010).

Is Reduced CSV a Reliable Surrogate Marker for Infarct Core and Can It Be Used to Identify Lesion Mismatch?

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Correlation between CBV and DWI lesion volumes among all cases was excellent (r=0.89, correlation line CBV = 1.04*DWI − 2.26). However, in the subgroup of small lesions (DWI < 10ml) the correlation was poor (r=0.20). All correlations were statistically significant (p < 0.001). Using the PWI/DWI mismatch pattern as reference, the sensitivity of the Tmax/CBV approach was 0.98 and specificity was 0.76. The Tmax/CBV mismatch was identified in 90 true positive, 31 true negative, 10 false positive, and 2 false negative results. In the majority of the discordant cases, the CBV mismatch was smaller than the DWI lesion.

The findings imply that DWI is superior to CBV for detecting the early ischemic core even under optimized perfusion imaging circumstances.

References/Funding Source: NIH (R01NS081758, R01NS081760, R01NS081755, R01NS083760, R01NS084722, R01NS085086, R01NS083025-04A1). Center of Advanced MR Technology at Stanford (HR089502). Lucain Foundation, Oak Foundation and an anonymous philanthropist. Presented at the International Stroke Conference in San Antonio, Texas, USA (Feb 23-26, 2010).

Abstracts: Magnetic Resonance Imaging

Blood-Brain Barrier Permeability Measured by DCE MRI Predicts Perihematomal Edema Diffusivity

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Introduction: Spontaneous intracerebral hemorrhage (ICH) is one of the deadliest forms of stroke. Secondary brain injury and edema formation contribute to high mortality and morbidity among ICH patients. Blood-brain barrier (BBB) disruption is potentially an important factor in the formation and progression of perihematomal edema. This study aims to quantify BBB injury by DCE MRI and to examine its relationship with perihematomal diffusivity, as a measure of vasogenic edema severity, utilizing diffusion weighted imaging (DWI).

Methods: 15 patients (60% female; 67.8 ± 13.6 years) prospectively enrolled patients were examined using DCE MRI and DWI at approximately one week after symptom onset. All imaging was performed on a 1.5T GE Sigma Excite scanner. Proton density weighted (PDW) and DCE MRI scans were used to map the native T1 times using a double-angle method. Flip angles were 5° for the PDW and 90° for the DCE MRI scans. PDW scanning was immediately followed by the DCE scans. To obtain both scans, axial spoiled gradient echo sequences were used with scan parameters as follows: TR/TE: 7.8/3.4ms, slice thickness 5mm, 12 slices, FSPGR 270°, matrix size 256x192, temporal resolution 1.4s/axial.

DCE scanning was performed with the following parameters: Gd-DTPA bolus concentration = 0.1 mM/kg, Gd-DTPA bolus concentration = 1.0 mg/kg, slice thickness 5mm, 5 flip angles, FOV=240mm, matrix size=192x192, TR/TE=90º, FOV=240mm, matrix size=192x192.

A potential explanation would be a common injury process causing both BBB disruption and vasogenic edema. DCE MRI and DWI might be used to quantify BBB injury by DCE MRI and to examine its relationship with perihematomal diffusivity.

Correlation between CBV and DWI lesion volumes among all cases was excellent (r=0.89, correlation line CBV = 1.04*DWI − 2.26). However, in the subgroup of small lesions (DWI < 10ml) the correlation was poor (r=0.20). All correlations were statistically significant (p < 0.001). Using the PWI/DWI mismatch pattern as reference, the sensitivity of the Tmax/CBV approach was 0.98 and specificity was 0.76. The Tmax/CBV mismatch was identified in 90 true positive, 31 true negative, 10 false positive, and 2 false negative results. In the majority of the discordant cases, the CBV mismatch was smaller than the DWI lesion.

The findings imply that DWI is superior to CBV for detecting the early ischemic core even under optimized perfusion imaging circumstances.

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Neuroimaging & fMRI

Remembering to Attend: Separating Attention and Memory Signals in Posterior Parietal Cortex
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While attention and declarative memory dynamically interact, the nature of these interactions remains underspecified. Recent proposals suggest that the consistent observation of functional activation in posterior parietal cortex (PPC) during episodic retrieval may reflect the engagement of attention mechanisms. However, a central tenet of these proposals is currently under debate: namely, whether separate attention and memory mechanisms exist in PPC, or whether PPC attention mechanisms are engaged in service of retrieval (by setting the stage for and then acting on the contents of memory during retrieval). To test these competing hypotheses, the present fMRI study incorporated an attentional orienting manipulation into a memory retrieval paradigm. Volunteers were scanned while being cued to extract attention to locations within tri-unique scenes in which tri-unique objects had been studied. To separate memory and attention effects in PPC, memory-based expectations (about object-scene and/or object-location associations) were either met or violated. We predicted functional heterogeneity in PPC, such that (1) dorsal PPC would exhibit top-down attentional orienting effects (when cues can shift spatial attention appropriately), (2) topoparietal junction would exhibit reflective attentional reorienting effects (when expectations were violated), and (3) angular gyrus would exhibit memory recollection effects (when associative information was successfully retrieved). BOLD data revealed all three patterns, indicating that dorsal and ventral PPC attention mechanisms do not fully account for parietal activation during episodic retrieval. Rather, additional PPC mechanisms appear to be specifically engaged when retrieving associative information from memory. These findings add to an emerging literature indicating high functional heterogeneity within PPC.

Steady-State Free Precession (SSFP) Diffusion Imaging Using 3D Rotating Spirals (3DRS)
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Although signal in SSFP-DWI is composed of both spin echo and multi-echo contributions, experiments have shown that motion induced artifacts in SSFP-DWI can still be reduced by correcting residual phase errors or averaging multiple DWI scans. In this work, we present a 3D SSFP rotational (3DRS) method for fast diffusion tensor imaging (DTI) which is based on our previously reported 3D-SSNAILS technique [1]. By combining SSFP-DWI and 3DRS readouts in the same measurement, data volume can rapidly be acquired with very high SNR efficiency and low sensitivity to motion artifacts. One key result of the proposed auto-calibrated SSNAILS approach is that the SSNAILS technique can be computed without calibration data acquired at any location. To accomplish that we only need to translate the surrounding sampling points to a set of grid points in the middle of the final calibration region. We then repeat the reconstruction for each coil to form the final image similar to the GRAPPA algorithm.

Resting-state fMRI is a Reliable Procedure for Mapping the Development of Neural Networks
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Resting-state fMRI (rs-fMRI) is emerging as a powerful procedure for studying whole brain connectivity. In this connectome, we provide the first empirical evidence of the longitudinal reliability of rs-fMRI in children. We compared rest-retest measurements across spatial, temporal, and frequency domains for each of an intricate connectivity networks (ICNs) (cingulo and sensorimotor networks) both within and between scans using Kendall’s W, concordance in spatial maps ranged from .55 to .86 across networks and comparisons. R scores for temporal concordance between networks ranged from .36 between sessions to .66 within session. Finally, there were no differences across measurements in low-frequency power of the ICNs. These reliable measurements across multiple domains (spatial, temporal, and frequency) for resting-state data in children indicate that these measures are reliable and useful for assessing the development of large-scale brain networks. The implications of these findings for task-free fMRI studies in development are discussed.

High-Resolution, Fat-Suppressed, Diffusion-Weighted MRI Of The Breast Using A Self-Navigated Multi-Shot Technique
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For breast MRI, with increasing resolution the readout time for conventional single-shot ME k-space requirements to the point that blurring and geometric distortions impair image acquisition. The strong gradients needed for diffusion-weighting (DW) worsen this problem. Parallel imaging can partially reduce these distortions, which was recently shown for breast MRI, using ASSET. Another approach is to use a multishot technique, such as SNAILS. We evaluated fat-suppressed echo sequence with an analytically designed interleaved variable-angle spiral readout trajectory, which has been applied successfully to high-resolution DWI in the brain. We implemented this in the body, for breast MRI, and compared it to ASSET-DW-EPI in healthy volunteers to show ASSET-EPI and SNAILS diffusion-weighted images. Even with ASSET, DW-EPI was not possible at a 256x256 matrix size.

Benign-Malignant Lesion Differentiation Using Functional ADC-Thresholding – Allowing Expert Radiologist Interpretation – Versus Conventional Thresholding Based On ADC Cut-Off Values
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Diffusion-weighted imaging (DWI) may aid in the discrimination of benign from malignant (breast) lesions. Approaches to benefit from the information contained in the DWI dataset have mostly been based on trying to define a cut-off value for the lesion ADC. This may be limited by the fact that the relative low SNR, the relatively high variability of lesion ADC – even within one hospital or patient population - and the limited potential of the results to be extrapolated to different field strengths, pulse-sequences or vendors. We used an approach in which the high CNR of DWI and the quantitative information of the ADC are presented to the radiologist in a “benefit of knowledge” manner (BAK-map) that increases the conspicuity of lesions of interest, much like phase-images are used to increase vascular conspicuity in susceptibility-weighted imaging. Radiologists can “visualize” the benefit of knowledge in their decision as a lesion is “BAK-bright” without having to choose an ADC-threshold value; Similar to, for example, a cystic lesion being interpreted as “T2-bright” without using T2-cut-off values. We performed a retrospective, HIPAA-compliant, IRB-approved analysis of DWI data of 103 consecutive women who underwent 1.5T MRI for the evaluation of breast cancer. Conventional ADC-thresholding was compared to BAK-mapping and to dynamic contrast-enhanced (DCE) MRI, for all pathology-verified lesions. The results confirm that lower ADCs are correlated with a higher chance of a malignant diagnosis, but that the discriminatory power of setting an ADC cut-off value – evaluated using ROC curves – is low. In attempts to reduce variability and improve the diagnostic value of lesion ADC to rescue ADC to show is unaffected. BAK-mapping may improve lesion discrimination in (breast) MRI. In theory, after large-scale validation of the results, a significant improvement in the diagnostic confidence of lesions with ADCs-3 and arguably even from BIRADS-4 to a benign diagnosis, and thus to spare a biopsy.
Diffusion Tensor Imaging Finds Different Patterns of Associations Between White Matter Structure, Age, and Language Skills in Preterm and Full-Term Children

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Background: Children born preterm have lower IQ and weaknesses in EF skills compared to full-term children. Prematurity increases the risk for periventricular injury, which in turn has been shown to impair auditory sentence comprehension in preterm-born children. However, the extent of white matter abnormalities in preterm children is yet to be systematically investigated.

Objective: To contrast white matter microstructure in children born preterm and full term in controls relative to age, IQ, language and reading scores.

Methods: Preterms (n=19, mean age 11.9 yr and controls (n=15, mean age 11.4 yr) were assessed on the following: IQ (Wechsler Abbreviated Scale of Intelligence), linguistic processing speed (Test for Reception of Grammar = 13.4 yr) were assessed on the following: IQ (Wechsler Abbreviated Scales of Intelligence), spatial memory capacity (Spatial Working Memory, Wechsler Memory Scale), and EF skills (Task Switching, Attention Switching, and Color-Word Interference Task). Diffusion Tensor Imaging (DTI) was pre-processed with Tract-Based Spatial Statistics. Tract-Based Spatial Statistics defined the centers of major white matter tracts throughout the brain. We evaluated group differences in the FA of these tracts and also ran correlation analyses between age, scores, and FA. After correcting for multiple comparisons, FA in children born preterm differed from that of controls.

Results: Age was correlated with FA in controls (p < .05), but not in preterms. The regions of significant differences included the corpus callosum (CC), superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFOF), and inferior longitudinal fasciculus (ILF). Preterms and controls did not differ in FA. A comparison of preterms with IQ = 100 (n=8), preterms with IQ < 100 (n=11) and controls showed significant differences after correcting for age, F = 4.97, p < .01. Correlations of FA with verbal memory, vocabulary, and reading in preterms approached significance, F < .06 but not controls. The regions of significant differences in verbal memory and vocabulary included the IFOF. Regions of differences in decoding also included the SLF and IFOF, but p > .05.

Discussion: High functioning preterm children appear to have normal white matter microstructure. Perinatal white matter injury in low functioning preterm children affects brain structure and function into adolescence. White matter microstructure did not explain individual differences in function in controls.

References/Funding Source

An fMRI Investigation of Individual Differences in Auditory Sentence Comprehension in Adolescent Children Born Prematurely

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Despite evidence that prematurity birth has long-range adverse outcomes on language processing, the specific relationships between preterm white matter abnormalities and auditory sentence comprehension in preterm born adolescents have not been previously well characterized in this population. This study utilized individual differences based on phonological representation in the left temporal cortex bilaterally. Moreover, changes in activation in both regions were associated with individual participant’s vocabulary and language ability. Similarly, increased sentence length and difficulty were associated with activations in both regions. In addition, participating preterms showed evidence that the key components of pre-maturity on auditory sentence comprehension. Twelve adolescents between the ages of 9-14 years (8 male, mean gestational age = 26.8 weeks) performed the sentence comprehension task where sentence length and difficulty were manipulated in a 2 x 2 factorial design. Participants had general knowledge of the task and were recruited from the community.

Methods: Preterms (n=19, mean age 11.9 yr and controls (n=15, mean age 11.4 yr) were assessed on the following: IQ (Wechsler Abbreviated Scales of Intelligence), spatial memory capacity (Spatial Working Memory, Wechsler Memory Scale), and EF skills (Task Switching, Attention Switching, and Color-Word Interference Task). Diffusion Tensor Imaging (DTI) was pre-processed with Tract-Based Spatial Statistics. Tract-Based Spatial Statistics defined the centers of major white matter tracts throughout the brain. We evaluated group differences in the FA of these tracts and also ran correlation analyses between age, scores, and FA. After correcting for multiple comparisons, FA in children born preterm differed from that of controls.

Results: Age was correlated with FA in controls (p < .05), but not in preterms. The regions of significant differences included the corpus callosum (CC), superior longitudinal fasciculus (SLF), and inferior fronto-occipital fasciculus (IFOF). Preterms and controls did not differ in FA. A comparison of preterms with IQ = 100 (n=8), preterms with IQ < 100 (n=11) and controls showed significant differences after correcting for age, F = 4.97, p < .01. Correlations of FA with verbal memory, vocabulary, and reading in preterms approached significance, F < .06 but not controls. The regions of significant differences in verbal memory and vocabulary included the IFOF. Regions of differences in decoding also included the SLF and IFOF, but p > .05.

Discussion: High functioning preterm children appear to have normal white matter microstructure. Perinatal white matter injury in low functioning preterm children affects brain structure and function into adolescence. White matter microstructure did not explain individual differences in function in controls.

References/Funding Source

Expected Value Information Improves Financial Risk Taking Across the Adult Life Span

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When making decisions, individuals must often compensate for cognitive limitations, particularly in the face of advancing age. Recent findings suggest that age-related variability in attentional skills may increase financial risk taking mistakes in older adults. In two studies, we sought to further characterize neural contributions to risk-taking and to determine whether decision aids could improve financial risk taking. In Study 1, neuroimaging analyses revealed that individuals whosemouseover activation correlated with the expected value estimates of financial risk taking across the adult life span.

In Study 2, presentation of expected value information improved decision making in both younger and older adults, but the addition of a distracting secondary task had little impact on decision quality. Remarkably, provision of expected value information improved the performance of older adults to match that of younger adults at baseline. These findings are consistent with the notion that mesolimbic circuits play a critical role in optimal choice, and imply that providing simplified information about expected value may improve financial risk taking across the adult life span.

References/Funding Source

Core White Matter Characteristics Related to Behavioral Problems in 9-16 Year Old Preterm and Full-Term Children

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Purpose: Preterm children have more behavior problems, including inattention and anxiety symptoms, than full-term peers. To date, the only study contrasting preterm and term children showed a functional difference in the nucleus accumbens activity mediates age-related suboptimal financial risk taking. Journal of Neuroscience, 30(4), 1426–1434.

Impact: Preterm children have more behavior problems, including inattention and anxiety symptoms, than full-term peers. To date, the only study contrasting preterm and term children showed a functional difference in the nucleus accumbens activity mediates age-related suboptimal financial risk taking. Journal of Neuroscience, 30(4), 1426–1434.
Neuroimaging & fMRI

Content-sensitive Novelty Encoding in the Medial Temporal Lobe: Insights from High-resolution fMRI and Distributed Pattern Analysis
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The ability to distinguish between novel and familiar stimuli plays a critical role in both biological and computational models. Current theories of medial temporal lobe (MTL) function propose that distinct MTL regions may differ in their sensitivity to novelty based on content. For example, early-onset Alzheimer’s disease patients show reduced sensitivity to novelty in the hippocampus and parahippocampal cortices. Here, we investigated whether content-based novelty discrimination exists in the MTL and parahippocampal cortices. To answer this question, we employed high-resolution functional magnetic resonance imaging (fMRI) and an incidental novelty detection task with five stimulus classes (faces, scenes, voice words, spoken words, sounds). Using this approach, we found a gradient distribution of face and scene novelty responses along the anterior-posterior axis of MTL cortices. Novelty responses in hippocampus were isolated to the anterior subfields and were similar across content. Additionally, a multivoxel pattern analysis revealed that despite overall sensitivity to specific content, MTL cortex was differentially engaged when novelty was restricted to a certain class of content. In contrast, hippocampal subfields DCAa-C3 and C4 failed to accurately discriminate between different content types, though subfields demonstrated a significant classification accuracy for faces and scenes. Together, these findings support a gradient distribution of content-sensitive novelty responding along the anterior-posterior axis of MTL cortex and provide evidence for content-general novelty encoding in the hippocampus.

References/Funding Source

To be presented at Society for Neuroscience 2010

Learning Exceptions to the Rule: High-resolution fMRI of Hippocampal Subfield Contributions to Category Learning
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The medial temporal lobe (MTL) and its connections with midbrain, prefrontal cortex (PFC), and striatum have been implicated in different forms of novelty processing. In the present study, we examine a unique novelty detection task where subjects learn categories containing items that violate a salient regularity. These “exceptions to the rule” are novel in the context of their category but become familiar with repeated exposure. We asked if the hippocampus is engaged during the detection of these exceptions to the rule and used high-resolution functional magnetic resonance imaging (fMRI) to study these processes. Our results reveal that CA1 and a combined region of CA2 and dentate gyrus are recruited during categorization of exception items as well as in response to prediction error. These findings are consistent with previous reports that the hippocampal circuit acts as a comparator to evaluate incoming information by comparing it with previously stored representations and forming new representations in response to prediction error. Specifically, we suggest that the CA fields and dentate gyrus are recruited both to encode new representations when exceptions are first encountered and to retrieve these representations when needed for accurate exception performance.

Detection of Sequence Violations in the Medial Temporal Lobe: Subregional Contributions to Memory-based Prediction
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Current research proposes that medial temporal lobe (MTL) subregions perform distinct computations to enable comparison between past and present experience. Hippocampus is thought to play a unique role in the detection of novelty within a sequence, whereas associated items appear in a new order. In contrast, midbrain and prefrontal cortex are suggested to be critical for detecting exceptions to the rule, both within and across subregions. To address this discrepancy, we implemented high-resolution functional MRI and an incidental novelty detection task using five stimulus classes (faces, scenes, voice words, spoken words, sounds). Using this approach, we found a gradient distribution of face and scene novelty responses along the anterior-posterior axis of MTL cortices. Novelty responses in hippocampus were isolated to the anterior subfields and were similar across content. Additionally, a multivoxel pattern analysis revealed that despite overall sensitivity to specific content, MTL cortex was differentially engaged when novelty was restricted to a certain class of content. In contrast, hippocampal subfields DCAa-C3 and C4 failed to accurately discriminate between different content types, though subfields demonstrated a significant classification accuracy for faces and scenes. Together, these findings support a gradient distribution of content-sensitive novelty responding along the anterior-posterior axis of MTL cortex and provide evidence for content-general novelty encoding in the hippocampus.

References/Funding Source

Presented at Cognitive Neuroscience Society 2010

Motivation During Associative Encoding Involving Subsequent Recall Responses in Medial Temporal Subregions
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Emerging evidence suggests that hippocampal memory processing is modulated by reward, resulting in enhanced encoding of episodic information—long-term memory for events. Current theories further propose that memory processing in hippocampal subregions may be differentially influenced by reward. While previous research has examined reward influences on episodic encoding, so far to date has examined how motivation during encoding influences hippocampal responses at retrieval. Using high-resolution functional magnetic resonance imaging (fMRI), the present study investigated the function of medial temporal lobe (MTL) subregions, including hippocampal subfields, midbrain, and nucleus accumbens during recall of associatively encoded items. Specifically, we examined how the motivation, defined as high versus low value or low monetary cues preceding object presentation indicated potential reward for successful retrieval of the associations. At retrieval, participants were presented with a cue object (a single object from a stimulus pair) and were asked to recall and imagine the associated object during a delay period. At the end of the delay period, a probe object was presented and subjects were asked whether the probe was the correct object (a “match”) or another object viewed at encoding.

Reduced Hippocampal Activity During Encoding in Cognitively Normal Adults Carrying the APOE ε4 Allele
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Apolipoprotein (APOE) ε4-related differences in memory performance have been detected before age 65. The hippocampus and the surrounding medial temporal lobe (MTL) structures are the first site affected by Alzheimer’s Disease (AD) and the MTL is the seat of episodic and visuospatial memory. However, reports on APOE ε4-related differences in these brain structures are not consistent across studies. We implemented a children’s card game (chock-a-block) for the first time in double-blind, randomized, and placebo-controlled functional magnetic resonance imaging (fMRI) studies. In addition, there is information about the function of the MTL during encoding of low value or low monetary cues preceding object presentation indicating potential reward for successful retrieval of the associations. At retrieval, participants were presented with a cue object (a single object from a stimulus pair) and were asked to recall and imagine the associated object during a delay period. At the end of the delay period, a probe object was presented and subjects were asked whether the probe was the correct object (a “match”) or another object viewed at encoding.

Neural Basis Of Hypnotizability Revealed By Resting State Functional Connectivity
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Hypnotherapy involves an aspect of the human brain that is relatively unexplored, with many potential challenges to both understanding and implementation. The present study investigated the neural basis of hypnotizability, as measured by the performance on a 60-minute induction task. The results of this study have implications for fMRI studies that investigate the task-positive network (TPN) and default-mode network (DMN) in APOE ε4 carriers to help evaluate AD risk in the otherwise cognitively normal population.
Flow Separation Control in a Conical Diffuser with an Annular Inlet

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In a combined cycle power plant, the high velocity exhaust from the power turbine has to be slowed down before reaching the steam generator. A conical diffuser is commonly used behind the turbine to slow down the flow and recover pressure. The inlet to the diffuser is an annulus due to the annular flow passage of the turbine. A large central separation bubble forms if the central hub end abuts abruptly because the flow is incapable of negotiating around a sharp corner. This separation causes non-uniform flow into the steam generator, and imposes fatigue loading on downstream components. Both have negative effects on the performance and the longevity of the steam generator. A long streamwise tail cone at the end of the hub can eliminate the separation, but it is often unfeasible for structural reasons. Experiments were performed in scaled flow models to investigate various means to manage both the central separation bubble and any separation on the outer diffuser walls. The Reynolds number is 60000 based on the annulus bulk velocity and hydraulic diameter. Full-field, three-component velocity data were measured in a series of diffuser models using phase contrast magnetic resonance velocimetry. The central separation bubble behind the hub extends the full length of the diffuser in the absence of any control. A Conical jet at the end of the hub can strongly reduce or completely eliminate the central separation bubble, depending on the jet blowing ratio. However, this can cause separation from the conical diffuser walls in some cases.

A backward facing step in the outer diffuser wall acts to fix the location of separation making it more amenable to control. Several control mechanisms for this outer separation bubble are under investigation.

Neuroimaging & fMRI

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Magnetic Resonance Imaging (MRI) is a widely used tool in medical diagnosis and research. It allows for a non-invasive view into the living body, providing high-resolution images of anatomical structures and functional brain activity. In recent years, MRI has been applied to the study of emotional processing and regulation, providing valuable insights into the neural mechanisms underlying these processes.

One such study, published in the Journal of Cognitive Psychotherapy, examines the neural mechanisms of emotion regulation using a modified Stroop task. Participants were divided into two groups: one receiving cognitive-behavioral therapy (CBT) and the other a waitlist control. The primary outcome measure was the ability to regulate emotional responses to negative stimuli.

The study found that participants in the CBT group showed greater reductions in emotional reactivity, as measured by changes in neural activity in the amygdala, compared to the waitlist control group. This suggests that CBT may effectively modulate the neural underpinnings of emotional processing, potentially offering a neurobiological basis for its therapeutic effectiveness.

Deficits in Anterior Cingulate-Amygdalar Circuitry During Implicit Emotion Regulation in Anxiety

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Objective: This study examined whether reductions in anterior cingulate-amygdala circuitry during implicit emotion regulation are related to better emotion regulation in social phobia (SP) and/or greater symptom improvement following therapy.

Methods: This was a randomized clinical trial of 17 patients with generalized social phobia (GSP) randomized to either two weeks of mindfulness-based stress reduction (MBSR) or a control condition (Active Control; ACC). MBSR participants underwent twice-weekly, 2-hour group sessions for 8 weeks, while ACC participants received support group and individual therapy.

Results: MBSR participants showed greater reductions in anterior cingulate-amygdala circuitry during implicit emotion regulation than ACC participants. This finding was particularly pronounced in the ACC participants who showed reduced amygdala activation in response to emotional stimuli compared to the MBSR participants. These findings suggest that MBSR may be effective in reducing emotional reactivity and improving neural circuitry involved in emotional processing.

Conclusions: This study provides evidence for the neural mechanisms underlying the therapeutic effects of MBSR in the treatment of social phobia, offering insights into the neurobiological basis of cognitive-behavioral therapy.

Neural Mechanisms Underlying MBSR in Healthy and Socially Phobic Individuals

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The overall goal of the present study was to elucidate the neural bases of emotional reactivity and cognitive regulation in social phobia (SP) and to identify the neural mechanisms underlying treatment change associated with cognitive-behavioral therapy (CBT) for SP. In this randomized clinical trial study, patients with social anxiety disorder are randomly assigned to CBT or waitlist, and are administered a battery of assessments in order to examine therapeutic change and brain systems related to emotion reactivity and regulation.

The study found that patients in the CBT group showed greater reductions in amygdala activation in response to emotional stimuli compared to the waitlist group. This suggests that CBT may effectively modulate the neural underpinnings of emotional processing, potentially offering a neurobiological basis for its therapeutic effectiveness.

References/Funding Source


The results of this study highlight the importance of targeting neural mechanisms underlying emotional processing as a means of improving therapeutic outcomes in the treatment of social anxiety disorder.
Neuroimaging & FMRI

The Feasibility of Detecting Neuroanatomical Effects of Type 1 Diabetes Mellitus in Young Children

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Type 1 diabetes mellitus (T1DM) impacts the developing brain and both hypoglycemia and hyperglycemia have been associated with neurocognitive and neurometabolic changes. Young children with T1DM have wide excursions in blood glucose during a period when the brain is undergoing dynamic changes including myelination and repair of synapses. Therefore, we hypothesized that frequent exposure to hyperglycemia during early childhood may potentially lead to changes in brain anatomy. Young children, ages 3 to less than 10 years, with T1DM and age, gender, and socioeconomic matched controls complete age-sorted self-rated MRI scans of the brain. Ninety-three percent of the children successfully MRI scanning respectively. In our cohort of 20 children with T1DM and 17 healthy controls, we found similar grey matter (GM: 862 ± 101 mm³ vs 838 ± 95 mm³), white matter (WM: 377 ± 63 mm³ vs 370 ± 57 mm³) and hippocampal (6.5 ± 0.8 mm³ vs 6.1 ± 0.8 mm³) volumes in subjects between the two groups. However, after controlling for age and gender, we detected a significant diagnosis by age interaction such that WM volume was unchanged in older children with T1DM, in contrast to healthy controls who showed the expected normal increase in WM volume with age. A similar trend was detected for hippocampal volume (diagnosis x age: p=0.01). We also noted that those T1DM children who had experienced seizures showed significantly reduced GM (p=0.049) and WM (p=0.049) volumes relative to children with T1DM who had not experienced seizures. We show that it is feasible to perform MRI in young children with T1DM and that early signs of neuroanatomical variation may be present in this population. Large cross-sectional and longitudinal studies of exaraymics are needed to define the impact of T1DM on the developing brain.

Dominance of Task-positive Over Default-mode Network Activity Mediates Adaptive and Maladaptive Rumination in Major Depressive Disorder

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Major Depressive Disorder (MDD) has been associated reliably with neurocognitive and neurometabolic changes that involve both adaptive and maladaptive rumination. Relative levels of activity in the task-negative network vs the default-mode network (TPN and DMN) of the intrinsic functional macro-architecture of the brain may represent an important substrate of adaptive and maladaptive rumination in MDD. We estimated TPN dominance over DMN from blood oxygen-level dependent data collected during eyes-closed rest in depressed and non-depressed persons. We calculated correlations between TPN dominance over DMN and the depressive, brooding, and reflect subscales of the Rumination Scale, controlling for associations between these measures and severity of depression. Further, for both groups of participants we estimated RFIC reactivity during presentations of aversive in TPN and DMN activity. We observed in MDD increased TPN dominance over DMN that was negatively correlated with maladaptive depressive rumination and positively correlated with adaptive, reflective rumination (see figure below). We also found in depressed participants increased RFIC activation at the onset of aversive in TPN activity that was positively correlated with TPN dominance over DMN. The current results show that an adaptive relation between the TPN and DMN may be indexed by RFIC-mediated awareness of negative emotional states.

The Neural Temporal Dynamics of the Intensity of Emotional Experience

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Despite the fact that emotions involve multiple time-varying components, little is known about the underlying neural basis of these temporal dynamics. In this paper, we assess these temporal dynamics by using time-varying hemodynamic response functions (HRF) to model BOLD responses to the presentation of emotional stimuli. We show that these time-varying HRFs lead to a better fit to the BOLD data and yield larger areas of significant activation than to conventional gamma-based canonical HRFs. We also report for the first time that intensity of emotional experience is associated with both magnitude of duration of brain activation. Specifically, greater intensity of emotional intensity was associated with greater magnitude of activation in the occipital cortex and with longer duration of activation in regions along the cortical midline associated with self-referential processing: the anterior medial frontal cortex and the posterior cingulate cortex. These data significantly advance our understanding of how the neural processes that mediate the intensity of emotional experience are due in part to elaborative self-referential processing that is captured by the duration of neural activity in cortical midline structures. These data also underscore the importance of using modeling techniques that will help elucidate the chronometry of both normal and psychopathological emotional processes.

Investigating Neural Primacy in Major Depressive Disorder: Multivariate Granger Causality Analysis of Resting-state FMRI Time-series Data

JP Hamilton, G Chen, ME Thomason, ME Schwartz, IH Gotlib
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Major Depressive Disorder (MDD) has been conceptualized as a neural network-level disease. Few studies of the neural basis of depression, however, have used analytic techniques that are capable of quantifying the dynamic interactions between and within these networks. Here, we used multivariate Granger causality analysis—a technique that estimates the extent to which precursing neural activity in one or more seed-regions predicts subsequent activity in target brain regions—to analyze blood-oxygen-level dependent (BOLD) data collected during eyes-closed rest in depressed and non-depressed persons. We found that activation in the hippocampal predicted subsequent increases in ventral anterior cingulate cortex (vACC) activity in depression, and that activity in medial prefrontal cortex and vACC were associated reliably with ruminative responding that in MDD children have used analytic techniques that are capable of correcting for associations between these measures and severity of depression.

References/Funding Source

Weingarter Foundation, American Diabetes Association June 2010

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References/Funding Source

Weingarter Foundation, American Diabetes Association June 2010

Psychophysical and Neural Investigations of Congenital Prosopagnosia

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Congenital prosopagnosia is a lifelong specific deficit in identifying faces that is not the result of stroke or other brain injury or gross physiological abnormality. MRI in prosopagnosics has been informative in revealing the neural basis with the largest such study to date) that led to finding any differences between prosopagnosics and controls in ventral occipito-temporal visual cortex. Noting that there are some differences between prosopagnosia and controls in the functional profile of face-selective regions in ventral visual regions, in ongoing work we have identified 14 prosopagnosics who show poorer performance than controls on tests of face recognition. Additionally, our prosopagnosic group performed worse on the NEPSY-II Test of Emotional Development, suggesting a subtle impairment in their perception of facial affect. Consistent with a deficit specific to face memory/perception, our subjects do not differ from controls in recognition of famous faces, or recognition memory for scenes and objects. We have collected and analyzed fMRI data from 10/14 subjects. In the scanning experiment, subjects viewed blocks of faces, places, and objects, alternating with fixation. Previously published data (Golbar et al 2010) from 9 subjects who participated in identical experiments was used for comparison. Anatomical regions of interest containing ventral visual cortex were drawn in each subject, extending anteriorly from V4, 2/3 of the distance to the temporal pole. The ROI was bounded medially by the collateral sulcus and laterally by the occipitotemporal sulcus. In regions within the ROI we found no differences between our prosopagnosics and controls in the spatial extent of object-selective (objects/brains) and multiple-activated regions (faces/objects). However, prosopagnosics had fewer face-selective voxels in the right hemisphere (faces/objects), suggesting prosopagnosics may differ from controls in the extent of face selectivity in ventral visual cortex.

References/Funding Source

NIDB-BCS-089406 and NIH-NIBS 1F32EB009351-01A1

Psychophysical and Neural Investigations of Congenital Prosopagnosia

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Neuroimaging & FMRI

High-resolution MRI Reveals Separate Limbic activations Surrounding Area MT+ 1,2
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Standard functional magnetic resonance imaging (fMRI) studies have identified overlapping regions in human lateral occipitotemporal cortex (LOTC) that are involved in both face and scene processing. These regions include both the anterior (medial occipital cortex, area 23) and the posterior (lateral occipital cortex, area 37) visual stream. Recent studies have suggested that the LOTC is involved in both the dorsal and ventral visual pathways. We investigated the functional role of dorsal and ventral PPC regions in memory. During an episodic encoding task, participants were required to remember words associated with face and scene images. We used fMRI to study the functional connectivity within the LOTC. Our results suggest that the LOTC is involved in the encoding of both face and scene images.

Face-selective Activation in the Posterior Superior Temporal Sulcus is Similar Across Children, Adolescents, and Adults 1,2
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Regions in the posterior superior temporal sulcus (pSTS) in humans respond more strongly to faces than to non-face stimuli and are thought to be involved in processing the dynamics of faces. Functional magnetic resonance imaging (fMRI) studies of this region report conflicting results on the development of this region, with some studies suggesting that the development of this region is not complete until adulthood. In this study, we aimed to investigate the development of this region in children, adolescents, and adults using fMRI. Our results suggest that the development of this region is not complete until adulthood.

References/Funding Source

Parietal Contributions to Episodic Retrieval: Effects of Memory and Decision Criteria 1,2
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While neuroimaging studies of episodic retrieval have consistently revealed activations in posterior parietal cortex (PPC), there remains much debate about the functional roles of dorsal and ventral PPC regions in memory. A parallel literature implicates PPC in processes engaged during prospective decision-making, suggesting similar processes may also contribute to episodic retrieval. The current study investigated the neural criterion in order to disentangle PPC responses associated with mnemonic evidence from responses associated with decision processes. Participants participated in a task in which they were instructed to determine whether a future event as distinct from previously-experienced events (e.g., pattern separateness) increased the physical variability of face stimuli. We hypothesized that a standard old/new recognition task would be more effective in identifying the regions involved in episodic retrieval.

References/Funding Source

Characterizing Face Representations in the Ventral Stream: Effects of Physical Variability and Distance from the Average Face 1,2
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MBI research has identified regions in the human fusiform gyrus (FFA) and the middle occipital gyrus (MOG) that respond selectively to faces. We propose two types of underlying mechanisms by which neurons in these regions represent different faces: highly consistent features, and coarse features. Our results suggest that these mechanisms may also contribute to episodic retrieval.

References/Funding Source

White Matter of the Early Visual Pathways

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Tension is thought to exist within the medial temporal lobes (MTL) when events share overlapping features, such as stimuli readily elicit an event as distinct from previously-experienced events (e.g., pattern separateness) increases physical variability of face stimuli. In an effort to better understand the neural mechanisms underlying this phenomenon, we investigated the neural correlates of this phenomenon using fMRI. Our results suggest that the tension is associated with the activation of the fusiform gyrus (FFA) and the middle temporal gyrus (MTG) that respond selectively to faces. These activations have consistent anatomical boundaries across different blocks (Study 2), responses in FFA and MOG were stronger for stimuli that provide higher statistical variability, suggesting that high statistical variability provides better cues for distinguishing between old and new events.

References/Funding Source

Abstracts: Magnetic Resonance Research

High-resolution Pattern Separation in the Medial Temporal Lobe VA Carr1, SE Favilla2, AD Wagner1
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We aimed to investigate the neural correlates of pattern separation in the medial temporal lobe (MTL). We found that high-level face representations in the ventral pathway, such as the fusiform face area (FFA), respond more strongly to faces with high variability than to faces with low variability. We also found that the FFA responds more strongly to faces with high variability than to faces with low variability. These results highlight the importance of controlling the physical variability of stimuli when investigating the functional properties of ventral visual cortex. Further, responses in FFA and MOG across all 3 studies can be explained by a new model that allocates more neurons with differential responses to frequently-experienced, typical faces near the average face. We propose similar coding principles may underlie the representation of other visual categories.
We used a probabilistic algorithm (Shenbrot 2008) to identify the most likely pathways between the callosal regions in children (Dougherty 2007). We also measured diffusion along each of the callosal pathways and compared diffusion with behavioral measures of phonological awareness. Fibers of the left pSTC project to the same callosal region previously shown to correlate with phonological performance. Our data also show a correlation between phonological awareness, and fractional anisotropy and radial diffusivity on the pSTC fiber track. In contrast, the MTF and VWFA callosal fibers project to a different region in the posterior callosum, and their diffusion properties do not correlate with phonological awareness. Combining fiber tracking with diffusion measurements, we have identified a correlation between neurobehavioral performance and local callosal properties.

References/Funding Source NIH EY 015000, JD Yeatman1, RF Dougherty1, E Rykhlevskaia1, GK Deutsch1, BA Wandell1, M Ben-Shachar2 (2010), White matter callosal projections from superior temporal phonological regions predict reading skills in children. Society for Neuroscience annual meeting, San Diego, CA.

Anatomical Properties of the Arcuate Fasciculus Predicts Phonological and Reading Skills in Children

JD Yeatman1, RF Dougherty1, E Rykhlevskaia1, GK Deutsch1, BA Wandell1, M Ben-Shachar2
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The left arcuate fasciculus (AF) is thought to comprise fibers that carry essential information for processing language. Yet, prior studies focused on whole-brain group comparisons suggesting that the essential reading-related white matter pathway is in the corona radiata, adjacent to the arcuate fasciculus, but not in the arcuate itself. We identified the left arcuate fasciculus using fiber tractography in each of fifty typically developing children. We identified the tract in individual children by identifying the judgment localizers identified left pSTC, and using the Deuk-Kallian-Atlas (Fischl 2004), we identified the likely position of the pSTC in the remaining children.

Molecular imaging is the art of looking inside of a living organism or cell to evaluate biological processes, observe normal cell behavior, identify aberrant behaviors, and develop interventions to halt or rectify such abnormalities. Through molecular and functional imaging we have made huge strides in bridging many other disciplines such as, biology, chemistry, physics, and computer science and ultimately changing and improving how we use imaging in medicine.
**Molecular Imaging**

**[18]**-Saxitoxin PET-MRI: A New PET-based Method for Imaging Pain in Living Subjects

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**Purpose:** The sensation of pain is dependent upon voltage-gated sodium channels (NaV), which are essential to the generation of action potentials and neural impulse conduction. NaV isoforms are assessed via 60 minute dynamic imaging of neuropathic pain-model rats (Spared Neuropathic Pain Model, SNP). Evaluation of [18F]STX in living rats using positron emission tomography-magnetic resonance imaging (PET-MRI) can potentially be used to identify neuropathic changes in living subjects.

**Methods:** NaV isoform-selective [18F]STX was made via cyanoborohydride substitution using a commercially-available automated radiochemistry module. The conjugation of [18F]STX with STX (synthesized in-house) afforded [18F]STX ([F]SFB) (Figure 1A) with a minimum specific radioactivity of 1.3 Ci/mM (48 GiCi/mM) and radiochemical purity (95%) in a total synthesis time of about 3.5 h from end of bombardment (eoB). In vivo biodistribution of [18F]STX was assessed via 60 minute dynamic imaging of nociceptive pain model mice (Spared Neuropathic Pain Model, SNP) and sham-operated rats as shown by increased MR signal and nerve concentrations. The control intact rat sciatic nerve by comparison showed no significant uptake (small white arrow). The control intact sciatic nerve by comparison showed no significant uptake (small white arrow).

**Conclusions:** [18F]STX shows tremendous potential as a specific radioligand for visualizing NaV, channels in vivo. Since [18F]STX is the only reported radioligand targeting NaV channels to date, it is a valuable lead compound for future tracer development to image pain and facilitate future image-guided therapies for humans.

**Oral Manganese as an MRI Contrast Agent for the Detection of Nociceptive Activity**

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Manganese-enhanced magnetic resonance imaging (MEMRI) is a potentially powerful diagnostic method for identifying and characterizing neural regions of pain processing for image-guided interventions. Manganese can enter nerves via voltage-gated calcium channels, which are selectively upregulated in pain. We gained manganese by oral gavage to two rat groups: one with spared nerve injury of their sciatic nerves and a sham-operated group. We found that rats with spared nerve injury have increased manganese ion uptake and retention in their nerves compared to the nerves of sham-operated rats as shown by increased MR signal and nerve concentrations. Therefore, manganese can specifically enhance nerves associated with pain.

**[18]**-Fluoride Ion PET-CT Predicts Painful Metastatic Bone Lesions in the Thoracicolumbar Spine

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Department of Radiology and Radiation Oncology, Stanford University, CA

**Purpose:** [18F]Fluoride ion PET-CT has emerged as a powerful and sensitive approach to studying areas of bone remodeling and turnover. The purpose of this study is to determine if there is a relationship between the extent of [18F]fluoride ion uptake in the thoracicolumbar spine and presence of painful metastatic lesion back pain in patients suffering from osteosarcoma metastatic disease.

**Method:** IRB approval was obtained. A retrospective review of 15 whole body [18F]fluoride ion PET-CT, which included 4 women and 12 men from ages 19-81. The same subjects had also received a [18F]FDG PET-CT scan with an average interval of 6.3 days (range 1-28) between studies. Subjects fell into 1 of 3 categories: 1) Subjects with metastatic lesions to the thoracolumbar spine and described ‘back pain’ on the entrance questionnaire (n=3), 2) Subjects with metastatic disease to the spine and described ‘no pain’ (n=6), and 3) Subjects (control) who described ‘no pain’ on their entrance questionnaire and had no metastatic lesions to the spine (n=6). Using the Bony-back CT to define the margins of the bone, representative rounded region-of-interests (ROIs) were placed at each vertebral level of the study from T1 to SI in both [18F]fluoride ion and [18F]FDG PET-CT studies. Mean SUV was recorded at each level and each patient was assigned a maximum mean SUV for their entire thoracolumbar spine. Data was analyzed using RTImage analysis software and t-test with unequal variances. Significance is p<0.05.

**Results:** Patients with spinal osseous metastases to the thoracolumbar spine (7.9±0.7) (p<0.013). By comparison, no significance differences were found with back pain, mets with no back pain and no mets were 6.9±0.1, 2.9±1.4 and 3.9±0.7, respectively (p<0.11).

**Conclusions:** [18F]Fluoride ion PET-CT may be helpful in predicting which metastatic lesions will be painful in the thoracolumbar spine, allowing for treatment planning.

**In Vivo Multiplexed Optical Imaging with Radiation Luminescence Excited Quantum Dots**

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**Abstracts:** Molecular Imaging

**References/Funding**

National Cancer Institute (NCI) R21 CA121842 (to Z.C.), A_Star BMRC (07/1/22/19/534) grant from Singapore (to B.X.), and the China Scholarship Council fellowship (to H.L.). HG Liu, XF Zhang, B Xing, PZ Han, SS Gambhir, Z Cheng. Molecular Optical Imaging with Radioactive Probes. Podus ONE, S(3): e0470.

**Noninvasive Molecular Imaging of Radioactive Probes Using Optical Imaging Techniques**

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**Abstracts:** Molecular Imaging

**References/Funding**

National Cancer Institute (NCI) R21 CA121842 (to Z.C.), A_Star BMRC (07/1/22/19/534) grant from Singapore (to B.X.), and the China Scholarship Council fellowship (to H.L.), HG Liu, XF Zhang, B Xing, PZ Han, SS Gambhir, Z Cheng. Radiation Luminescence Excited Quantum Dots for In Vivo Multiplexed Optical Imaging. Small, 6(10): 1087-1091.
Targeting of HER2-Expressing Tumors Using Affibody-HSA Bioconjugates

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Objectives: Affibody molecules represent a novel class of new protein scaffolds for imaging and drug delivery. In this study, we explored whether Affibody molecules could be used to shift the in vivo behavior of Affibody proteins.

Methods: HSA was modified by 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). The resulting bioconjugate DOTA-HSA-ZHER2 was further radiolabeled with 18F through both liver and kidneys. Co-injection of the probe with 100 µg cyclic peptide was cyclized by 2 oxidation to form a disulfide bridge. The purified cyclic peptide was then labeled with 64Cu for positron emission tomography (PET) imaging of HER2 positive tumors. The resulting PET probe, 18F-FBA, displayed a high specific activity and good tumor-to-normal tissue contrast of 18F-FBO-MUT-DS, displayed a high specific activity and good tumor-to-normal tissue contrast. HER2:342 bioconjugates were intravenously injected into SKOV-3 tumor-bearing mice at different time points after intravenous injection of 64Cu-DOTA-HSA-ZHER2:342. (n=3). (D) biodistribution studies further demonstrated that the probe had excellent tumor uptake (6.92 %ID/g at 1 h post-injection) and was cleared through both liver and kidneys. Co-injection of the probe with 100 µg cyclic peptide was cyclized by 2 oxidation to form a disulfide bridge.

Conclusion: 18F-FBO-MUT-DS displays excellent HER2 targeting ability and tumor PET imaging quality. Two helix small peptides are suitable for development of 18F based PET probes.

Reference:

In-Labeled Knottins for Tumor Angiogenesis Targeting

G Ren1, Z Mao1, H Lu1, R Kimura1, Y Wang1, J Cochran2, Z Cheng1
Department of Radiology, MIPS, Bi-X Program and Biomedical Engineering, Stanford University, CA

Objectives: Integrin receptors play a pivotal role in tumor angiogenesis. Ex vivo autoradiography and microPET imaging of SKOV-3 ovarian cancer tumors showed excellent radiochemical purity (> 95%) and tumor targeting. The biodistribution of both peptides was examined for micro positron emission tomography (µPET) imaging of tumor integrin receptors. These results demonstrated high tumor uptake and good tumor-to-normal tissue ratio compared with the control peptides, high tumor accumulation, and good tumor-to-normal tissue ratio compared with the control peptides.

Conclusion: In summary, these results suggest that the in vivo pharmacokinetics could be finely tuned by modifications of the peptide structure. The microPET could monitor the in vivo biodistribution of peptides and provide useful information for the rational design and optimization of peptide with various biological functions.

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Conclusion: In summary, these results suggest that the in vivo pharmacokinetics could be finely tuned by modifications of the peptide structure. The microPET could monitor the in vivo biodistribution of peptides and provide useful information for the rational design and optimization of peptide with various biological functions.
Molecular Imaging

A Cy5.5 Labeled Affibody Molecule for Near-infrared Fluorescent Optical Imaging of Epidermal Growth Factor Receptor Positive Tumors

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Department of Radiology, MIFS, Bio-X Program, Stanford University, CA

Objectives: Affibody protein is an engineered protein scaffold with a three-helix bundle structure. Affibody molecule of small size (~7 kD) have great potential for targeting cancer biomarkers in vivo. In this study, we aimed to develop an Affibody based molecular probe for in vivo optical imaging of epidermal growth factor receptor (EGFR) positive tumors.

Methods: An anti-EGFR Affibody molecule, Ac-Cys-ZEGFR:1907 (7 kD), was site-specifically conjugated with a near-infrared (NIR) fluorophore, dye Cy5.5-mono-maleimide. Using fluorescence microscopy, the binding specificity of the probe Cy5.5-ZEGFR:1907 was measured using high EGFR expressing A549 cells and low EGFR expressing MCF7 cells. The EGFR binding affinity of Cy5.5-ZEGFR:1907 (Kd) was 43.6 ± 8.4 nM as determined by flow cytometry. For in vivo imaging study, the probe showed fast tumor targeting and good tumor contrast as early as 0.5 h post-injection in A549 tumors, while MCF7 tumors could be barely visualized. Ex vivo imaging study also demonstrated that Cy5.5-ZEGFR:1907 had high tumor, liver and kidney uptakes at 24 h p.i.

Conclusion: Cy5.5-ZEGFR:1907 shows good affinity and high specificity to EGFR. It is a promising NIR probe for EGFR targeted cancer optical imaging.

Small-Animal PET Imaging of Human Epidermal Growth Factor Receptor Positive Tumor with a 64Cu Labeled Affibody Protein

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Department of Radiology, MIFS, Bio-X Program, Stanford University, CA

Objectives: EGFR is over-expressed in many cancer types, making it an attractive target for cancer imaging and therapy. Affibody proteins against EGFR have been reported recently. We thus are interested in evaluating their potential for positron emission tomography (PET) imaging of EGFR positive cancers.

Methods: An Affibody molecule (Ac-Cys-ZEGFR:1907)binding to EGFR was prepared through a conventional solid phase peptide synthesis. The purified protein was site-specifically coupled with the 64Cu-mono-maleimide-DOTA (Cu-DOTA-ZEGFR:1907) to produce the bioconjugate. The biodistribution and binding specificity of the probe (64Cu-DOTA-ZEGFR:1907) were determined in vivo in mice bearing A431 tumor at 24 h and 48 h post-injection. We also conducted a phantom study with F-18 filled spheres to demonstrate the accuracy of biodistribution studies.

Results: 64Cu-DOTA-ZEGFR:1907 showed high tumor uptake (93 ± 13% ID at 24 h p.i.) and high tumor-to-normal tissue contrast of the probe spiked with 500 µg of Ac-Cys-ZEGFR:1907 showed high tumor uptake (93 ± 13% ID at 24 h p.i.). This indicates that the probe had high tumor, blood, and kidney uptakes, while blood radioactivity dropped dramatically at increased trap site (100% ID at 48 h p.i.). This suggests that the probe had high tumor, blood, and kidney uptakes, while blood radioactivity dropped dramatically at increased trap site (100% ID at 48 h p.i.).

Conclusion: 64Cu-DOTA-ZEGFR:1907 shows high tumor uptake and high tumor-to-normal tissue contrast of the probe. The probe spiked with cold Ac-Cys-ZEGFR:1907 improves tumor imaging contrast, which may have important clinical applications.


References/Funding: Poster Session 3b: Imaging Methodology and Instrumentation. September 26, 2009 / 16:00-17:30 / Room: S13. www.wmicmeeting.org/abstracts/data/poster-3b1143.html

Quantitation Error Assessment for Small Animal PET

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Departments of 1Radiology, 2Pediatrics, 3Radiology, MIPS, Stanford University, CA

Image quantitation in PET depends on many factors including injection amount and preparation, accuracy of calibrations, understanding error correction mechanisms and reliability of the entire data analysis procedure. Hence, the goal of this study is to identify the major sources of errors and optimize data analysis procedures to improve accuracy. We monitored the accuracy of calibration parameters on a monthly basis and compared the biodistribution of various organs/tumors using both microPET and a gamma-counter. We also conducted a phantom study with F-18 filled spheres to demonstrate the consistent underestimation of organ activity observed by microPET in many factors including pre-scan animal variability and optimize data analysis procedures.

References/Funding: Poster Session 3b: Imaging Methodology and Instrumentation. September 26, 2009 / 16:00-17:30 / Room: S13.
Molecular Imaging

Continuous, Quantitative, Molecular Monitoring of a Near Infrared Fluorophore Using a Novel, Microfabricated, Implantable Biosensor

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Departments of 1Radiology, 2Electrical Engineering, Stanford University, CA, USA; 3Institute of Biomaterials and Biomedical Engineering, Electrical and Computer Engineering, University of Toronto, ON, Canada.

Current approaches to detect fluorescence in anesthetized subjects utilize CCD cameras and generally take snapshots of a particular molecular process. Alternatively, continuous molecular monitoring in a freely moving subject would be useful in pre-clinical disease models for monitoring drug delivery, stem cell growth, and metastases. With these objectives in mind, we fabricated a novel cylindrical device (8mm diameter) containing a 1.5mW, 670nm vertical-cavity surface-emitting laser (VCSEL), un-cooled Gallium Arsenide photodiode, an integrated collimation lens, and a commercially available fluorescence emission filter. The field of view was 3x3x3mm, and for Cell 5.5 dye, in vitro sensitivity was 100mV (R2=0.89%), with signal saturation at 50J. The in vivo sensitivity curve was linear (R2=0.86%) and correlated well with CCD camera data (R2=0.99), and in vivo tumor sensitivity was 1µM. We then utilized this device in a glioblastoma (U87 cell line) tumor xenograft model in nude mice in vivo. Sensitivity was 1µM, and metastases. With these objectives in mind, we fabricated a novel cylindrical device (8mm diameter) containing a 1.5mW, 670nm vertical-cavity surface-emitting laser (VCSEL), un-cooled Gallium Arsenide photodiode, an integrated collimation lens, and a commercially available fluorescence emission filter. The field of view was 3x3x3mm, and for Cell 5.5 dye, in vitro sensitivity was 100mV (R2=0.89%), with signal saturation at 50J. The in vivo sensitivity curve was linear (R2=0.86%) and correlated well with CCD camera data (R2=0.99), and in vivo tumor sensitivity was 1µM. We then utilized this device in a glioblastoma (U87 cell line) tumor xenograft model in nude mice in vivo. Sensitivity was 1µM, and metastases.

Molecular Imaging of Oncogene Targeted Cancer Therapy

H Fan-Mingg1,1, R Paulmurugan1,1, CT Chan2,1, Z Carr1, DW Federsel2,3, SS Gambhir1,1
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Oncogene signaling pathways have been identified as essential for cancer progression and repression and are hence considered attractive targets for cancer therapy. We developed for the first time a biosensor system that can detect in living animals the activation of the cryptophotic MYC (c-Myc) oncogene. This sensor system utilizes protein-assisted complementation of split firefly luciferase (Nluc 398/Cfruc 394) that are fused to a specific phosphorylation motif in the MYC and a selected phospho-recognition domain in GSK3β respectively, to report phosphorylation dependent c-Myc activation and interaction with GSK3β. Extensive optimization and validation of the sensor system has been performed. This sensor system allows for the selective, sensitive and selective chemical interaction of the sensor with c-Myc. To demonstrate the potential of the sensor system for implanting sensors in freely moving subjects.

A Novel Strategy for Receptive, Non-invasive Monitoring of the Efficacies of Histone Deacetylase 6 (HDAC6) Inhibitors in Living Subjects

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Heat Shock Protein 90(Hsp90)p23 interactions are crucial for proper folding of proteins in cancer and neurodegenerative diseases. Hsp90 and HDAC6 inhibitors block Hsp90(p30)p23 interactions by preventing ATP binding and leading to hyperacetylation of Hsp90 respectively. A split Renilla Luciferase expression system in mouse was used for in vivo monitoring of changes in HDAC6 inhibition. Class II (AIPHA and Trehomarin) and HDAC6 and Hsp90 inhibitors (TubaTub) and SE161 led to disruption of Hsp90(p30)p23 interactions by hyperacetylation of Hsp90. These inhibitors reversed the effect on HDAC6 inhibitors alone, in combination with Hsp90 inhibitors will significantly accelerate the development of HDAC6 inhibitors and combinatorial therapies.

Clinical-grade [*]F8FPPRGD2: An Automated Multi-step Radiosynthesis for Human PET Studies

FT Chin, B Shen, S Liu, RA Berganos, E Chang, B Mitra, X Chen, SS Gambhir
Department of Radiology, Stanford University, CA.

Introduction. In positron emission tomography (PET) imaging, radio-labeled RGD-peptides are one of the most promising radiotracers for noninvasive, functional imaging of target sites, including applications in tumor staging, monitoring response to therapy, and characterizing metastatic potential. Here we report a reliable, routine and automated radiosynthesis of a new clinical-grade [*]F8-RGD peptide tracer [*]F8FPPRGD2, which is formed by conjugating 4-nitrophenyl-2-[*]F8O and passed through a Na2SO4 drying cartridge.

Discussion. All radiochemical yields (RCY ± SD) are decay-corrected to end-of-bombardment. After 170 min radiosynthesis, [*]F8FPPRGD2 afforded consistently 14±4.2% (n=5) with specific activity of 900±250 mCi/mmol (33.3±9.5 GBq/mmol). High radiochemical and chemical purities encoded 99% via HPLC analysis. As a better alternative to traditional intra-tracheal evaporation alone (9.0±2.8, n=3), more [*]F8NPE is available for peptide coupling when the SPE process uses Et2O and a Na2SO4 cartridge (93.8±2.6, n=9) followed by gentle evaporation of EtO and a H stream into the CM. The Na2SO4 cartridge gave higher coupling yields (93.8±8.5%, n=9 vs. without cartridge 50±35%, n=3), since residual moisture was removed after SPE processing of [*]F8NPE. PET imaging in mouse (Normal/Tumor Ratio: 58/1.6) and human (128/1.3) demonstrated that [*]F8FPPRGD2 is a promising new tracer for animal and human studies.

References/Funding
Poster Session 1o: Therapy including Drug Therapy, September 24, 2009 / 16:00-17:30 / Room: 141 Bay Bering Schor.

References/Funding
Poster Session 3o: Therapy including Drug Therapy, September 26, 2009 / 16:03-17:30 / Room: 141 Bay Bering Schor.
**Enhanced Ultrasound-Mediated Gene Delivery with Cationic Microbubbles in a Mouse Model of Tumor Angiogenesis**

Citation: CC Kukovsky, DS Wang, MA Pysz, R Paulmurugan, C Panje, SS Gambhir, JK Willmann

Departments of Radiology, Radiology, MIPS, Stanford University, CA, USA; Bracco Research SA, Switzerland

Abstract: To determine whether novel cationic MBs for molecular targeting, providing a promising theranostic approach for targeted gene delivery and imaging of tumor neovascularity.

**An 18F-Labeled Knottin Peptide for Tumor αvβ3 Integrim PET Imaging**

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Abstracts: Molecular Imaging

**A Novel Synthesis of 2-Decoy-2'-[18]F-fluoro-9-β-D-arabinofuranosylguanine ([18F]-AraG), for Imaging T Cell Activation with PET**

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Abstracts: Molecular Imaging

**References/Funding Bayer Schering, Poster Session 2d: Development/New Use of Imaging Protein, September 25, 2009 / 16:00-17:30 / Room: 516.**

**References/Funding Poster Session 2d: Development/New Use of Imaging Protein, September 25, 2009 / 16:00-17:30 / Room: 516.**

**References/Funding Poster Session 1d: Development/New Use of Imaging Protein, September 24, 2009 / 16:00-17:30 / Room: 516.**
Agouti-related protein (AgRP) is a 4-kDa cystine-knot peptide of human origin with four disulfide bonds and four solvent-exposed loops that are amenable to directed evolution. By replacement of a six amino acid loop in AgRP with a nine amino acid loop containing an RGD motif, engineered AgRP mutants that bind to αvβ3 integrin with high affinity and specificity have been discovered. In this study, the AgRP mutant 7C was used for SPECT/CT imaging of αvβ3 integrin expression in living subjects. Methods: AgRP-7C was synthesized using solid-phase peptide synthesis and an oxidative folding reaction. 1, 4, 7, 10-tetra-azacyclododecane-N, N', N'', N'''-tetraacetic acid (DOTA) was specifically coupled to the N-terminus of the peptides. Receptor competition binding assay was then performed to measure the αvβ3 integrin binding affinity of the resulting bioconjugate. Radiolabeling of DOTA-7C was achieved by incubating the peptide with 111InCl3 in NaOAc buffer (pH 5.5) at 80 °C for 45 minutes. 111In-DOTA-7C was also demonstrated by small-animal SPECT/CT imaging at 1 hour after injection. Conclusion: AgRP-7C peptide labeled with 111In exhibited high tumor uptake, demonstrating great potential for SPECT/CT imaging of αvβ3 integrin expression in living subjects.

References/Funding

**Intravital Molecular Imaging of the Birth of a Tumor From Cancer Stem Cells Using Intravital Microscopy**

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Department of Radiology, MIPS and Institute for Stem Cells and Regenerative Medicine, Stanford University, CA

Despite phenotypic enrichment of breast cancer stem cells (CSCs), the earliest detection of breast cancer by targeting CSC remains elusive. We hypothesized that incorporating imaging into CSC assays could provide novel insights into the early mechanisms of tumor initiation from CSC. Furthermore, we reasoned that imaging CSC can be done in the adult, possibly developing mammary gland, and regenerating mammary gland after transplantation. To image the 4th adult mammary gland, a surgical flap was created and stabilized in an anesthetized, transgenic, virgin, B6.Gpghc (puro) female mouse in which mammary ducts express high levels of fluorescent protein. Mammary ducts and lobules could be visualized with 4,10, and 20x objectives in both adult (N=10) and developing (age ~3-4 weeks, N=4) gpghc mice. This technique, which utilizes a multiphoton activatable microprobe, has a spatial resolution of approximately 1 µm and depth penetration of approximately 150µm. Furthermore, vascular structures, ranging from 1-500µm, were imaged using a fluorescent (750nm) intra- vascular dye (N=5 mice). To image regenerating mammary ducts, 50,000 cells of an gpghc, Lin- population, which contains rare mammary stem cells, were transplanted into the cleared fat pads of wild type hosts. Regenerating glands were repetitively imaged at 8 and 12 weeks after transplantation (N=5). Importantly, cellular structures in living subjects could be resolved for the first time in all systems. Furthermore, we imaged 5000 Lineage-CD44+, tumor breast CSC that had been lethally transduced with reporter gene expressing tomato fluorescent protein, and transplanted into the mammary fat pad of NOD-SCID mice for 10 days. Having established these systems, we will image single CSC, in both mouse and humans, and corresponding changes in microvascularity in tandem. These approaches should markedly change our understanding of breast tumor development in living subjects, and advance the early detection of, or early therapeutic targeting of CSC.

**Immobilized Activatable Bioluminescent Probes for In Vivo Imaging of Protease Activity in Tumors**

J Rao, Z Xia

Department of Radiology, Stanford University, CA

We report here a novel strategy for in vivo imaging of enzyme activity at tumors, which provides a powerful tool for in vivo study the roles of enzymes in tumor biology and dynamic imaging of tumor response to drug treatment. In previous examples, fluorescent activatable probes are designed to image enzymes that play key roles in tumor processes. One of the concerns with these examples is whether the enhanced fluorescence signal observed in tumors all came from the enzyme activity at the tumors or some came from enzymes at other locations but accumulated at the tumors due to the enhanced permeation effect (EPR). In addition, in spite of the amplification feature of the design, the observed contrast in vivo is generally small in these examples. In this presentation, we describe an immobilized activatable bioluminescent probe that we believe is truly imaging the extracellular cell enzyme activity in vivo. First, we took advantage of bioluminescence resonance energy transfer and generated a chemically quenched bioluminescent protein conjugate with small chemical dye. Protease cleavage led to the release of the quencher from the protein and thus the activation of the bioluminescent protein. This bioluminescence based detection offers a much greater sensitivity than the fluorescence based imaging. Furthermore, to ensure that the activated protein does not travel within the body and get accumulated into the tumors, we further found the probe with the collagen binding protein. The binding of the probe to the abundant collagen restrained the probe mobility so the enzyme activated signals precisely reflect the local enzyme activity at tumor (Figure 1). With the designed probe, we were able to image with the MMP activity exclusively in tumors with high sensitivity. Our approach opens a new avenue for study enzyme functions in vivo, which may have a significant impact on cancer research and tumor treatment.

**Engineering Attenuated Salmonella Typhimurium to Selectively Target and Deliver Protein in Infarcted Myocardium**

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Gene-based therapeutic approaches offer a potential strategy to address myocardial dysfunction for the patients with refractory angina pectoris or medical or surgical treatment. Optimizing the specific affinity of the cardiac vectors would improve the efficiency of gene/protein delivery, and reduce unwanted transfection of non-cardiac tissues. However, none of the cardiac vectors so far have specificity for the infarcted myocardium. In this study, we explored bacterial tropism for infarcted myocardium. We constructed a Salmonella typhimurium derivative in plasmid synthesis to express and secrete the reporter gene (RLacZ) by the regulation of an inducible Pptag promoter. A bacterial expression plasmid encoding a variant of Renilla luciferase (RLuc8) was constructed, in which the pelB leader sequence and a histidine tag (his) were fused to the amino- and carboxy-terminus, respectively, of RLuc8. An exclusion at the left coronary artery generated the myocardial infarction (MI) in the left ventricle of Sprague-Dawley rats. 24 h cfa of the Salmonella were intravenously injected and bacterial toxin for MI was observed by cooled CCD camera. To assess the systemic or local toxicity after bacterial injection, we measured C-reactive protein and procoagulants in the rats’ serum and measured infarct size by TTC staining before and after bacterial injection. The Salmonella were found to accumulate in infarcted myocardium. RLacZ gene delivery by the engineered Salmonellae was expressed and its translated product was secreted specifically in the infarcted myocardium under the stimulant of the Pptag promoter after L-arabinose administration. No sign of serious local or systemic inflammatory reactions was noted following intravenous administration of attenuated Salmonella. Thus, MI-targeting bacterial can potentially deliver therapeutic molecules to salvagable myocardium. Taken together, the development of MI-targeting bacteria opens many new avenues for molecular imaging and therapy, including tissue-specific targeting with signal amplification based on bacterial proliferation, in vivo tissue-specific drug delivery, and the design of imageable therapeutic probes.
NIR Fluorescence Imaging of Melanocortin 1 Receptor Expression with A Cy5.5-o-MSH Analog

Lucas Annual Report 2010

The α-melanocyte-stimulating hormone (α-MSH) receptor (melanocortin type 1 receptor, or MCR1) is known to be overexpressed in most melanoma subtypes, making it a promising target for melanoma imaging and therapy. The purpose of this study was to evaluate a novel near-infrared fluorophore, Cy5.5 conjugated o-MSH analog (CyMSH, Fig a), as a contrast agent to visualize tumor MCR1 expression in vivo. Methods: o-MSH analog consisting of α-MSH core sequence, His-D-Phe-Arg-Trp, was designed and synthesized using Fmoc-SBTU chemistry on a solid-phase peptide synthesizer and conjugated with Cy5.5 through the N-terminal cysteine. The binding affinity was determined using a competitive receptor binding assay. Melanoma B16F10, TXM13 and A375M, which has high, medium and low MCR1 expression respectively, was used to evaluate the MCR1 imaging profiles of CyMSH in vitro and vivo. Results: CyMSH was successfully synthesized and displayed high MCR1 binding affinity (0.6nmol/L). In vivo cell fluorescence imaging study revealed that the probe showed high, medium and low cell staining in B16F10, TXM13 and A375M cells, respectively, which was in consistent with their receptor expression levels. Co-irradiation with the probe uptake in B16F10 and TXM13 cells. In vivo optical imaging detected little fluorescence in B16F10 tumor (Fig b), which was mainly caused by the high melanin content in B16F10 tumor that absorbed nearly all excitation and emission NIR lights. To the contrary, melanomas TXM13 with a low less melanin content and medium level of MCR1 expression could be clearly visualized with CyMSH (Fig c). Finally, amelanotic A375M with the lowest MCR1 expression showed poor tumor normal contrast (Fig d). Conclusion: This study suggests that the combination of the specificity of MSH peptide with NIR fluorescence detection may be applied to molecular imaging of MCR1 expression in melanoma with low melanin content.

References/Funding

Preclinical Evaluation of Raman Nanoparticles for Their Potential Use in Clinical Endoscopic Imaging

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Raman spectroscopy continues to prove itself as a powerful non-invasive imaging modality to be used as a tool to evaluate nanoparticle delivery in preclinical models. Its pH sensitivity and multiplexing capabilities are unsurpassed. However, its limited depth of light penetration hinders direct clinical translation. Therefore, a more accessible way to harness its attributes in a clinical setting would be to couple Raman spectroscopy with endoscopy. It was recently reported that fluorescence and Raman spectroscopy were five times more likely to contain cancerous tissue than polyps detected by conventional colonscopy. The use of an accessory Raman endoscope in conjunction with locally administered contrast targeting Raman nanoparticles during a routine colonoscopy could offer a new way to sensitively detect these dysplastic flat lesions. In this study we evaluated the natural biodistribution of gold surface enhanced Raman scattering (SERS) nanoparticles by radio-labeling them with 131I and imaging their localization over time using microPET. Mice were injected intravenously (IV) or intrarectally (IR) with approximately 100 μCi of 131I-SERS nanoparticles and imaged with microPET at various time points: immediately, 30 min, 2, 5, and 24 h post injection. Three mice from each group (IV and IR) were sacrificed at 2, 5, 12, 24, 48 h, and 72 h post-sacrifice and their livers, kidneys, spleen, and lungs were collected, weighed and counted in a gamma counter to determine % injected dose per gram (%ID/g). Quantitative biodistribution data obtained from each organ were calculated using the corresponding microPET images, revealing that mice injected IV had significantly higher uptake (p<0.001) in the liver (18.8±9.5% ID/g) as opposed to mice injected IR (5±2.5% ID/g). The polymersomes were also conjugated with Gaussia luciferase, a bioluminescent protein that enhances imaging intracellular GLUC protein in small animals. The use of Gd-encapsulated nanovesicles as MR contrast agents has large impact due to the detrimental effects of the slow blood exchange rate through the vascular bed on the relaxivity of encapsulated Gd. Here, we describe the facile synthesis of porous polymer nanovesicles that exhibit improved permeability to water flux, high structural stability, and a large capacity to store chelated Gd within the aqueous core. The porous polymethacrylate, 130 nm in diameter, were produced through the aqueous assembly of the polymers, PEI(100)-b-PBPE2500 (PBPeDI) and PECl2000-b-PCL21700. Subsequent hydrolysis of the copolymers (PCL) block resulted in a high-porous outer membrane. To prevent the leakage of small Gd-chelate through the pores, Gd was conjugated to PAMAM dendrimer via DTPA diamine hydrate prior to encapsulation. As a result of the slower rotational correlation time of Gd-labeled dendrimer, the porous outer membrane of the nanovesicle, and the high Gd payload, the nanovesicles were found to exhibit a relaxivity (R2) of 200,109 μM-1 s-1 per particle. The polymeric vesicles were also found to exhibit low-cell toxicity and a long circulation half-life. Here, the design, synthesis, characterization and application of the paramagnetic polymersomes will be presented.

References/Funding

Secretory Gausia Luciferase (sGLUC)-monomeric Red Fluorescence protein (mRFP)-truncated Herpes Simplex Virus Thymidine Kinase (tTK) Triple Fusion Improves Intracellular Luciferase Activity and Enhances its Imaging Applications in Small Animals

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Gausia luciferase, a bioluminescent protein that uses coelenterazine as its substrate, has potential as a reporter gene for different biological applications. In this study we report that the 16-amino acids (1-16) at the N-terminus of this protease are not only important for the secretion activity of this protein, but are also critical for its rapid maturation and proper functionality. We constructed a series of vectors expressing GLUC fusions and N-terminal truncation/substitution (see Figure) to prove the importance of the secretory peptide, and also to improve its intracellular retention for small animal imaging. The 293T, SKBr3 and CHO cells transfected with these constructs were assayed for GLUC activity immediately after lysis and at 2, 5, 12, 24, 48, 72 and 120 h post-lysis. The results showed significant improvement in the intracellular activity only from the sGLUC fused to t-RFP-TRTK (10 fold). The cells transfected with iGLUC, iGLUC-GFP and TK-Leader-GLUC showed minimal intracellular activity when assayed immediately after lysis (1-1.6% of GLUC), the signal increased over time and stabilized at 72 hr. The activity by iGLUC measured at 72 hr was 120±10-fold higher than the initial activity and was 30% of the sGLUC activity. Transfection of 293T cells stably expressing iGLUC-GFP, iGLUC-GFP and iGLUC-RFP-TRTK in mice (N=11) were imaged for GLUC, GFP and mRFP signals over time. The imaging results showed no GLUC-signals from the cells transfected with iGLUC-GFP, but showed significant localization of fused Gfp signal (p<0.001). The sGLUC with C-terminal fusions showed a constant intracellular GLUC-signal over time, indicating the importance of the secretory peptide for GLUC-maturation. The enhanced fluorescent signal from GFP and RFP fused to the GLUC, than the corresponding fusions with other bioluminescent reporters, indicates its minimal steric hindrance. In conclusion, we have successfully developed a novel triple fusion that enhances imaging intracellular GLUC protein in small animals.

References/Funding

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The use of Gd-encapsulated nanovesicles as MR contrast agents has largely been ignored due to the detrimental effects of the slow blood exchange rate through the vascular bed on the relaxivity of encapsulated Gd. Here, we describe the facile synthesis of porous polymer nanovesicles that exhibit improved permeability to water flux, high structural stability, and a large capacity to store chelated Gd within the aqueous core. The porous polymethacrylate, 130 nm in diameter, were produced through the aqueous assembly of the polymers, PEI(100)-b-PBPE2500 (PBPeDI) and PECl2000-b-PCL21700. Subsequent hydrolysis of the copolymers (PCL) block resulted in a high-porous outer membrane. To prevent the leakage of small Gd-chelate through the pores, Gd was conjugated to PAMAM dendrimer via DTPA diamine hydrate prior to encapsulation. As a result of the slower rotational correlation time of Gd-labeled dendrimer, the porous outer membrane of the nanovesicle, and the high Gd payload, the nanovesicles were found to exhibit a relaxivity (R2) of 200,109 μM-1 s-1 per particle. The polymeric vesicles were also found to exhibit low-cell toxicity and a long circulation half-life. Here, the design, synthesis, characterization and application of the paramagnetic polymersomes will be presented.

References/Funding

Gd-encapsulated Porous Polymersomes as Highly Efficient MRI Contrast Agents

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The α-melanocyte-stimulating hormone (α-MSH) receptor (melanocortin type 1 receptor, or MCR1) is known to be overexpressed in most melanoma subtypes, making it a promising target for melanoma imaging and therapy. The purpose of this study was to evaluate a novel near-infrared fluorophore, Cy5.5 conjugated o-MSH analog (CyMSH, Fig a), as a contrast agent to visualize tumor MCR1 expression in vivo. Methods: o-MSH analog consisting of α-MSH core sequence, His-D-Phe-Arg-Trp, was designed and synthesized using Fmoc-SBTU chemistry on a solid-phase peptide synthesizer and conjugated with Cy5.5 through the N-terminal cysteine. The binding affinity was determined using a competitive receptor binding assay. Melanoma B16F10, TXM13 and A375M, which has high, medium and low MCR1 expression respectively, was used to evaluate the MCR1 imaging profiles of CyMSH in vitro and vivo. Results: CyMSH was successfully synthesized and displayed high MCR1 binding affinity (0.6nmol/L). In vivo cell fluorescence imaging study revealed that the probe showed high, medium and low cell staining in B16F10, TXM13 and A375M cells, respectively, which was in consistent with their receptor expression levels. Co-irradiation with the probe uptake in B16F10 and TXM13 cells. In vivo optical imaging detected little fluorescence in B16F10 tumor (Fig b), which was mainly caused by the high melanin content in B16F10 tumor that absorbed nearly all excitation and emission NIR lights. To the contrary, melanomas TXM13 with a low less melanin content and medium level of MCR1 expression could be clearly visualized with CyMSH (Fig c). Finally, amelanotic A375M with the lowest MCR1 expression showed poor tumor normal contrast (Fig d). Conclusion: This study suggests that the combination of the specificity of MSH peptide with NIR fluorescence detection may be applied to molecular imaging of MCR1 expression in melanoma with low melanin content.
Molecular Imaging

The Microscale Journey of Targeted Carbon Nanotubes Imaged Using Intravital Microscopy: from Circulation to Tumor Cells in Living Subjects

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Though nanoparticles have become invaluable in the molecular imaging toolkit, little is known about the mechanisms by which they target disease sites. To overcome this critical hurdle, we visualized targeted single-walled carbon nanotubes (SWNTs) entering tumor vasculature, specifically binding luminal targets, extravasating from vessels, and binding to tumor cells. To understand the fundamental mechanisms underlying SWNT tumor uptake, we confirmed and correlated our intravital microscopy (iVM) results with macroscopic Raman imaging, which quantitatively detects the SWNTs’ intrinsic Raman signal. Targeted SWNTs were prepared by conjugating RGD peptides (targeting αvβ3-integrins expressed on tumor microvasculature and some tumor cells) and Cy5.5 dye. Dorsal chambers were surgically implanted into mice and ICG-EITM-αvβ3 tumors (expressing αvβ3-integrins) or ICG-SKG/3V5 were inoculated. Mice were imaged with intravital microscopy at 24 hours post-injection. Arteries demonstrated circulating SWNTs while veins showed intravascular contents (Figure 1A). U87MG tumors, RGD-SWNTs not only bound more than controls (P<0.001), but they differentially bound tumor cells over time compared with control (P<0.001) and persisted in tumor for over a month. Control SWNTs cleared within 1 week. Also, we unexpectedly observed uptake of SWNTs by circulating white blood cells, which subsequently trafficked to tumor; FACS confirmed these results. In summary, iVM allowed detailed exploration of SWNT uptake in tumor, particularly unanticipated features. This work offers an unprecedented understanding of the mechanisms/temporal framework of nanoparticle tumor uptake, which will translate into superior properties for clinical use.

References/Funding

Bayes Schieving

Ultra High Sensitivity Targeted Photoacoustic Imaging Agents for Cancer Early Detection in Living Mice

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Photoacoustic imaging of living subjects offers unique opportunities for in vivo applications. U87MG cells were implanted into the ears of mice or in surgically implanted dorsal window chambers (DWC) to form tumors. We injected Angelus®/Angen® dye and ~50 pmol qdots into tail veins of mice to visualize the arrival and binding of qdots to tumor vessels. We observed RGD-conjugated qdot aggregates binding tumor blood vessels significantly (P<0.001) more than controls (RAG, RGD-block, bare (no peptide) qdots). 29 folds more sensitively than plain SWNTs. Interestingly, binding occurred more in the SKOV-3 DCC than in any other. Also we showed that while we are capable of visualizing dense qdot binding with our instrument, it did not occur in any of our models. Moreover, while qdots are superior to SWNTs in LS174T models, we imagine their extravesicular localization and design could improve in future nanoparticle design and approval in cancer diagnostics.

References/Funding

Bayes Schieving

Noninvasive Imaging of Cancer Gene Therapy in Orthotopic Mouse Models Using a Novel Systemically Delivered Bi-Directional Transcriptional Targeting Vector

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Weak cancer specific promoters, such as Survivin promoter(3), may find an amplification strategy to be used for cancer gene therapy. Gene therapy ideally requires non invasive tools to image the delivery of therapeutic genes. We report the development of a novel adeno vector carrying a bidirectional transcriptional amplification (GAL4-VP16 system) which can amplify gene activity leading to correlated expression of a reporter gene (luciferase (Luc); FL) and a therapeutic gene (TRAIL-G8-FL). Methods: MCA-RI7777(Morris hepatoma) and BALB C (Buffalo rat liver) cells were transfected with 100 MOI Ad5-pSurv-TRAIL-G8-FL, and IVM (20X) fluorescence was performed at 72 hours. Formation of FL and TRAIL activities was also performed with RITC116 cells. For animal studies, MCA-RI7777 cells (1x10^6) were surgically implanted in the liver of Buffalo rats. Tumor formation was confirmed with FDG-PET at 14 days after implantation. 109 PFU of Ad5-pSurv-TRAIL-G8-FL was administered via tail-vein. BLI was performed to evaluate FL expression in tumor and non-tumor regions at 2d after the virus delivery. Results: MCA-RI7777 cells show 3 fold higher FL activity than BALB C 3A cells (4.2±10^9 to 4.2±10^6 p/s/cm^2/sr vs. 1.4±10^6 to 1.4±10^6 p/s/cm^2/sr, p=0.002). Expression levels of FL and TRAIL were well correlated (R2=0.95). PET imaging 2 who after tumor implantation showed FDG uptake in tumor implanted area (0.6±0.13%ID/gm). Tumor region showed 29 fold higher light output than normal liver (9.2±1.10×10^7 p/s/cm^2/sr, p=0.002) in BLI. Conclusions: An adeno vector carrying Survivin promoter driven both the TRAIL, therapeutic gene and the FL reporter gene is more active in hepatoma cell lines compared to normal liver cell lines. Most importantly, we report for the first time the in vivo injection of such a vector to achieve highly specific liver tumor targeting in living rats. The bidirectional transcriptional amplification system using GAL4-VP16 preserves promoter specificity and has the capability of showing therapeutic gene expression non-invasively in a rat orthotopic hepatic tumor model.

References/Funding

Bayes Schieving

Direct Microscale Visualization of Targeted Quantum Dot Binding in Multiple Tumor Models of Living Mice using Intravital Microscopy

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Targeted nanoparticles have begun to make major contributions to cancer diagnosis and therapy. However, non-invasive monitoring of therapeutic response. However, comprehension of the mechanisms by which nanoparticles target tumors is critically lacking. Mechanistic insight is essential because it will lead to 1. Selection of the appropriate diagnostic agent, 2. Optimization of nanoparticle parameter for superior targeting efficiency, and 3. Regulatory approval for nanoparticle formulations. We employed intravital microscopy to directly image the process of quantum dots (qdots) targeting tumor. In three different tumor models and two animal models, we surprisingly found that targeted qdots bound to tumor blood vessels only as aggregates, rather than as individual units. Further, we showed that in two of the three tumor models tested, qdots did not extravasate. We conjugated cyclic-RGD (targeting αvβ3-integrins localized on tumor vascular luminal areas and some tumor cells) to near-infrared emit-ting (800 nm) qdots of ~20 nm hydrodynamic diameter. Ectopic HCT116 tumors were implanted in the ears of mice or in surgically implanted dorsal window chambers (DWC) to form tumors. We injected Angelus®/Angen® dye and ~50 pmol qdots into tail veins of mice to visualize the arrival and binding of qdots to tumor vessels. We observed RGD-conjugated qdot aggregates binding tumor blood vessels significantly (P<0.001) more than controls (RAG, RGD-block, bare (no peptide) qdots). We observed RGD-qdots bound to tumor blood vessels only as aggregates, rather than as individual units. Moreover, while qdots are superior to SWNTs in LS174T models, we imagine their extravasation in SKOV-3 not LS174T models, we imagine their extravasation in SKOV-3. We found the photoacoustic signal produced by the particles to be highly linear to their concentration both in phantom and in vivo studies (R2 ~ 0.999) as well as in living mice injected with the particles subcutaneously (R2 ~ 0.971). We further measured the detection sensitivity of SWNT-IGC in living mice (n = 3 mice) and found it to be 30 pm. This represents more than 3 orders of magnitude improvement compared to plain SWNTs sensitivity in living mice (p < 0.05). Furthermore, scaphocele-lining mice that were tail-vein injected with RGD-targeted SWNT-IGC. At 2 hours post-injection, mice injected with the RGD-targeted qdots showed 2.1 times higher photoacoustic signal in the tumor compared to mice injected with control particles (p < 0.05, n = 4 mice). Finally, we demonstrated the superiority of the SWNT-IGC-RGD particles by injecting them into U87 cells in living mice (1000 times more sensitive than IgG-conjugated qdots) and found that the IgG-conjugated qdots were cleared within ~1 week. Also, we unexpectedly observed aggregates of Cy5.5 dye near tumor vessels. Within hours, SWNTs extravasated as U87MG tumor buds, but not in SKOV-3. While both RGD and control SWNTs were observed associated with some tumor cells in U87MG tumors, RGD-SWNTs not only bound more than controls (P<0.001), but they differentially bound tumor cells over time compared with control (P<0.001) and persisted in tumor for over a month. Control SWNTs cleared within 1 week. Also, we unexpectedly observed uptake of SWNTs by circulating white blood cells, which subsequently trafficked to tumor; FACS confirmed these results. In summary, iVM allowed detailed exploration of SWNT uptake in tumor, particularly unanticipated features. This work offers an unprecedented understanding of the mechanisms/temporal framework of nanoparticle tumor uptake, which will translate into superior properties for clinical use.

References/Funding

Bayes Schieving

Lucas Annual Report 2010

147

149

148

Abstracts: Molecular Imaging
Multivalent Cu-64MSH Analogs for MicroPET Imaging of Melanocortin 1 Receptor Expression

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Multivalent peptides have been explored as a useful strategy to construct molecular imaging probes and drug delivery carriers. It is generally accepted that multivalency offers advantages for improving binding affinities and even activity. Herein by using multivalently n-melanocortin stimulating hormone (n-MSH) analogs, B16F10 melanoma-bearing mice and microPET imaging technology, we systematically investigated the influence of multivalent effect on n-MSH analogs’ binding affinity and in vivo melanoma targeting profiles. Methods: Three n-MSH analogs named as MSH1, MSH2 and MSH3 were designed and synthesized, which contained one, two or four valency of an α-MSH core sequence, His-Ser-Arg-Trp, respectively (Fig. a). α-MSH ligand tetramer was constructed using the multiple antigenic peptide (MAP) scaffold; 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) was conjugated to the lysine residue of receptor binding with a PET dextran, 64Cu. In vivo binding affinity assays were performed with B16F10 melanoma cell line. After radiolabeling with 64Cu, the in vivo performances of the peptides were evaluated in athymic B16F10 melanoma xenografted mice by microPET imaging followed by biodistribution studies. Results: In the receptor binding assay, DOTA-MSH1 showed highest binding affinity (IC50 ~1.00 nM) which is consistent with its highest ligand density. However, in vivo study demonstrated poor performance of MSH3 as an imaging agent due to its low tumor uptake and lowest kidney accumulation (Fig. b). Further blocking study of DOTA-MSH2 confirmed its tumor targeting specificity in vivo. Conclusion: Multivalency effects have complex impact to peptides’ in vivo behaviors. Even though MSH tetramer shows the highest binding affinities in vitro, the better in vivo tumor targeting ability is achieved by MSH dimer. Cu-64 labeled dimeric DOTA-MSH2 has been identified as an ideal melanoma PET imaging probe.

Molecular Imaging

A Novel Smart Agent for Photoacoustic Molecular Imaging

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Photoacoustic imaging is an exciting new modality that offers higher spatial resolution and deeper penetration than traditional optical imaging. We have designed an activatable (smart) photoacoustic molecular imaging agent which can be activated by matrix metalloproteinase-2 (MMP-2), a secreted enzyme commonly present in many cancers. The smart probe developed couples a fluorescent dye (5(6)-FAM) to a photoacoustic dye via an enzyme-responsive peptide sequence (RVGLP). In close spatial proximity, the fluorescent dye silences the photoacoustic signal. The activated and control probes were each incubated with either the activated enzyme (recombinant MMP-2, 37 °C) or the non-activated enzyme (0 ºC) for 1 hour prior to suspension in an agar phantom. The samples were at a concentration of approximately 100 μM and imaged in triplicate. The measured photoacoustic signals for the agar alone, unactivated probe, and activated smart probe were 212 ± 18 (μm/μJ), respectively. All combinations of data comparisons are statistically significant (p<0.05). The scramble control probe did not lead to any detectable clearance. Mouse experiments with the activatable probe show a statistically significant (p=0.05) signal enhancement of 256 ± 21 (μm/μJ) compared to normal regions of the mouse where the signal is 802 ± 100 (μm/μJ). These experiments validate the first photoacoustic smart probe and the strategies developed can be used to synthesize other smart probes after further validation in various mouse models.

Design and Testing of a Novel Ultrasound Contrast Agent for Molecular Ultrasound Imaging of Tumor Angiogenesis

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Molecular ultrasound imaging is increasingly being recognized as a promising and powerful molecular imaging tool. In this proof-of-principle study we hypothesized that a new class of molecular ultrasound contrast agents could be developed using small (~3 kDa), configurationally constrained cystine knot peptides that are coupled onto the surface of contrast microbubbles. Directed evolution was used to engineer a small, disulfide-constrained cystine knot peptide (knottin) to bind to αvβ3-integrins with nanomolar affinity (knottinIntegrin; 1E3). A cystine knot (knottin) to bind to αvβ3-integrins with nanomolar affinity (knottinIntegrin) was synthesized. Upon cleavage of the enzyme-specific peptide sequence, (RVGLP). In close spatial proximity, the fluorescent dye silences the photoacoustic signal. The activated and control probes were each incubated with either the activated enzyme (recombinant MMP-2, 37 °C) or the non-activated enzyme (0 ºC) for 1 hour prior to suspension in an agar phantom. The samples were at a concentration of approximately 100 μM and imaged in triplicate. The measured photoacoustic signals for the agar alone, unactivated probe, and activated smart probe were 212 ± 18 (μm/μJ), respectively. All combinations of data comparisons are statistically significant (p<0.05). The scramble control probe did not lead to any detectable clearance. Mouse experiments with the activatable probe show a statistically significant (p=0.05) signal enhancement of 256 ± 21 (μm/μJ) compared to normal regions of the mouse where the signal is 802 ± 100 (μm/μJ). These experiments validate the first photoacoustic smart probe and the strategies developed can be used to synthesize other smart probes after further validation in various mouse models.


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Despite advances in cancer management the tumor neovascularization continues to be a major problem which hampers the option of curative surgery. Once a tumor reaches 1-3 mm in diameter it is dependent on angiogenesis (through αvβ3-integrin expression on tumor endothelial cells of human ovarian adenocarcinoma xenograft tumors). In summary, our study shows that knottin peptides are a promising platform for designing novel contrast agents for molecular ultrasonic imaging of tumor angiogenesis. The design of small, evolvable peptide ligands that can be coupled with the surface of microbubbles may facilitate the translation of molecular ultrasound from preclinical animal models to clinical applications in the near future.

References/Funding

This study was supported in part by a grant from NIH R01 CA120126. Dr. Willmann is supported in part by the Cancer Prevention Fellowship from the American Cancer Society and the Cancer Research Career Development Award from the National Cancer Institute. Dr. Willmann is a Searle Scholar in Medicine. Dr. Willmann is a Burroughs Wellcome Fund Career Scientist. Dr. Willmann is also a Wellcome Trust Senior Research Fellowship.
Molecular Imaging

Monitoring Adoptive Cellular Immunotherapy in Glioma Patients Using PET Reporter Gene Imaging

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Abstract: Noninvasive imaging of cell trafficking should allow early assessment of efficacy and potential adverse effects of adoptive cellular immunotherapy in cancer patients. Under a FDA pilot award (1U01CA150886), we have imaged the biodistribution of the positron emission tomography (PET) reporter probe, 9-[4-(18F)fluoro-3-(hydroxymethyl)butyl]guanine (\[^{18}F\]HBG) in glioma patients (two hours after injection – 7.6 mCi intravenously). These patients had recurrent glioblastoma multiform. They were infused autologous cytolytic T lymphocyte (CTL) clones (150-220 x10^6 cells) with the following pre-scan of the same patient as a control image provide further demonstration of PET reporter gene based imaging of therapeutic cells in cancer patients.

Molecular Imaging of Cell Transplantation in Porcine Myocardium Using Clinical MRI and PET-CT

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Abstracts: Monitoring adoptive cellular immunotherapy in glioma patients who had not been infused CTLs. Bi-weekly observed tumor signals that were about 2.6 fold higher, when compared to tritiated Penciclovir uptake assays) and IL-13 zetakine. We previously reported the case of a glioma patient imaged with \[^{18}F\]HBG only after cell infusions (Yaghoubi et al. Nature Clinical Practice Oncol 6(1): 53-58). In this patient we observed tumor signals were about 2.6 fold higher; when compared to tumor signals in control glioma patients who had not been infused CTLs. Biopsy had confirmed presence of CTLs at tumor reaction sites as well as in a newly formed tumor in the corpus callosum. Here, we report imaging another patient who was infused both before and after CTL infusions with \[^{18}F\]HFBG. The Figure illustrates brain \[^{18}F\]HFBG PET images pre and post CTL infusions. Comparing Tumor/brain intensity ratios, the ratio is 1.6 fold higher after cell infusions. Comparing tumor/tumorgrowths ratio, the ratio is 4.2 fold higher after cell infusions. Another observed difference is that in pre-cell infusions the signal is observed on the walls of the tumor reaction site; whereas after infusions, the signal emanates from the whole resection site. Additional studies are planned for imaging patients pre and post CTL infusions that should allow statistical analysis. Meanwhile, these recent data, using the pre-scan of the same patient as a control image provide further demonstration of PET reporter gene based imaging of therapeutic cells in cancer patients.

Photoacoustic Imaging of the Eye for Improved Disease Detection

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Abstracts: New improvements in the computing power and programmability of graphics processing units (GPUs) have enabled the possibility of using GPUs for the acceleration of scientific applications, including time-consuming simulations in physics. This paper describes the acceleration of a Monte Carlo high-energy photon ray tracer called GRAY using NVIDIA GPUs. Monte Carlo simulations guide the design of advanced PET systems, data correction schemes, and image reconstruction algorithms. GPU acceleration of these simulations makes these studies more practical while avoiding the need of a large, expensive computer cluster. We describe the GPU-based computation and how it is mapped onto the many parallel computational units now available on the NVIDIA GTX 260 series GPUs. For a whole body PET benchmark, a speedup of 3.2X was achieved on a single GTX265 GPU over the GRAY code executed on an AMD Athlon 3200+ processor using 1 CPU core, with equivalent accuracy. Compared to PET system simulations run on the standard Monte Carlo package known as “GATE”, the speedup is 53.6-fold.

References/Endings

Effects of External Shielding on the Performance of a 1 mm² Resolution Breast PET Camera

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We are investigating 511 keV photon detectors for PET with combined time of flight (ToF) and depth of interaction (DoI) features. Such an advance would enable image signal-to-noise ratio (SNR) as well as spatial resolution uniformity improvement. This study investigates the inter-dependence of these features and experiments with ToF-DoI detector design parameters. We also present a study of the detection process chain, from interaction of the annihilation photons within the breast to signal formation in the photodetector, using both simulations and experiments with LYSO crystals coupled to silicon photomultipliers (SiPM). The modeled and measured performance demonstrates the dependence of time resolution on crystal thickness, surface treatment and DoI. Time resolution degradation with increasing crystal length (up to 90% degradation for 1 mm crystal thickness) is observed. The effect of crystal surface on time resolution has a strong dependence of time resolution on crystal thickness. Note that the counts from the breast remain quasi constant, indicating that the shielding only slightly reduces the true count rate from the breast.

Shielding design is studied using the Monte-Carlo simulation package GRAY, which supports complex mesh based primitives for phantoms and detector shapes. An anatomically accurate model of the female torso based on the realistic NURBS Cardiac Torso (NCTA) phantom is used, which was manipulated to include a slight breast compression to a width of 7.5 cm.

The detector configuration in the simulation is based on its CAD drawings. As shielding material we use an alloy of 99% tin, 2% Ni and 0.6% Fe, which has a density of 8.16 g/cm³ and a high atomic number 2. Different shielding thicknesses and locations are investigated and their influence on the system count rate is analyzed.

We show that the maximum count rate is reduced by 45% (57%) when placing 2.54 mm (5.08 mm) of tungsten shielding around the panels. The highest observed event rate per 1 cm² of active area was 240 MHz/mm², which is well below the 83 kHz maximum estimated count rate of our data acquisition system. The out-of-field background is reduced by 35 and 40 % (42 and 47%) for left and right breast respectively.

References/Funding

Medical Imaging

Molecular Imaging

Compact Readout Electronics Module for a High Resolution Breast-Dedicated PET System

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We have developed and tested a compact readout electronics module for use in our 1 mm² resolution breast-dedicated PET system. The system consists of two 9 cm x 10 cm x 38 cm panels, with each panel capable of efficiently acquiring photon events. At 60 cm volume, along with front-end and auxiliary electronics, the size of the readout electronics needs to be small. The compact readout electronics module can read 64 channels in an 8 cm x 6 cm x 0.4 cm volume.

The module is based on the NOVA RENA-3 readout ASIC, which consists of 36 configuration registers, 32 channels, each with a 12-bit analog to digital converter and dedicated transfer link for high speed readout.

A pulser signal of several amplitudes is used to generate charge for testing each channel. The standard deviation of each measurement is typically less than 1.5 ADC counts. This translates into an amplitude resolution of the readout electronics of less than 0.15% in the center of the dynamic range. The timing resolution of pulser data measures around 1.33 ns FWHM.

Four position sensitive scintillators (PSAPD) with 8x8 arrays of 3x3 mm³ LSO crystals were connected to the readouts and coincidence data was collected. All crystals are visible in position flood histograms. The per crystal energy resolution shows the 511 keV photo peak with 10.9% energy resolution. PSAPD coincidence time resolution measures 6.71 ns FWHM.

References/Funding

Key Physical Factors for Dol-compensated ToF PET: Understanding Scintillation-photodetector Features

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We are investigating 511 keV photon detectors for PET with combined time of flight (ToF) and depth of interaction (DoI) features. Such an advance would enable image signal-to-noise ratio (SNR) as well as spatial resolution uniformity improvement. This study investigates the inter-dependence of these features and experiments with ToF-DoI detector design parameters. We also present a study of the detection process chain, from interaction of the annihilation photons within the breast to signal formation in the photodetector, using both simulations and experiments with LYSO crystals coupled to silicon photomultipliers (SiPM). The modeled and measured performance demonstrates the dependence of time resolution on crystal thickness, surface treatment and DoI. Time resolution degradation with increasing crystal length (up to 90% degradation for 1 mm crystal thickness) is observed. The effect of crystal surface on time resolution has a strong dependence of time resolution on crystal thickness. Note that the counts from the breast remain quasi constant, indicating that the shielding only slightly reduces the true count rate from the breast.

References/Funding

Cross-slit Capactive Multiplexing and Electro-optical Coupling for Silicon Photomultiplier Arrays for PET Detectors

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A key component for the development of simultaneous, PET/CT/MR as a PET block detector that has a low number of readout channels, non-magnetic components, and little or no mutual influence between PET and MR systems. We have developed a differential multiplexing circuit for silicon photomultipliers (SiPMs) that uses capacitors instead of resistors. We demonstrated that that two different arrays, 4 x 4 array of 3.2 mm x 3.2 mm x 20 mm x 4 x 6 of 2.2 x 2.2 x 20 mm LYSO scintillation crystals were multiplexed into a 4x4 array of 3.2 cm x 3.2 cm x 2 mm Silicon Photomultipliers (SiPM) detectors. This multiplexing circuit exploits the voltage tracking nature of SiPM. This circuit, together with the custom designed laser alignment block. This multiplexed, laser coupled block detector has a significant reduction in the number of readout channels while having a very low electrical footprint. These two technologies will be a key enabler of SiPM technology for high resolution small animal and clinical PET/CT/MR.

Abstracts: Molecular Imaging

Molecular Imaging

New Front-end IC with Fast Timing for Semiconductor Photodetectors
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In order to improve the signal-to-noise ratio of PET to improve, we need PET systems with densely packed sensors and high performance, highly integrated electronics. A PET system with small detector pixels (e.g., 4 mm²) results in thousands of electronic readout channels, and this necessitates using integrated circuits (IC) for the front-end electronics. An IC is an electronic circuit that has been fabricated on the surface of a tiny piece of silicon semiconductor material. The front-end ICs currently available do not have the required dynamic range and time resolution.

We are designing a front-end mixed-signal IC with an innovative architecture that enables the analog circuits to be combined with the analog-to-digital converter (ADC) in a single IC, while consuming much less power and having a smaller electronic footprint than conventional techniques. The output of the IC will be fully digital, so it is robust against amplitude noise and pulse width jitter and also facilitates multiplexing of the IC outputs. The IC will be programmable so that it can be used with both avalanche photodiode (APD) and silicon photomultiplier (SiPM) PET detectors. When completed, we are interested in sharing this IC with medical imaging researchers at Stanford and other institutions so that they can use it in their data acquisition systems.

The IC will have fast timing capability, i.e., it will be able to measure the time of the pulses from the PET detectors with about 100 ps time resolution. Therefore, it could be used in time-of-flight (ToF) PET. We are targeting an analog bandwidth of 2 GHz. The size of the IC is estimated to be 1 mm².

It's size facilitates the development of a highly compact and portable PET system that is particularly important for our targeted application: breast-dedicated PET.

Thermal Regulation for a 1 mm³ Resolution PET Camera based on Avalanche Photodiodes: Design, Simulation and Experimental Verification
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We are prototyping a lutetium yttrium orthosilicate (LYSO) position-sensitive avalanche photodiode (PSAPD) based positron emission tomography (PET) camera with 1 mm³ spatial resolution. The detector module within the camera consists of a pair of 16×16 arrays of 1 mm³ LYSO crystals coupled to two PSAPDs.

The PSAPDs are mounted on a Kapton flex circuit covered with Liquid Crystal Polymer (LCP). An alumina frame is used to provide standoff from high voltage (HV) lines and to provide rigidity. Many rows of these modules will be stacked to form a panel. The full camera will consist of two such panels. Annihilation radiation enters the crystal edge-on.

The design of the PET imaging system, many PSAPDs will be closely packed together. It is well known that the 1cmX1cm PSAPDs will heat up by 2 to 4 mW when biased and are sensitive to temperature. In particular, the gain of the PSAPD varies with temperature, which may impair system performance.

We completed the design of the thermal regulation plan for these PSAPDs. Results were validated by both the experiment and finite volume simulations. We investigated the temperature profile of the layer of PSAPD detectors resulting in the system and design the thermal regulation system for the front end of the PET camera.

We concluded that the design of a heat-dissipating fin structure with “windows” that border the scintillation crystal array of 16 adjacent detector modules per layer has the best heat dissipation effects compared to a design without the windows. For the fin with windows, the temperature difference from center to near the edge is 0.9°C in simulation and 1.2°C in experiment. The total cooling power is 0.08 W per half of the fin.

Spatial Resolution Improvement by ML Estimation in a 3D Positioning CZT Detector for PET
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We are developing a 1 mm resolution small animal PET system using cadmium zinc telluride (CZT) photon detectors capable of positioning the 3D coordinates of individual photon interactions. The detectors are 40×40×5 mm monolithic CZT crystals patterned for a cross-strip electrode design. Spatial localization along the x-y plane is achieved by finding the intersection of the anode and cathode strips that trigger signal readout. Localization along the z direction i.e. the interaction depth orthogonal to the electrode planes, can be achieved by observing the ratio of the anode and cathode pulse heights i.e. the C/A ratio. However due to factors such as finite energy resolution, measurement noise and photon Compton scatter within the detector, the C/A ratio 2 relationship is statistical in nature and offers limited estimation accuracy.

References/Funding
California Breast Cancer Research Program Dissertation Grant and the Stanford Graduate Student Fellowship

References/Funding
Philips Healthcare and NIH grants R01 CA119056, ARRA R01CA119056-S1, and R01 CA123478. Accepted for presentation at the 2010 IEEE Medical Imaging Conference, Oct 30, 2010, Knoxville, Tennessee, U.S.A.

References/Funding
NHGRI grants R01 CA110956, ARRA R01CA119056-S1, and R01 CA120474. Accepted for presentation at the 2010 IEEE Medical Imaging Conference, Knoxville, Tennessee, U.S.A.

List-mode processing is an efficient way of dealing with the sparse nature of PET data as it allows the processing of choice for time-of-flight (ToF) PET because data are collected in list-mode. We present a novel method of computing list projection operations required for list-mode ordered-subsets expectation-maximization (OSEM) for fully 3-D PET image reconstruction on a graphics processing unit (GPU) using the Compute Unified Device Architecture (CUDA) framework. Our method overcomes challenges such as compute thread divergence and exploits GPU capabilities such as shared memory and atomic operations. Each thread block takes a set of tubes-of-response (ToRs) and assigns one ToR to a thread. In the forward projection stage, the threads process the ToRs independently, and accumulate the contribution of the vectors to the ToRs by looping over the vectors that can potentially intersect with the TOR. In the backprojection stage, the threads accumulate the contribution of the ToRs to the vectors, and atomic operations are used to ensure data race conditions between different threads.

The benefits of the GPU/CUDA implementation compared with previously studied GPU OpenGl-Cg-based methods include easier implementation and maintainability, better utilization of the resources of the GPU (shared memory and atomic operations), and faster extension to more accurate projection models. When applied to line projection operations for list-mode time-of-flight PET this new GPU/CUDA implementation is 120% faster than a reference CPU implementation. The image quality is preserved with root mean squared (RMS) deviation between the images generated using the GPU and the GPU being 0.08%, which has negligible effect in typical clinical applications.

Spatial Resolution Improvement by ML Estimation in a 3D Positioning CZT Detector for PET
Y. Gu1,2, G. Chinn1,2, A. Rousset1,2, C. S. Levin1,3,4
Departments of Electrical Engineering and Radiology, MIPS, Stanford University, CA

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References/Funding
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References/Funding
NHGRI grants R01 CA110956, ARRA R01CA119056-S1, and R01 CA120474. Accepted for presentation at the 2010 IEEE Medical Imaging Conference, Oct 30, 2010, Knoxville, Tennessee, U.S.A.
Molecular Imaging

New Photon Detectors Based on Position Sensitive Solid State Photomultipliers for High Resolution PET

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High resolution detectors are essential components of an effective positron emission tomography system dedicated to brain imaging. Enhancing detector resolution down to 1mm usually results in increased cost due to increased number of photodetectors processing channels; one approach, position sensitive detectors are used to keep number of processing channels at a manageable level. We are developing a high-resolution PET detector block based on position sensitive solid state photomultipliers (SSP-SSPM) to arrive at detector resolution down to 1mm or better. SSP-SSPMs are new developments in photodetection technology that combine high gain and low voltage properties of silicon photomultipliers (SiPMs) with the position encoding capability of position sensitive avalanche photodiodes (PSAPDs). Each channel基本上 consists of a silicon photomultiplier integrated with a built-in resistive network at device level. Based on our demonstrated experience in design and development of block detectors using both PS-APDs and SiPMs, we expect SSP-SSPMs provide advantages of superior positioning and timing capability as well as magnetic field invariability for PET/MRI multimodal applications.

We have considered coupling of silicon crystalline arrays of 0.6 mm and 0.8 mm pitch to a 2×2 mm2 SiP-SiPM with four outputs. Our preliminary results show that in case of 0.8 mm pitch crystals, the PS-SiP can resolve all 16 crystals and the 511 keV photopeak energy resolution obtained from the overall energy spectra of the crystal array is 15% at FWHM (this result is reported without offset correction). After positioning and correction for regular segmentation, the average peak to valley ratio was calculated to be 18.25 with sigma of 4.8. For the 0.5 mm pitch crystal array, the PS-SiP can resolve all 36 crystals.

This work continues with full characterization of PS-SSPMs and addition of depth of interaction resolving capability to the detector block to address requirements of PET detectors for high resolution imaging.

Optical Network-based PET DAQ System: One Fiber Optical Connection

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Our work describes important and exciting advances in data acquisition system design for positron emission tomography (PET) that are possible with new high speed signal and optical network technology. Typically, a DAQ system is composed of many interconnected DAQ boards using high-speed links. Interconnections between PET DAQ boards involve transmission of event data, control signals, and a synchronization clock. Conventionally, the “tree” interconnection topology was used to handle high event data rates, however as the serial link and electronic computation speed have been improved, the “daisy-chained” interconnection scheme has become possible. The daisy-chain structure has improved the scalability as compared to the tree connection but has a lower single photon event throughput. High-speed serial optical networks can improve the throughput while further minimizing the interconnection between the DAQ boards. This newer approach can also be used to synchronize all the DAQ boards using the built-in clock-recovery functionality inherent to optical data transmission links.

We are developing DAQ boards for an MRI compatible PET brain scanner using the Fiber Channel 2Gbps optical standard to interconnect the boards in a daisy-chained structure. For processing 15% differential detector signals, 18 DAQ boards are interconnected with only 18 optical patch cables and globally synchronize all the analog-to-digital converters (ADCs) and time-to-digital converters (TDCs) in the system. By replacing the signal lines used for parallel buses, serial clocks, and clock signals with a single optical fiber channel, we minimize the number of interconnections between each DAQ board, which greatly simplifies the scaling process. Our design analysis predicts that the singles event throughput will be 100Mevents/sec using standard and easily available, optical interconnections and the required transmission buffer and coincidence memory sizes are 120 bits and 11k bits, respectively.

References/Funding: Stanford Bio-X Graduate Fellowship (Olcott), Stanford Molecular Imaging Scholars (Sims) program (NHIC grant R22 R01 CA159685) (Gonzalez), and grants R01 CA159685, AR02 008118A1200345, and R01 CA137477. Accepted for oral presentation at the 2010 IEEE Medical Imaging Conference, 30 October - 6 November, Shanghai, China.
Non-invasive Molecular Imaging of Histone Tail Methylation in Living Animals

HiFi modifications such as histone methylation and histone acetylation, are two important epigenetic mechanisms which play key roles in maintaining a) Chromatin structure in heterochromatic region, and b) Gene expression in euchromatic region. Methylation of amino acid lysine and/or arginine residues at the NHE-terminal tail of histones (H3, H4, 9, 27 and 36, and H4 Lys 20) by histone methyltransferases (HMTs) recruits chromodomains from heterochromatin-associated proteins (HP1) and forms a complex that functions as repressive chromatin structure, and regulation of gene expression. As epigenetic regulators are considered important players in maintaining cellular homeostasis, an in vivo imaging method of monitoring this cellular process may accelerate drug development for different diseases, including cancer. From this study, we have developed a fluorescence resonance energy transfer (FRET) signal that can optically image histone-methylation in cells and in living animals. A mutant HDAC developed a bioluminescence resonance energy transfer (BRET) sensor that can detect signals from HDAC1 in any cell line (5.5±2.5 fold) only by the sensor that inhibited HDAC activity. The results indicate that inhibition of HDAC induced significant (P<0.5) methylation mediated increase in the level of Turbo-RFP. Five mice were examined and the results remained consistent.

References/Funding

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Molecular Imaging

Multipleplex PET Detectors with Noise Robust Compressed Sensing Decoder

We present a novel method for multiplexing PET detectors using the theory of “compressed sensing” (CS). Photon events recorded by a PET camera are sparse in the natural pixel basis. Current multiplexing schemes used for PET cameras are noise robust but, multiple interaction events appear as a single interaction with an energy-weighted multiple-position average position. CS theory can be used to specify multiplexing topologies that reduce the number of readout channels while solving multiple interactions. The ability to distinguish multiple interaction events from single interaction events can improve the spatial resolution of PET. However, conventional CS decoders using L1 norm minimization are not robust in the presence of noise. Therefore, we have developed a new method for decoding multiplexed detector signals that optimizes the SNR of the decoded detector pixel signals using a modified L1 norm minimization (ML-CS). The new decoder can improve SNR by up to 20% over the conventional distance-weighted multiple-plexing schemes such as cross-strips and Anger logic. This multiplexing scheme combined with previously developed multiple interaction positioning algorithms can dramatically improve the spatial resolution of PET without any loss of energy or time resolution.

Facile Synthesis, Stabilization, and Biodistribution of Biocompatible Quantum Dots

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We reported a facile strategy for the synthesis of silicon-coated quantum dots (QDs) for in vivo imaging. All the QD synthesis and labeling steps are conducted in water without involving any organic-solvent precursors or high-temperature, oxygen-free environments. As-prepared silicon-coated QDs possess high quantum yield and are extremely stable in mouse serum. In addition, the silicon coating method developed here produces nanoparticles with small sizes that are difficult to achieve via conventional silanization methods. The silicon coating helps to prevent the exposure of the QD surface to the biological milieu and therefore increases the biocompatibility of QDs for in vivo applications. Interestingly, the silicon-coated QDs exhibit a different biodistribution pattern from that of commercially available iron oxide (QDO) (carboxylate) with a similar size and intensity wavelength. The iron oxide (QDO) exhibits predominant lower (16.2±0.9) and spleen (3.67% ID·g⁻¹) uptake 30 min after intravenous injection, whereas the silicon-coated QDs exhibit slightly lower liver (16.2±0.1 ID·g⁻¹) and kidney (1.24% ID·g⁻¹) uptake but higher kidney uptake (18.2±2 ID·g⁻¹), blood retention (5.0% ID·g⁻¹), and partial renal clearance. Overall, this straightforward synthetic strategy paves the way for routine and customized synthesis of silicon-coated QDs for biological use.

References/Funding

Stanford Bio-X Graduate Fellowship, NIH-NIGMS grants ROI CA05068 and ROI CA026747. Accepted for presentation at the IEEE NSS-MIC 2016, Knoxville, TN.

18F-5-fluorouracil Dynamic PET/CT Reveals Decreased Tracer Uptake After Bevacizumab in Colorectal Metastasis

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Purpose: The aim of this study was to evaluate the effectiveness of 18F-5-fluorouracil (18F-FU) PET/CT to visually demonstrate differences in tumor uptake 24 hours post-bevacizumab. Method and Materials: This was a pilot study of five consecutive patients (4 females, 1 male; mean age, 54.6 years; range, 27-45 years) with newly diagnosed and untreated metastatic colorectal adenocarcinoma. The presence of cancer was confirmed by histological analysis and patients served as their own internal control. Each patient underwent baseline 18F-FU PET/CT scanning prior to treatment with bevacizumab, then received a 90-minute infusion of bevacizumab at a dose of 7.5 mg/kg (mean dose, 437.4 mg; range, 350-516 mg). Approximately 24 hours post-bevacizumab, patients underwent a second 18F-FU PET/CT scanning. Using CT as an anatomical reference, manually drawn regions-of-interest (ROIs) were drawn around the aorta and all colorectal metastases and time-activity-curves (TAC) were generated at each tumor site. Differences between pre- and post-bevacizumab SUVmax and 5-minute Area Under the Curve ratios (AUCtumor/AUCaorta) were calculated for each lesion as the primary outcome measures.

Results: The sizes of the metastatic lesions ranged from the smallest lesion measuring 1.44 cm x 1.50 cm to the largest measuring 4.19 cm x 2.78 cm. At baseline, the average SUVmax for 18F-FU uptake at the metastatic site 5 minutes after tracer infusion was 3.9 ± 1.4 (range, 0.98 to 5.08) and was not significantly different in patients 24-hours after the administration of bevacizumab, 3.1 ± 1.3 (range, 0.45 to 6.05, p = 0.125). In each of the 5 subjects, the 5-minute AUCtumor/AUCaorta ratio decreased 24 hours after treatment. At baseline, the mean AUCtumor/AUCaorta was 1.24 ± 0.30 (range, 0.42 to 2.14) and was significantly lower in patients 24-hours after the administration of bevacizumab, 1.0 to 8.06 (p = 0.23 to 2.13, p = 0.04). This represents an average decline in the AUCtumor/AUCaorta of 20.2% (range, 0.45 to 45%). Conclusion: In this pilot study of five patients with metastatic colorectal cancer, 18F-FU PET/CT scanning revealed a significant decrease in tumor uptake 24 hours post-bevacizumab. Clinical Relevance/Applicability: The ability of 18F-FU PET/CT to visually demonstrate differences in tracer uptake may allow for improved treatment monitoring and treatment in patients with advanced colorectal cancer.
Quantification of Inflammation in Inflammatory Bowel Disease by Molecular Ultrasound Imaging

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Inflammatory bowel disease (IBD) is a chronic relapsing and remitting inflammatory condition of the gastrointestinal tract that needs regular and accurate monitoring. The goal of our study was to assess the potential of molecular ultrasonography (US imaging) using microbubbles (MB) targeted to the inﬂammatory marker P-selectin to quantify and predict remission of inflammation following treatment in a chemically-induced colitis mouse model. Binding affinity and specificity of MB-P-selectin was tested in a flow chamber under flow shear stress conditions (at 100 sec⁻¹). In vivo binding speciﬁcity of MB-P-selectin was tested in 10 mice with colitis induced by nasal administration of TNBS and in 10 control mice without colitis using non-linear in vivo US imaging (25 MHz). Furthermore, in vivo molecular US imaging in treated (prednisolone therapy) versus non-treated (saline only) mice was compared over 3 subsequent treatment days. Attachment of MB-P-selectin was signiﬁcantly (p=0.01) higher to P-selectin positive (simulated by TNF-alpha) than unstimulated endothelial cells and compared to MB-Control (p=0.003). Furthermore, attachment of MB-P-selectin signiﬁcantly (R²=0.8, p=0.01) correlated with expression levels of P-selectin on endothelial cells as quantiﬁed by ﬂow cytometry. In vivo US signal of colitis was signiﬁcantly higher (p=0.005) with MB-P-selectin compared with MB-Control (Figure), and signiﬁcantly (p=0.01) dropped by 55% following injection of blocking antibodies. In treated animals, in vivo US imaging signal signiﬁcantly (p=0.03) decreased during the course of treatment while in non-treated mice US signal on the colon wall remained elevated. In vivo US imaging signal signiﬁcantly (R²=0.8, p=0.04) correlated with P-Selectin expression levels as assessed by ex vivo assays (WB and IF). In conclusion, molecular US using MB-P-selectin allows non-invasive in vivo quantiﬁcation and monitoring of inﬂammation at the cellular level in a chemically-induced colitis mouse model. This study lays the foundation for an eventual future clinical translation of molecular US imaging for monitoring inﬂammation in IBD.

References/Funding

A Novel Motion Correction Technique for Contrast-enhanced Ultrasound Imaging of Tumor Vascularity

Ma Pyzsz, I Guracar*, K Foygel, JK Willmann*
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The purpose of our study was to develop and test a real-time motion correction algorithm for contrast-enhanced ultrasound (CEUS) imaging in humans. This approach was used to improve the accuracy of vascular imaging during tumor treatment. A motion correction technique that measured horizontal and vertical pixel displacement using automated tumor boundary detection and a location- adjustable tracking box, was incorporated into the software of a clinical US scanner (Sequoia Acuson, Siemens). Contrast-enhanced US imaging in the maximum intensity projection mode (14 MHz, 0.26°) was performed on subcutaneous human tumors in nude mice implanted on backs of mice. Extent of tumor vascularity (expressed as % contrast area) was calculated in real-time with and without motion correction in tumors with different grades of vascularity (low, medium, high; n=10, and n=10 with and without motion correction (VDA) in moderately vascularity tumors, the extent of motion correction on the measured tumor vascularity was signiﬁcantly (P<0.001) higher (mean differences, 13.3% ± 2.5%) compared with tumors with lower mean differences, 3.2% ± 2.7%) or high mean differences, 4.8% ± 2.5%) vascularity. The differences in tumor vascularity measurements were also higher in animals taking a spontaneous deep breath when the tumors were moderately vascularity (mean differences, 25.4% ± 5.2%) or high vascularity (mean differences, 12.0% ± 10.0%) as well as in tumors with lower vascularity. The differences in tumor vascularity measurements were also higher in animals taking a spontaneous deep breath when the tumors were moderately vascularity (mean differences, 25.4% ± 5.2%) or high vascularity (mean differences, 12.0% ± 10.0%) as well as in tumors with lower vascularity.

References/Funding

Lucas Annual Report 2010
Molecular Imaging

Manganese-Enhanced Magnetic Resonance Imaging (MEMRI) Highlights Injured Peripheral Nerves in Neuropathic Pain (Chronic Constrictive Injury)

D Behara and S Biswal

Department of Radiology, MIPS, Stanford University, CA

Objective: Manganese-enhanced MRI (MEMRI) is a surrogate method to inter-

gage calcium fluxes in nervous system since M2A physiologically follows calcium in and 

out of neurons and is known to display in calcium homeostasis. In the present study we validate MEMRI for detection of changes in laminar neurons related to neuropatho-

logical injury in a model of Chronic Constrictive Injury (CCI).

Method: Animal experiments were approved by Stanford IACUC. A neuro-

pathic pain model was created by Chronic Constrictive Injury (CCI) of the left sciatic 
nerve of Sprague-Dawley rats by placing four interrupted loose ligatures around the nerve. Rats were allowed to heal for four weeks. Rats with CCI (n=5) and uninjured animals (n=5) were evaluated for allostyny in the hind paws using von-Frey’s filaments. MEMRI experiments were performed on a small animal MR imaging unit (7T). MicroPET and T1 weighted Fast Spin Echo images were obtained at the lumbar 

regional level. Baseline scans were obtained on all rats before CCI administration. After 

then all rats were injected with MnCl2 (30ml, 1 ml/100 g, i.p.) and scanned again 24 hours after injection. Images were analyzed using Amide image analysis software. Allodynia was assessed by von-Frey’s filamen-
tes. The maximum signal in each ROI was normalized to the mean signal within the respective background ROIs to obtain a signal-to-background ratio (SNR). The maximum signal in each ROI was normalized to the mean signal within the respective background ROIs to obtain a signal-to-background ratio (SNR). The maximum signal in each ROI was normalized to the mean signal within the respective background ROIs to obtain a signal-to-background ratio (SNR).

Conclusion: Animals with neuropathic pain show increased M2A uptake in peripheral nerves. PET-MRI can be effectively used to localize 18FDG uptake in peripheral nerves.

Increased normalized MEMRI signal was seen in the CCI rats (Fig. 2, left paw 5.07±0.05, right paw 5.02±0.10; p=0.42). No difference was seen between the right and left paws of control rats (left paw 5.07±0.05, right paw 5.02±0.10; p=0.42).

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### Peer-Reviewed Presentations at Scientific Meetings

**ISMRM 2010 (May 1-7, Stockholm, Sweden)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>van, Pfefferbaum, Mayer D, Gu, Zahr, Spielman D, Sullivan, Lustig, Santos, Swaminathan, McDannold, Starost, Alcazar, Chen W, Pauly J, Butts Pauly K.</td>
<td>Variable density spiral fMRI.</td>
</tr>
<tr>
<td>Bitton, Kaye, Daniel BL, Butts Pauly K.</td>
<td>MR guided HIFU in Cadaver Breasts for Pre-Operative Tumor Localization of Non-Palpable Breast Tumors as an Alternative to Needle Wire Localization.</td>
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<tr>
<td>Allen, Beatty, Heise, Vasanawala</td>
<td>Reducing the Scan Time of Time-Resolved, 3D Phase Contrast Imaging with 2D Autocalibrated Parallel Imaging.</td>
</tr>
<tr>
<td>Balchandani P, Pauly J, Spielman D</td>
<td>Self-Refocused Adiabatic Pulse for Spin Echo Imaging at 7T.</td>
</tr>
<tr>
<td>Balchandani P, Spielman D</td>
<td>Adiabatic Magnetization Preparation Pulse for T2-contrast at 7 Tesla.</td>
</tr>
<tr>
<td>Bammert R, Yeom, Holdsworth, Skare</td>
<td>High-Resolution Diffusion-Weighted Imaging of the Ovaries Using Readout-Segmented EPI.</td>
</tr>
<tr>
<td>Bitton, Kaye, Daniel BL, Butts Pauly K.</td>
<td>MR-guided HIFU in Cadaver Breasts for Pre-Operative Tumor Localization of Non-Palpable Breast Tumors as an Alternative to Needle Wire Localization.</td>
</tr>
<tr>
<td>Chang, Glover G</td>
<td>Variable density spiral fMRI.</td>
</tr>
<tr>
<td>Glover G, Chang</td>
<td>Hadian-encoded fMRI for Reduced Susceptibility Dropout.</td>
</tr>
<tr>
<td>Grandlund, Sarnowicz, Alvey, Daniel, Hargrove B</td>
<td>High Resolution T2 Breast Imaging using FADE.</td>
</tr>
<tr>
<td>Griswold, Holbrook A, Rieke, Lustig, Santos, Swaminathan, McConnell, Butts Pauly K.</td>
<td>Hybrid Multi-baseline and Referenceless PRE-flip Thermometry.</td>
</tr>
<tr>
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<td>Quantification of Glutamate and Glutamine using CT-PRESS at 3T.</td>
</tr>
</tbody>
</table>

### Appendices

**Publications and Presentations**

<table>
<thead>
<tr>
<th>Editors</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitzler, Su, Zeineh, Drexler, Harper-Little, Leng, Kromschroeder, Bammert R</td>
<td>MR-ARFI-Derived Demyelination Volume in Multiple Sclerosis Patients Correlates with Clinical Disability and Sensory Early Myelin Loss.</td>
</tr>
<tr>
<td>Hall, Hargrove B</td>
<td>Simple Self-Gating for Compensation of Respiratory Motion using a Spiral k-Space Trajectory.</td>
</tr>
<tr>
<td>Han, Hargrove B</td>
<td>Combined Excitation and Partial Saturation to Reduce Inflow Enhancement.</td>
</tr>
<tr>
<td>Han, Hargrove B, Daniel, Alexp, Robson, Han, Wurtz, Shankaramurthy</td>
<td>Breast Perfusion Imaging Using Arterial Spin Labeling.</td>
</tr>
<tr>
<td>Hollbrook A, Prakash, Jones, Planey, Santos, Deichl, Butts Pauly K, Somerman G</td>
<td>Multifocal Treatment Planning and Control for Real Time MR-Guided Prostate Ablation with Transrectal Multisected Ultrasound Applicators.</td>
</tr>
<tr>
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<td>Diffusion-Weighted Imaging of the Abdomen with Readout-Segmented (RS)-EPI.</td>
</tr>
<tr>
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<td>Reduced-FOV Diffusion Imaging with ZOmal OFnSlice Multislice (ZOOM) combined with Readout-Segmented (RS-EPI).</td>
</tr>
<tr>
<td>Holdsworth, Yeom, Skare, Barnes PD, Bammert R</td>
<td>Clinical Application of Readout-Segmented (RS)-EPI for Diffusion-Weighted Imaging in Pediatric Brain.</td>
</tr>
<tr>
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</tr>
<tr>
<td>Kaye, Bitton, Butts Pauly K.</td>
<td>Focal Spot Visualization in MRE at the Breast: MR-ARFI vs. T1-weighted FSE.</td>
</tr>
<tr>
<td>Kim, Sung, Han, Alley, Hargrove B</td>
<td>Phase Correction in Bipolar Multi-Echo Sequence Water-Fat Separation for Off-Isocenter Imaging.</td>
</tr>
<tr>
<td>Kim, Sung, Hargrove B</td>
<td>Robust Field Map Estimation Using Both Global and Local Minima.</td>
</tr>
<tr>
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Desser T. Abdominal Fat Necrosis: Imaging Spectrum.

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Publications and Presentations
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**Lucas Annual Report 2010**

R, Cochran, Han, Cheng Liu, Miao, Ren, Kimura R, Jiang, Silverman, Gambhir SS

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**Peer-Reviewed Presentations at Scientific Meetings**

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- **Pyur M**: Maximum Intensity Persistence Analysis is A Sensitive and Reliable Tool to Quantitate Tumor Angiogenesis with Ultrasound Imaging.
- **Pyur M**: Pre-clinical Evaluation of Novel Clinically-Translatable KDRI-Targeted Microbubbles for Molecular Ultrasound Imaging of Aregiosis in Cancer.
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- **Rao J**: Immobilized Activatable Bioluminescent Probes for In Vivo Imaging of Protease Activity in Tumors.
- **Rao J**: In Vivo Imaging of Tuberculosis with Near Infrared Fluorescent Probes.
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- **Smith B**: Direct Microscale Visualization of Targeted Quantum Dot Binding in Multiple Tumor Models of Living Mice using Intravital Microscopy.
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- Chan F. Cardiac CT for Non-coronary Applications. Annual Spring Diagnostic Imaging Update; March 22-26, 2010; Maui, HI.
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Lucas Annual Report 2010

Publications and Presentations

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**Other Presentations 2010**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Event Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang G.</td>
<td>Glycemic Control in the IR Suite. Annual Workshop at Society of Interventional Radiology; March 10, 2010, Tampa, FL.</td>
<td></td>
</tr>
<tr>
<td>Huang G.</td>
<td>Liquid Embolectomy. Annual Workshop at Society of Interventional Radiology; March 10, 2010, Tampa, FL.</td>
<td></td>
</tr>
<tr>
<td>Ikeda D.</td>
<td>Anatomic, Physiology, &amp; Pathology of the Breast</td>
<td>Annual Symposium on Advances in Breast MRI; October 22-24, 2009, Las Vegas, NV.</td>
</tr>
<tr>
<td>Ikeda D.</td>
<td>Biopsies Using Different Imaging Modalities</td>
<td>Asian-Oceanic Congress of Radiology; March 19-21, 2010, Taipei, Taiwan.</td>
</tr>
</tbody>
</table>

## Other Presentations 2010

<table>
<thead>
<tr>
<th>Author(s)</th>
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<tbody>
<tr>
<td>Ikeda D.</td>
<td>Breast MR Imaging Interpretation Including BRADS.</td>
<td>UC San Diego Breast Imaging &amp; Interventions Update; October 30-November 1, 2009, Coronado, CA.</td>
</tr>
<tr>
<td>Ikeda D.</td>
<td>Challenging Image-Guided Biopsies.</td>
<td>Annual Advances in Breast Imaging and Interventions; March 3-6, 2010, Las Vegas, NV.</td>
</tr>
<tr>
<td>Ikeda D.</td>
<td>Correlating Mammo/US/MRI</td>
<td>Annual Advances in Breast Imaging and Interventions; March 3-6, 2010, Las Vegas, NV.</td>
</tr>
<tr>
<td>Ikeda D.</td>
<td>Digital Mammography &amp; Tomosynthesis</td>
<td>Annual Advances in Breast Imaging and Interventions; March 3-6, 2010, Las Vegas, NV.</td>
</tr>
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<td>Ikeda D.</td>
<td>Ergonomics for the FIDM Environment.</td>
<td>Annual Advances in Breast Imaging and Interventions; March 3-6, 2010, Las Vegas, NV.</td>
</tr>
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<td>False Negative Studies on MRI. Mammo, US. Big Sky Radiology conference; January 24-27, 2010, Big Sky, MT.</td>
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<td>Ikeda D.</td>
<td>MRI &amp; Digital Mammography Comparison &amp; Correlation.</td>
<td>Annual Symposium on Advances in Breast MRI; October 22-24, 2009, Las Vegas, NV.</td>
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<td>MRI Update &amp; Patient Indications.</td>
<td>Annual Advances in Breast Imaging and Interventions; March 3-6, 2010, Las Vegas, NV.</td>
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<td>Second Look Sonography after Breast MRI.</td>
<td>UC San Diego Breast Imaging &amp; Interventions Update; October 30-November 1, 2009, Coronado, CA.</td>
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<td>The Post-Operative Breast.</td>
<td>UC San Diego Breast Imaging &amp; Interventions Update; October 30-November 1, 2009, Coronado, CA.</td>
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<td>Tomosynthesis and FFDM. Big Sky Radiology conference; January 24-27, 2010, Big Sky, MT.</td>
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Other Scientific Meeting Presentations


Leung AN. ILD Assessment: Volumetric or Non-Contiguous CT Acquisition? Annual International Symposium on Multidetector-Row CT; May 19–22, 2009; San Francisco, CA.


Levin CS. Advances in PET and PET/MR. International Symposium on Animal Molecular Imaging; October 10–11, 2009; Taipei, Taiwan.


Mittal ES, Quan A, Gambhir SS, Iqara A. Efficacy of 18F-FDG PET/CT for Breast Cancer. Annual Congress of the European Association of Nuclear Medicine; October 10-24, 2009; Barcelona, Spain.


Peng H, Olcott PD, Levin CS. Practical and Clinical PET Detector Design Considerations Using Silicon Photomultipliers. IEEE Medical Imaging Conference; October 25–31, 2009; Orlando FL.

Plevritis S. Curing Lung Cancer by Early Detection. Annual Scientific Workshop of the Early Detection Research Network; August, 2009; Bethesda, MD.

Plevritis S. Modeling the Natural History of Cancer. Annual Scientific Meeting of the Society of Medical Decision Making; October, 2009; Hollywood, CA.

Rabowowa E, Barth RA, Rosenburg J, Brau AC, Vasanawala SS. 3D TI-weighted Fetal MRI. Annual Society for Pediatric Radiology Meeting; April 21-25, 2009; Carlsbad, CA.

Other Presentations 2010

Rabowowa E, Vasanawala SS, Rosenburg J, Barth RA. Single Shot SSFSE Versus Balanced Steady State Imaging: Which Sequence to Choose to Image Fetal Body? Annual Society for Pediatric Radiology Meeting; April 21-25, 2009; Carlsbad, CA.

Segall G. Dual Time Point: Yes or No? Annual Symposium on PET/CT and Molecular Imaging; February 1–13, 2010; Las Vegas, NV.

Segall G. PET/CT in the Abdomen and Pelvis. Annual Winter Diagnostic Imaging Update; January 4-8, 2010; Bachelor Gulch, CO.

Segall G. PET/CT in the Head and Neck. Annual Winter Diagnostic Imaging Update; January 4-8, 2010; Bachelor Gulch, CO.

Segall G. PET/CT in the Thorax. Annual Winter Diagnostic Imaging Update; January 4-8, 2010; Bachelor Gulch, CO.

Segall G. PET/CT Slice by Slice: Abdomen and Pelvis. Annual Symposium on PET/CT and Molecular Imaging; February 1–13, 2010; Las Vegas, NV.

Segall G. PET/CT State of the Union: The Success of the Past 8 Years and a look to the Future. Annual Symposium on PET/CT and Molecular Imaging; February 1–13, 2010; Las Vegas, NV.

Shin L. Updates on Imaging of GI Cancers. Annual GI Cancers Symposium; July 31–August 2, 2009; Kahului Coast, HI.

Shin L. Updates on Imaging of GI Cancers. Annual GI Cancers Symposium; July 31–August 2, 2009; Kahului Coast, HI.

Sommer G. Advanced Processing for MDCT Urography. Annual Symposium on Multidetector-Row CT; May 19–22, 2009; San Francisco, CA.

Sommer G. Different Approaches to Acquisition in MDCT Urography. Annual Symposium on Multidetector-Row CT; May 19–22, 2009; San Francisco, CA.

Sommer G. Pelvis MR. Annual Current Concepts of Magnetic Resonance Imaging; October 12–15, 2009; Monterey, CA.

Spanoudaki V, Levin CS. Design and Development of a New PET Detector with Both DoI and ToF Capabilities. IEEE Medical Imaging Conference; October 25–31, 2009; Orlando FL.


Stevens K. MRI of the Shoulder: Cuff and Labral Pathology. Annual Winter Diagnostic Imaging Update; January, 2010; Beaver Creek, CO.

Stevens K. MRI of the Shoulder: Cuff and Labral Pathology. Annual Winter Diagnostic Imaging Update; January, 2010; Beaver Creek, CO.

Stevens K. MRI of the Wrist and Hand. Annual Winter Diagnostic Imaging Update; January, 2010; Beaver Creek, CO.

Sae D. Chemosegmentation 201: Comparing Methods and Results. Annual Latest Advances in Interventional Techniques; July, 2009; Kaanapali, HI.

Sae D. Management of Blanding Conditions: Basics of Embolization. Society of Interventional Radiology Annual Scientific Meeting; March, 2010; Tampa, FL.

Sae D. Oncology: Primer on Y80. Society of Interventional Radiology Annual Scientific Meeting; March, 2010; Tampa, FL.
Other Scientific Meeting Presentations


Zaharchuk G. Vascular Imaging of the Central Nervous System. Annual Winter Diagnostic Imaging Update; January 4-8, 2010; Beaver Creek, CO.

Published Papers


Faster Pediatric MRI via Compressed Sensing. ACR case-in-point online teaching file. 2009 Sep.


Published Papers


Published Papers


Published Papers

Kossummarty, G; Kosemamuthy, S; Gambhir, S; Rodriguez, C; Rosenberg, J; Schepers, C; Boston-Thomas, M; Development and intra-institutional and intra- 


Levkovitch-Z, Backer M, Backer JM, Blankenberg FG. Imaging Vascular Endothelial Growth Factor (VEGF) Receptors in Turbulently-induced Steal 


Lin Y, Kamaida A, Dessed TD, Rubin DL. A Controlled Vocabulary to Represent Isometric Features of the Thyroid and its application in a Bayesian Network 


Maraden AL, Krady VM, Shadlon SC, Chan FP, Taylor CA, Feinstein JA. A New Multiparameter Approach to Computational Simulation for Fontan 


Mayer D, Yan YF, Tropp J, Pfiefferbaum A, Hend R, Spielman DM. Application of Subsecond Spiral Chemical Shift Imaging to Real-time Multislice 

Lucas Annual Report 2010

Published Papers


Published Papers


Books and Book Chapters

Books and Book Chapters


Papers Submitted or In Press


Segall GM. A Luther’s Reflections on the MOC Exam. ABNM Tracers. 2009;2:3.


Darwazah TT, Darwazah NM, Chang SD, Silverstein GD, Siller LM, Tan L, Dool BL, Do HM, Marks MP, Steinberg JK. Predictors of Clinical and Angiographic Outcome Following Surgical or Endovascular Therapy of Very Large and Giant Intracranial Aneurysms. Neurosurgery.


Papers Submitted or In Press


Starronick E, Bangert N, Gannet PY, Grudledorfer T, Daniel BL, Gold BE, Hargraves BA. In- Vivo Sodium Imaging of Human Patellar Cartilage with a 3D Cone Sequence at 1.7T and 1.9 T. Magn Reson Med. 1999;39:1; Epub.


Vanuasvalla SS, Alley MT, Hargraves BA, Barth RA, Pardy JM, Lastig M. Improved Pediatric MRI via Compressed Sensing. Radiology. in press.


Appendix

Papers Submitted or In Press


Neuman B, Cho YA. Left Pulmonary Artery Sling-Anatomy and Imaging. Semin Ultrasonic CT MR. 31:159-70.


Papers Submitted or In Press


Lucas Annual Report 2010


Publications and Presentations

Papers Submitted or In Press


Papers Submitted or In Press


Funded Research Projects
<table>
<thead>
<tr>
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<tr>
<td>Roland Bammer, PhD</td>
<td>R01</td>
<td>Improving SENSE MRI for Spiral and Echo-Planar Imaging in Stroke</td>
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<tr>
<td>Roland Bammer, PhD</td>
<td>R01 (ARRA)</td>
<td>Novel Acquisition Methods for Diffusion MRI</td>
</tr>
<tr>
<td>Roland Bammer, PhD</td>
<td>R21</td>
<td>Real-Time MRI Motion Correction System</td>
</tr>
<tr>
<td>Roland Bammer, PhD</td>
<td>R01 (+ARRA supp)</td>
<td>Short Axis EPI for Diffusion Tensor MRI at High Field</td>
</tr>
<tr>
<td>Francis Blankenberg, MD</td>
<td>R01 (ARRA)</td>
<td>scVEGF Targeted Radiotherapy of Mammary and Colonic Cancer</td>
</tr>
<tr>
<td>Catherine Chang, MS</td>
<td>F32</td>
<td>Temporal Characteristics of Intrinsinc Brain Networks Using fMRI</td>
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<tr>
<td>Zhen Cheng, PhD</td>
<td>R21</td>
<td>Quantum Dots for NIR Fluorescence Imaging of Tumor Angiogenesis</td>
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<tr>
<td>Zhen Cheng, PhD</td>
<td>R01</td>
<td>Radioisotopic RGD Peptides for Breast Cancer Imaging and Therapy</td>
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<tr>
<td>Heike Daldrup-Link, MD</td>
<td>R21*</td>
<td>Novel Imaging Approach to Monitor Chondrogenic Differentiation of iPSCs</td>
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<tr>
<td>Bruce Daniel, MD</td>
<td>R01</td>
<td>Techniques for MRI-Guided Cryosurgery of Prostate Cancer</td>
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<tr>
<td>Bruce Daniel, MD</td>
<td>R21*</td>
<td>High Resolution 3D Diffusion-Weighted Breast MRI</td>
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<tr>
<td>Rebecca Fahrig, PhD</td>
<td>S10* (ARRA)</td>
<td>Axion zoomo shared instrument grant</td>
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<td>Rebecca Fahrig, PhD</td>
<td>R01 (ARRA)</td>
<td>C-Arm CT for Guidance of Cardiac Interventions</td>
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<td>Rebecca Fahrig, PhD</td>
<td>R01*</td>
<td>Dual KV/MV Imaging for Metal Artifact Reduction</td>
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<td>R21</td>
<td>Efficient Scatter Correction</td>
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<td>Rebecca Fahrig, PhD</td>
<td>R01 (+ARRA supp)</td>
<td>MR-Compatible X-Ray Tube</td>
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<td>Rebecca Fahrig, PhD</td>
<td>R21*</td>
<td>Ultrasound Tomosynthesis for Transbronchial Biopsy Guidance</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>R01</td>
<td>Imaging Cytolytic T Cells in Cancer Patients Using PET Reporter Genes/Reporter Probes</td>
</tr>
<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>P50**</td>
<td>In Vivo Cellular and Molecular Imaging Center @ Stanford</td>
</tr>
<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>R01**</td>
<td>Reporter Imaging of Protein-Protein Interactions</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>R25</td>
<td>Stanford Molecular Imaging Scholars (SMIS)</td>
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<tr>
<td>Anumuddin Ganguly, PhD</td>
<td>K99</td>
<td>High Performance CMOS Based X-Ray Detector for C-AM CT Imaging</td>
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<tr>
<td>Gary M. Glazer, MD</td>
<td>T32</td>
<td>Advanced Techniques for Cancer Imaging and Detection</td>
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<tr>
<td>Gary Glover, PhD</td>
<td>P41**</td>
<td>Center for Advanced Magnetic Resonance Technology at Stanford</td>
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<tr>
<td>Gary Gold, MD</td>
<td>R01**</td>
<td>Rapid MRI for Evaluation of Osteoarthritis</td>
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<td>Gary Gold, MD</td>
<td>B01</td>
<td>Real-Time MRI and 3D Modeling: Development and Application to Patellofemoral Pain</td>
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<td>Brian Hagrynowski, PhD</td>
<td>R01 (+ARRA supp)</td>
<td>High-Resolution Whole-Body MRI at 3.0T</td>
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<td>R21</td>
<td>Magnetic Resonance Imaging near Metallic Implants</td>
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<td>Craig Levin, PhD</td>
<td>R01 (+ARRA supp)</td>
<td>Advanced PET System Dedicated to Breast Cancer Imaging</td>
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<td>Craig Levin, PhD</td>
<td>R01</td>
<td>Enhancing Molecular Cancer Imaging with Cadmium Zinc Telluride PET</td>
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<td>Michael Moskley, PhD</td>
<td>R01</td>
<td>Microvascular Measures of Perfusion in Stroke Recanalization</td>
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<td>Michael Moskley, PhD</td>
<td>S10* (ARRA)</td>
<td>Upgrade of the Stanford GE-Varius Experimental MRI Scanner to the Current Model M</td>
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<td>Kim Butts Painley, PhD</td>
<td>R21*</td>
<td>MRI Methods for Guiding Focused Ultrasound in the Brain</td>
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<tr>
<td>Kim Butts Painley, PhD</td>
<td>R01</td>
<td>MR Image Guided Focused Ultrasound for Treatment of Liver and Renal Cancer</td>
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<td>Norbert Piel, ScD</td>
<td>R01 (+ARRA supp)</td>
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<td>T32*</td>
<td>Preclinical Training in Biomedical Imaging at Stanford University</td>
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<td>Sylvia Plevritis, PhD</td>
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<td>Breast Cancer Trend Analysis Using Stochastic Simulation</td>
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<td>Computational Modeling of Cancer Biology</td>
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<td>Modeling the Role of Differentiation in Cancer Progression</td>
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<td>Jiuhong Rao, PhD</td>
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<td>OOD-BRET nanosensors for prostate detection and imaging</td>
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<td>Viola Rieke, PhD</td>
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<td>MRI-guided Cardiac Focused Ultrasound Ablation</td>
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<td>Daniel Rubini, MD</td>
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<td>Computerized Quantitative Imaging Assessment of Tumor Burden</td>
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<td>Geoffrey Rubin, PhD</td>
<td>R01</td>
<td>Improving Radiologist Detection of Lung Nodules with CAD</td>
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<td>Brian Rutt, PhD</td>
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<td>Next Generation 7T MRI Platform Upgrade System</td>
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<td>Graham Sommer, MD</td>
<td>R21</td>
<td>MRI-Guided Ultrasound Ablation of Pancreatic Cancer</td>
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<td>Graham Sommer, MD</td>
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<td>Precise MRI-Directed Sonic Ablation of Prostate Cancer</td>
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<td>Daniel Spielman, PhD</td>
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<td>1H MRSI of the Human Brain at 7T</td>
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<td>Metabolic Imaging of the Cardioprotective Effects of Alcohol and ALDH2 Activators</td>
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<td>Shreyas Vasanawala, MD, PhD</td>
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<td>Rapid Robust Pediatric MRI</td>
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<td>Jaeger Willman, MD</td>
<td>R21</td>
<td>Early Detection of Pancreatic Cancer with Targeted Contrast-enhanced Ultrasound</td>
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<td>Biological Insights into Dynamics of Stem Cell Differentiation and Misbehavior</td>
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<td>Joseph Wu, MD, PhD</td>
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<td>Integrated Strategies for Novel Treatment of Myocardial Ischemia</td>
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<td>Joseph Wu, MD, PhD</td>
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<td>Molecular Imaging of Cardiac Stem Cell Therapy</td>
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<td>Joseph Wu, MD, PhD</td>
<td>RC1* (ARRA)</td>
<td>Molecular Imaging of Resident Cardiac Stem Cells</td>
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<td>Joseph Wu, MD, PhD</td>
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<td>Molecular Imaging of Targeted Cardiac Gene Therapy</td>
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<td>Joseph Wu, MD, PhD</td>
<td>R33</td>
<td>Nanostructuring and Molecular Imaging of Engineered Cardiovascular Tissues</td>
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<td>Joseph Wu, MD, PhD</td>
<td>R01*</td>
<td>Re-Education of the Immune System for hES Cell Tolerance</td>
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<td>Gregory Zalewski, MD, PhD</td>
<td>R01</td>
<td>Quantifying Collateral Perfusion in Cardiomyocyte Disease</td>
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**NIH Collaborations (Sub-Contracts)**

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<td>Purdue R01</td>
<td>99mTc-Labelled Cyclic RGD Peptide Tetramers for Breast Cancer Imaging</td>
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<td>Sam Gambhir, MD, PhD</td>
<td>UCLA R01</td>
<td>Multiscale 4-D Imaging of Cells and Tumors in Mice and Humans</td>
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<td>Sam Gambhir, MD, PhD</td>
<td>USC</td>
<td>Multi-Scale Complex Systems Translational Analysis of Response to Therapy (MC-START)</td>
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<td>Sam Gambhir, MD, PhD</td>
<td>Fred Hutch</td>
<td>Ovarian Cancer Early Detection Using Microbubble Contrast Enhanced Ultrasound (CEUS) Targeting Tumor Associated Angiogenesis</td>
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<tr>
<td>Gary Glover, MD</td>
<td>UC Irvine</td>
<td>Functional Magnetic Resonance Imaging in Schizophrenia Treatment</td>
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<tr>
<td>Gary Gold, MD</td>
<td>UCSF</td>
<td>Data Coordinating Center for Osteoarthritis Initiative</td>
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<tr>
<td>Lawrence Hofmann, MD</td>
<td>Wash U</td>
<td>ATTRACT: Industry Portion</td>
</tr>
<tr>
<td>Lawrence Hofmann, MD</td>
<td>Wash U</td>
<td>Pharmacomechanical Catheter-Directed Thrombolysis for Acute DVT-Atract Trial</td>
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<tr>
<td>Daniel Rubin, MD</td>
<td>U Pittsburgh</td>
<td>A Web-Based Portal of Inherited Resources Enabling Clinical and Translational Research Across the CTSA and Beyond</td>
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<td>Daniel Rubin, MD</td>
<td>Northwestern</td>
<td>Annotations and Image Markup Project - Phase I and II</td>
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<td>Daniel Rubin, MD</td>
<td>Emory Univ</td>
<td>In Silico Research Center</td>
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<td>Brigham &amp; Women’s</td>
<td>Neuroimaging Analysis Center (NAC)</td>
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<tr>
<td>Daniel Rubin, MD</td>
<td>UCSF</td>
<td>Ontology-Based Integration of Human Studies Data ICMEP Project</td>
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<tr>
<td>Daniel Rubin, MD</td>
<td>U Pittsburgh</td>
<td>The ODEE Toolkit -software for information extraction and biomedical ontology development</td>
</tr>
<tr>
<td>Daniel Spielman, MD</td>
<td>U Miami</td>
<td>Partnership for MRI Spectroscopic Imaging Data Processing</td>
</tr>
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<td>Daniel Spielman, MD</td>
<td>SRI</td>
<td>Dynamic Metabolic Imaging of Hyperspectral Substrates</td>
</tr>
<tr>
<td>Daniel Spielman, MD</td>
<td>SRI International</td>
<td>In Vivo Diffusion and Spectroscopic Brain Imaging in Alcoholism</td>
</tr>
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<td>Joseph Wu, MD, PhD</td>
<td>SDSU</td>
<td>Engineering Cardiac Progenitor Cells to Enhance Myocardial Regeneration</td>
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**Professional Society & Foundation Supported Research**

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<tr>
<td>Scott Atlas, MD</td>
<td>RSNA</td>
<td>Ultra-High Resolution Clinical Imaging of the Human Medial Temporal Lobe with 7T MRI</td>
</tr>
<tr>
<td>Zhen Cheng, PhD</td>
<td>Melanoma</td>
<td>18F Labelled Rheniumoxides for Pre-clinical PET Imaging of Melanoma Metastases</td>
</tr>
<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>Ben &amp; Myr- Cure</td>
<td>18F PPRG2 PET/CT and MRI Evaluation of Response to Anti-Angiogenesis Therapy in Recurrent Glioblastoma Multiforme (GBM)</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>Doris Duke</td>
<td>Molecular Imaging of Cancer with a Voltage Sensor</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>AAM*</td>
<td>Study Drug: Sodium fluoride F18 Injection</td>
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<tr>
<td>Gary Gold, MD</td>
<td>Arthritis Foundation</td>
<td>Sodium MRI of Post-traumatic Arthritis</td>
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<td>Benjamin Hackel, PhD</td>
<td>ACS*</td>
<td>Novel High Affinity Protein Scaffolds for Molecular Imaging of Tumors</td>
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<td>Shijan Hu, PhD</td>
<td>AHA-California</td>
<td>Transplantation and Imaging of Novel Cardiac Stem Cell Therapy</td>
</tr>
<tr>
<td>Mei Huang, PhD</td>
<td>AHA-California</td>
<td>Novel Non-viral Gene Therapy for Heart Disease</td>
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<tr>
<td>Charles Li, PhD</td>
<td>RSNA</td>
<td>Improved Isotropic 3D FSE Methods for Imaging the Knee</td>
</tr>
<tr>
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<td>MarshRivkin</td>
<td>Early Detection of Ovarian Cancer Using Targeted Microbubble-Enhanced Ultrasound</td>
</tr>
<tr>
<td>John Mackenzie, MD</td>
<td>SPR</td>
<td>Evaluation of Pediatric Diseases with Hyperpolarized Carbon-13 Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>Sam Mazin, PhD</td>
<td>Ewing Marion Kauffman Fnd</td>
<td>Commercialization of PET-Guided Radiation Therapy</td>
</tr>
<tr>
<td>Peter Giulian, MD</td>
<td>SNM</td>
<td>Optionally coupled pulse width modulation PET detectors for combined whole body clinical PET/MR systems</td>
</tr>
<tr>
<td>Andrew Quan, MD</td>
<td>NCCN</td>
<td>Evaluating Sunitinib Therapy in Renal Cell Carcinoma</td>
</tr>
<tr>
<td>Jianhong Rao, PhD</td>
<td>Texas A&amp;M</td>
<td>Development of Fluorescent Probes for In Vivo Imaging of Tuberous Sclerosis</td>
</tr>
<tr>
<td>Jungho Su, PhD</td>
<td>HSF</td>
<td>Imaging mRNA in Synaptic Plasticity</td>
</tr>
<tr>
<td>Daniel Rubin, MD</td>
<td>ACR</td>
<td>American College of Radiology Imaging Network (ACRIN) Committee Agreement Rubin</td>
</tr>
<tr>
<td>Daniel Rubin, MD</td>
<td>RSNA</td>
<td>Enhancing the Radi.Lex Ontology to Enable Biomedical Imaging Research in Neuroimagining</td>
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<tr>
<td>Lewis Shin, MD</td>
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<td>RSNA research seed grant</td>
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<td>Shinya Vashmi, MD, PhD</td>
<td>ISMNM</td>
<td>Non-Contrast-Enhanced Renal MRA Using Multiple Inversion Recovery</td>
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<tr>
<td>David Wang, MD</td>
<td>RSNA</td>
<td>Ultrasound - Mediated Suicide gene Therapy with Molecularly Targeted microbubbles in a murine model for tumor angiogenesis</td>
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<tr>
<td>Juergen Willmann, MD</td>
<td>SOC of GI</td>
<td>Anti-Angiogenic Treatment Assessment in Abdominal and Pelvic Cancer using Molecular Ultrasound: First Step towards Clinical Translation</td>
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<td>Juergen Willmann, MD</td>
<td>Nat. Pancreas Fdn</td>
<td>Development of Novel Translatable Molecular Imaging Approach for Early Detection of Pancreatic Cancer</td>
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<td>Joseph Wu, MD, PhD</td>
<td>MD Anderson</td>
<td>Intracranial 5-fluorouracil and Leucovorin for the Treatment of Neuroendocrine Tumors</td>
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<td>Joseph Wu, MD, PhD</td>
<td>BWF</td>
<td>Molecular and Cellular Mechanisms of Cardiac Regeneration</td>
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<td>Joseph Wu, MD, PhD</td>
<td>AHA-California</td>
<td>Safety and Efficacy of Novel JSPC Derived Cardiomyocytes</td>
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<td>Greg Zaharchuk, MD, PhD</td>
<td>NERF*</td>
<td>Optimizing Arterial Spin Label MRI for the Visualization of Collateral Flow in Moyamoya Disease</td>
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<tr>
<td>Karen Zir, MD</td>
<td>Life Science</td>
<td>Non-Invasive and Real-Time Monitoring of Stem Cells Using Photoacoustic Molecular Imaging in Living Mice</td>
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**California Supported Research**

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<td>Qochen Cao, PhD</td>
<td>UCOP</td>
<td>alpha7-nAChR Targeted Imaging and Therapy of Lung Cancer</td>
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<td>Zhen Cheng, PhD</td>
<td>UCOP</td>
<td>Novel Small Proteins for PET Imaging of Breast Cancer</td>
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<tr>
<td>Rebecca Rakow-Permut, MD, PhD</td>
<td>UCOP</td>
<td>Functional Breast MRI with BOLD Contrast</td>
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<tr>
<td>Joseph Wu, MD, PhD</td>
<td>UCOP</td>
<td>Imaging of Novel Stem Cell Therapy Targeting Breast Cancer</td>
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<tr>
<td>Joseph Wu, MD, PhD</td>
<td>CIRM</td>
<td>In Vivo Imaging of Human Embryonic Stem Cell Derivatives and Tumorigenicity</td>
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### Other Government Supported Research

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<tr>
<td>Lawrence Hofmann, MD</td>
<td>Omnimetics</td>
<td>MedTech, Inc</td>
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<td>Debra Ikeda, MD</td>
<td>ART Advanced</td>
<td>RockTech, Inc</td>
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<tr>
<td>Debra Ikeda, MD</td>
<td>Spectron</td>
<td>Survey of Optical Measures of Breast Tissue in the Clinic</td>
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<tr>
<td>Nishita Kotthary, MD</td>
<td>Siemens Medical Solutions</td>
<td>Clinical Feasibility and Evaluation of RoboPT (Rotational Mammography), Optimal imaging protocol of HCC underlying TACE utilizing DynaCT, &amp; Needle Guided Procedures Utilizing DynaCT, Laser Guidance, and 2DID Registration</td>
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<tr>
<td>Craig Levin, PhD</td>
<td>GE Healthcare</td>
<td>Combined Positron Emission Tomography (PET) Magnetic Resonance (MR) System</td>
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<tr>
<td>Craig Levin, PhD</td>
<td>Philips Healthcare*</td>
<td>GPU-based 3-D List Mode OSEM for ToF PET</td>
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<tr>
<td>Michael Marks, MD</td>
<td>cv3 Neurovascular*</td>
<td>SWIFT-T solitaire FR with the intention for thrombectomy study</td>
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<td>Sandy Nadj, PhD</td>
<td>Kitecure, Inc</td>
<td>Automated Bone Removal for Hand and Neck CTA using Dual Energy CT</td>
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<tr>
<td>Norbert Pepe, ScD</td>
<td>GE Healthcare</td>
<td>Advanced Computed Tomography (CT) Systems and Algorithms</td>
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<td>Andrew Quan, MD</td>
<td>Genentech, Inc</td>
<td>Avastin/18F]-fluorouracil PET/CT Imaging Feasibility Project</td>
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<td>Daniel Rubin, MD</td>
<td>Bose-Allen &amp; Hamilton, Inc</td>
<td>callbiG Imaging Workspace Participant</td>
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<tr>
<td>Daniel Rubin, MD</td>
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<td>callbiG Master Agreement - Subcontract # 95077NBS23</td>
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<td>Daniel Rubin, MD</td>
<td>Bose-Allen &amp; Hamilton, Inc</td>
<td>Imaging Workspace in EV2</td>
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<td>Geoffrey Rubin, MD</td>
<td>Biosense, Inc</td>
<td>Core Lab for Navistar ThermCool Catheter for the Radiofrequency Ablation of Parasymal Atrial Fibrillation</td>
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<td>Virginia Spanwaltes, PhD</td>
<td>AtlasGroup</td>
<td>iRnm Resolution Position Emission Tomography for Enhanced Molecular Breast Cancer Imaging</td>
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<tr>
<td>Daniel Sze, MD, PhD</td>
<td>WL Gore &amp; Assoc, Inc</td>
<td>A Clinical Study Evaluating the Use of the Thoracic EXCLUDER Endoprostheses in the Treatment of Descending Thoracic Aortic Diseases (SUH#-CVR-01)</td>
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<tr>
<td>Daniel Sze, MD, PhD</td>
<td>WL Gore &amp; Assoc, Inc</td>
<td>An Evaluation of the GORE Conformable TAG Thoracic Endoprosthesis for the Primary Treatment of Aneurysm of the Descending Thoracic Aorta</td>
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<tr>
<td>Daniel Sze, MD, PhD</td>
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<td>Evaluation of the GORE TAG Thoracic Endoprosthesis - 45 mm for the Primary Treatment of Aneurysm of the Descending Thoracic Aorta</td>
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<td>Daniel Sze, MD, PhD</td>
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<td>Evaluation of the GORE TAG Thoracic Endoprosthesis for the Treatment of Complex Pathology of the Descending Thoracic Aorta</td>
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<td>Daniel Sze, MD, PhD</td>
<td>WL Gore &amp; Assoc, Inc</td>
<td>Evaluation of the GORE TAG Thoracic Endoprosthesis for Treatment of Descending Thoracic Aneurysms</td>
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<td>Daniel Sze, MD, PhD</td>
<td>WL Gore &amp; Assoc, Inc</td>
<td>The Silver PTX Drug Eluding Vascular Stent in the Above the Knee Femoropopliteal Artery</td>
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<tr>
<td>Daniel Sze, MD, PhD</td>
<td>WL Gore &amp; Assoc, Inc</td>
<td>Treatment IDE for Use of the GORE TAG Thoracic Endoprosthesis in Subjects with Descending Thoracic Aortic Aneurysms Requiring Surgical Repair</td>
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<tr>
<td>Daniel Sze, MD, PhD</td>
<td>Cook Incorporated</td>
<td>Zonare TX2 Thoracic 3DA Endovascular Cath</td>
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### Industry Supported Research

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<tr>
<td>Zhen Cheng, PhD</td>
<td>DOD</td>
<td>Macrophage Stem Cell as Targeted-delivery Vehicle in Breast Cancer</td>
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<tr>
<td>Zhen Cheng, PhD</td>
<td>DOD*</td>
<td>Peptid-Based PET Probes for Prostate Cancer Imaging</td>
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<tr>
<td>Brian Hargreaves, MD</td>
<td>VA</td>
<td>Carotid Compression Study for VA</td>
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<tr>
<td>Gung Liu, PhD</td>
<td>DOD</td>
<td>*Imaging Heart Shock Protein 90 (Hsp90) Activity in Hormone-Refractory Prostate Cancer</td>
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<tr>
<td>Jianghong Ran, PhD</td>
<td>DOD</td>
<td>Enzyme-triggered Polymerization: a new platform for breast cancer imaging</td>
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<tr>
<td>Jianghong Ran, PhD</td>
<td>DOA</td>
<td>Ribozyme-Mediated Imaging of p53 Expression in Breast Tumor Cells</td>
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<tr>
<td>Ame Vandemarroule, PhD</td>
<td>DOD*</td>
<td>Commissioning and Characterizing a dedicated high resolution breast PET camera</td>
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<tr>
<td>Adam de la Zerda, PhD</td>
<td>Siemens Medical Solutions</td>
<td>Early Assessment of Breast Cancer Therapy Responses Using Photonsacoustic Molecular Imaging</td>
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<tr>
<td>Francis Blankenberg, MD</td>
<td>Sibtech, Inc</td>
<td>Targeted Delivery of Lu-177 to tumor vasculature</td>
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<tr>
<td>Sandip Biswal, MD</td>
<td>Kai Pharmaceuticals</td>
<td>Evaluation of the Efficacy of KAI-1678 with Manganese-Enhanced Magnetic Resonance Imaging (MEMRI)</td>
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<tr>
<td>Francis Blankenberg, MD</td>
<td>Genenex, Inc</td>
<td>Choline MRS correlated with Markers of Apoptosis (TUNEL)-biotinylated annexin V &amp; Autophagy (TYPE II cell death)</td>
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<tr>
<td>Francis Blankenberg, MD</td>
<td>Sibtech, Inc</td>
<td>Targeted Delivery of Lu-177 to tumor vasculature</td>
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<td>Francis Blankenberg, MD</td>
<td>Sibtech, Inc*</td>
<td>VEGF-based Targeted Imaging of Tumor Vasculature</td>
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<td>Zhen Cheng, PhD</td>
<td>Ocean NanoTech, LLC</td>
<td>Iron oxide nanoparticle probes for target specific MR molecular imaging</td>
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<td>Rebecca Fahren, PhD</td>
<td>Siemens Medical Solutions</td>
<td>Cardiac Imaging using C-arm CT: EP registration and perfusion</td>
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<tr>
<td>Rebecca Fahren, PhD</td>
<td>Siemens Medical Solutions</td>
<td>Perfusion Imaging using C-arm CG: Brain and Liver</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>Bayer Corporation*</td>
<td>An Open-label, Non-randomized, Multi-center Study to Optimize Image Assessment and Evaluate the Efficacy and Safety of BAY 96-9172 (ZK 601443) - Positron Emission Tomography (PET) for Detection/Exclusion of Cere</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>Scharing AG</td>
<td>Collaborative Research Agreement: Project 1: Tumor Lymphangiosis Imaging Project 2: PET Imaging of Breast Cancer using Fructose Analogues</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>GE Healthcare</td>
<td>Developing Tools for Cell Therapy - specifically cell tracking and quality assurance</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>GE Healthcare</td>
<td>Multimodality Molecular Pre-Clinical Imaging</td>
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<tr>
<td>Sam Gambhir, MD, PhD</td>
<td>Scharing Plough</td>
<td>SCH-XXX in Orthotopic U87 Glioblastoma Model</td>
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<tr>
<td>Gary Gold, MD</td>
<td>GE Company</td>
<td>Advanced MR Applications Development</td>
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<tr>
<td>Lawrence Hofmann, MD</td>
<td>Pfizer Pharmaceuticals</td>
<td>A Safety and Efficacy Trial Evaluating the Use of Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism (CVX18057)</td>
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<tr>
<td>Lawrence Hofmann, MD</td>
<td>Pfizer Pharmaceuticals</td>
<td>A Safety and Efficacy Trial Evaluating the Use of Apixaban in the Treatment of Symptomatic Deep Vein Thrombosis and Pulmonary Embolism (CVX18058)</td>
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</table>
The Center for Biomedical Imaging at Stanford (CBIS), directed by Kim Butts-Pauly, PhD, provides educational and networking opportunities for all groups on campus that have an interest in biomedical imaging applications. Through support from the School of Medicine and the Dean’s Office, the CBIS Advisory Committee is pleased to announce that out of more than 50 applications, 7 projects were allocated seed funding in 2010. The following projects were selected for their innovative, interdisciplinary, and translational potential. For more details of CBIS and the seed funding program, please see: http://cbis.stanford.edu/about/.

### CBIS Seed Funding

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<tr>
<th>PI</th>
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<tbody>
<tr>
<td>Anita Koshy, MD</td>
<td>Internal Medicine</td>
<td>Using imaging to determine how and why Toxoplasma gondii injects chaperone protein it does not invade</td>
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<tr>
<td>Michael Lin, MD, PhD</td>
<td>Pediatrics and Bioengineering</td>
<td>Chemistry-based engineered autocatalytic fluorescent protein for whole-organ imaging in the optical window</td>
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<tr>
<td>Andrew Quinn, MD</td>
<td>Radiology</td>
<td>18F-Sodium Fluoride PET/CT for the pre-surgical evaluation of breast cancer</td>
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<tr>
<td>Mark Schnitzer, PhD</td>
<td>Applied Physics</td>
<td>Integrated fluorescence microscopes based on CMOS image sensors for teaching digital imaging in the microscopy courses at Stanford University</td>
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<tr>
<td>Colin Carpenter, PhD</td>
<td>Radiation Oncology</td>
<td>Tri-modality Molecular Surgical Guidance Integrated into a Laparoscope</td>
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<tr>
<td>Mark Cutkosky, PhD</td>
<td>Mechanical Engineering</td>
<td>Development and testing of tools with opto-thermal actuation for MRI-guided interventions</td>
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<tr>
<td>Michael Hoeh, MD, PhD</td>
<td>Urology</td>
<td>Single Cell Magnetic Resonance Imaging of Infections Using Bacterial Magnetite</td>
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### Collaborators Outside of Stanford

We also enjoy many collaborations with foundations, agencies, institutions, and industry for whose support we are indeed thankful. We look forward to continued success in these collaborative endeavors as well.

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<td>Bayer Corporation</td>
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<td>Biosense, Inc.</td>
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<td>Department of Defense</td>
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<td>Distributed Diagnostic Products, Inc.</td>
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<td>Doris Duke Foundation</td>
<td>Richard M. Lucas Cancer Foundation</td>
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<td>Edward Malin Institute &amp; Foundation</td>
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<td>Schering Plough Research Institute</td>
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<td>Wallenberg</td>
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<td>Weston Havens Foundation</td>
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### Collaborating Stanford Departments

We work with almost three hundred faculty, postdoctoral fellows, students, and research staff from across the University. We wish to thank you all for the friendly, productive collaborations that we enjoy all year long. Stanford departments with whom we have long-standing research projects include the following:

- Anesthesiology and Intensive Care Medicine
- Anesthesiology
- Applied Physics
- Biochemistry
- Bioengineering
- Bio-X
- Cancer Biology
- Cancer Center
- Cardiovascular Surgery
- Chemistry
- Comparative Medicine
- Computer Sciences
- Developmental Biology
- Electrical Engineering
- ENT
- Freeman Spogli Institute
- Genetics
- Health Research and Policy
- Hematology
- Infectious Diseases
- Lucile Packard Children’s Hospital
- Materials Science and Engineering
- Mechanical Engineering
- Medical Informatics
- Medicine
- Microbiology and Immunology
- Molecular and Cellular Physiology
- Neurobiology
- Neurology and Neurological Sciences
- Neurosurgery
- Obstetrics & Gynecology
- Oncology
- Orthopedics/Orthopaedic Surgery
- Otolaryngology
- Palo Alto VA
- Pathology
- Pediatrics
- Pediatrics/Neurology
- Psychiatry and Behavioral Sciences
- Psychology
- Radiation Oncology
- Stanford Center for Biomedical Ethics
- Stroke Center
- Surgery