International Symposium on Metabolic Imaging and Spectroscopy

HONORING THE 100TH BIRTHDAY OF BRITTON CHANCE

JUNE 18-19, 2013

BRB II/III Auditorium

Perelman School of Medicine
University of Pennsylvania

International Symposium on Metabolic Imaging and Spectroscopy

HONORING THE 100TH BIRTHDAY OF BRITTON CHANCE

JUNE 18-19, 2013

BRB II/III Auditorium
Perelman School of Medicine
at the University of Pennsylvania

Contents

Tuesday, June 18, 2013

Lobby and Auditorium, BRB II/III | University of Pennsylvania

REGISTRATION

7:00 A.M. – 7:50 A.M. Breakfast and Registration

WELCOME AND INTRODUCTION

7:50 A.M. **Lin Z. Li, Ph.D.**
University of Pennsylvania

Mitchell Schnall, M.D., Ph.D.
University of Pennsylvania
Life, Times, and Legacy of Britton Chance

KEYNOTE LECTURE

8:00 A.M. **Kevin Brindle, Ph.D.**
University of Cambridge; Cancer Research UK, Cambridge Research Institute
Studies of tumor metabolism using hyperpolarized ^{13}C magnetic resonance spectroscopy

CANCER (I)

Moderator: **R. Nick Bryan, M.D., Ph.D.**

8:45 A.M. **Celeste Simon, Ph.D.**
University of Pennsylvania
Cancer cell adaptation to metabolic stress

9:10 A.M. **Bruce Tromberg, Ph.D.**
University of California, Irvine, California
Bedside optical imaging of tissue perfusion and metabolism

9:35 A.M. **David Mankoff, M.D., Ph.D.**
University of Pennsylvania
Glucose metabolism and perfusion in human breast cancer measured by imaging: an index of therapeutic resistance?

10:00 A.M. Coffee Break

BLOOD VOLUME, FLOW, OXYGENATION, AND HYPOXIA

Moderators: **Jerry Glickson, Ph.D.** / **Ravinder Reddy, Ph.D.**

10:15 A.M. **Harold Swartz, M.D., Ph.D.**
Geisel Medical School at Dartmouth, Hanover, New Hampshire
Repeated measurements of pO_2 in human subjects

10:40 A.M. **Felix Wehrli, Ph.D.**
University of Pennsylvania
Time-resolved MRI oximetry for quantifying $CMRO_2$ and vascular reactivity

11:05 A.M. **Arjun Yodh, Ph.D.**
University of Pennsylvania
Optical cerebral blood flow and hemoglobin concentration monitoring in brain

11:30 A.M. **Eiji Takahashi, Ph.D.**
Saga University, Japan
Imaging the gradients of oxygen in cells and tissues using GFP

FLASH HIGHLIGHTS OF POSTERS

11:55 A.M. Introduction to selected posters by **Rong Zhou, Ph.D.** / **David Busch, Ph.D.**

LUNCH BREAK

12:20 P.M. – 1:35 P.M. Lunch break and poster viewing

GLYCOLYSIS

Moderator: **David Boas, Ph.D.**

1:35 P.M. **Nimmi Ramanujam, Ph.D.**
Duke University
Simultaneously quantifying tumor oxygenation and glycolysis in vivo via quantitative spectroscopy

2:00 P.M. **Abass Alavi, M.D., Ph.D.**
University of Pennsylvania
Revolutionary impact of FDG-PET imaging on biological research and practice of medicine

2:25 P.M. **Jerry D. Glickson, Ph.D.**
University of Pennsylvania
Tumor acidification as a treatment approach

2:50 P.M. Coffee Break

LIVER / LUNG / KIDNEY

Moderator: **Xingde Li, Ph.D.**

3:00 P.M. **Morris Birnbaum, M.D., Ph.D.**
University of Pennsylvania
The regulation of hepatic metabolism

3:25 P.M. **Steve Kadlececk, Ph.D.**
University of Pennsylvania
Measurement and modeling of lung metabolism using hyperpolarized ^{13}C

3:50 P.M. **Yu Chen, Ph.D.**
University of Maryland
Intra-operative assessment of transplant kidney function using optical methods

NOVEL TECHNIQUES (1)

Moderator: **Kyung Kang, Ph.D.**

4:15 P.M. **Linda Powers, Ph.D.**
University of Arizona
Real-time in-situ detection of microbes – from discovery to diagnostics

4:40 P.M. **Eva Sevick-Muraca, Ph.D.**
The University of Texas Health Science Center at Houston
Discovery in translation: near-infrared fluorescence lymphatic imaging

5:05 P.M. **Xingde Li, Ph.D.**
Johns Hopkins University
Multiphoton micro imaging

PANEL: KEY ISSUES IN METABOLIC IMAGING / SPECTROSCOPY RESEARCH

Moderator: **Bruce Tromberg, Ph.D.**

5:30 P.M. – 6:15 P.M.

Emily Conant, M.D., University of Pennsylvania
Jeffrey Evelhoch, Ph.D., Merck Research Laboratories
David Mankoff, M.D., Ph.D., University of Pennsylvania
Eva Sevick-Muraca, Ph.D., The University of Texas Health Science Center at Houston
Stephen Tang, Ph.D., University City Science Center
Huiming Zhang, Ph.D., National Cancer Institute

RECEPTION

7:00 P.M. – 9:00 P.M. American Philosophical Society
Benjamin Franklin Hall
427 Chestnut Street, Philadelphia, PA

SPEAKERS:
Clyde F. Barker, M.D., American Philosophical Society
Helen Davies, Ph.D., University of Pennsylvania
Mark R. Chance, Ph.D., Case Western Reserve University
Tomoko Ohnishi, Ph.D., University of Pennsylvania
John M. Maris, M.D., Children's Hospital of Philadelphia
Duane F. Bruley, Ph.D., University of Maryland, Baltimore

Wednesday, June 19, 2013

REGISTRATION

7:00 A.M. – 7:50 A.M. Breakfast and Registration

INTRODUCTION

7:50 A.M. **Arjun Yodh, Ph.D.**
University of Pennsylvania

KEYNOTE SPEECH

7:52 A.M. **Douglas C. Wallace, Ph.D.**
Children's Hospital of Philadelphia
Mitochondrial medicine and metabolic diseases

MITOCHONDRIA / REDOX STATE

Moderator: **Shoko Nioka, M.D., Ph.D. / Lihong Wang, Ph.D.**

8:35 A.M. **Robert S. Balaban, Ph.D.**
National Institute of Heart, Lung, Blood Institute, Maryland
The systems biology of the mitochondria

9:00 A.M. **Lin Z. Li, Ph.D.**
University of Pennsylvania
Imaging redox state as diagnostic/prognostic biomarkers

9:25 A.M. **Murali Krishna Cherukuri, Ph.D.**
National Cancer Institute
Nitroxide-based EPR/MRI imaging of redox status in vivo

9:50 A.M. **Chris Cooper, Ph.D.**
University of Essex
NIR spectroscopy of cytochrome c oxidase

10:15 A.M. Coffee break

CANCER (2)

Moderator: **Hanli Liu, Ph.D.**

10:30 A.M. **Peter Vaupel, M.D., Ph.D.**
University Medical Center, Mainz, Germany
Hypoxia in tumors: Pathogenesis-related classification, characterization, and clinical implications

10:55 A.M. **John Kurhanewicz, Ph.D.**
University of California San Francisco, California
Hyperpolarized ^{13}C MR of prostate cancer in the clinic

11:20 A.M. **Brian Pogue, Ph.D.**
Dartmouth College
Receptor concentration imaging in vivo: imaging molecules not perfusion

FLASH HIGHLIGHTS OF POSTERS

11:45 P.M. Introduction to selected posters by **Brian Saltzberg, Ph.D.** / **He N. Xu, Ph.D.**

LUNCH BREAK

12:15 P.M. - 1:35 P.M. Lunch break and poster viewing

BRAIN

Moderators: **Qingming Luo, Ph.D.** / **Joseph LaManna, Ph.D.**

1:35 P.M. **Hanli Liu, Ph.D.**
University of Texas, Arlington
Brain atlas-guided volumetric diffuse optical tomography to study human cognitive functions

2:00 P.M. **Qingming Luo, Ph.D.**
Huazhong University of Science and Technology; Britton Chance Center for Biomedical Photonics, China
Optical imaging: from brain function to neural connectivity

2:25 P.M. **Maria Angela Franceschini, Ph.D.**
Massachusetts General Hospital, Harvard Medical School
Neonatal applications of advanced NIRS

2:50 P.M. **John Detre, M.D.**
University of Pennsylvania
CBF as a biomarker of brain function

3:15 P.M. **David Boas, Ph.D.**
Harvard Medical School, Massachusetts General Hospital, Massachusetts
Optical microscopy of cerebral energy metabolism

3:40 P.M. **Michelle Puchowicz, Ph.D.**
Case Western Reserve University
Metabolic effects of ketosis on cerebral glucose consumption

4:05 P.M. Break

NOVEL TECHNIQUES (2)

Moderator: **Andrew Tsoukas, Ph.D.**

4:20 P.M. **Ravinder Reddy, Ph.D.**
University of Pennsylvania
Recent advances in CEST-MRI

4:45 P.M. **Warren Warren, Ph.D.**
Duke University
Improving contrast in molecular imaging: long-lived hyperpolarized magnetic resonance and nonlinear optics

5:10 P.M. **Lihong Wang, Ph.D.**
Washington University in St. Louis
Photoacoustic tomography: Ultrasonically breaking through optical diffusion and diffraction limits

PRESENTATION OF POSTER AWARDS AND SUMMARY

5:35 P.M. **Arjun Yodh, Ph.D. / Brian Pogue, Ph.D. / Lin Li, Ph.D.**

Lecture abstracts

Revolutionary impact of FDG-PET imaging on biological research and practice of medicine

Presenter: Abass Alavi
abass.alavi@uphs.upenn.edu

Abass Alavi, MD, MD (Hon), PhD (Hon), DSc (Hon)
Department of Radiology, University of Pennsylvania
Philadelphia, PA, 19104
United States

Currently, positron emission tomography (PET) is considered the fastest growing medical imaging modality with enormous potential for conducting research and providing patient care. This revolution is mainly due the introduction of FDG, hybrid PET/CT, and the approval by the FDA/CMS for certain clinical applications. Over the past 3 decades, FDG-PET has been a driving force for pushing molecular imaging to a prominent position in the 21st century. Attempts have been made to introduce a multitude of other tracers to overcome the perceived deficiencies of FDG with regard to its specificity and sensitivity in certain cancers. However, research has demonstrated that these tracers do not deliver more than what is achievable with FDG alone. FDG is responsible for the rise and progress of PET and PET/CT in many domains. In fact, the introduction of FDG has resulted in making molecular imaging a distinct entity in medicine. The application of novel quantitative techniques, including multiple-time-point imaging, partial volume correction and measuring global disease activity, have substantially enhanced the role of FDG-PET imaging in many settings. Likely, PET/MRI will become a powerful modality in assessing CNS disorders, hepatic abnormalities, and musculoskeletal diseases. At this point, we have only scratched the surface. I have to point out that without the introduction of FDG, PET imaging would have remained as pure research tool, and as such, it would have remained confined to only major research oriented institutions around the world.

Studies of tumour metabolism using hyperpolarized ^{13}C magnetic resonance spectroscopy

Presenter: Kevin Brindle
kmb1001@cam.ac.uk

Kevin M. Brindle
Departmment of Biochemistry and CRUK Cambridge Institute, University of Cambridge
Cambridge, Cambridgeshire, CB2 0RE, United Kingdom

We have been developing methods for detecting the early responses of tumours to therapy, including magnetic resonance (MR) imaging of tumour cell metabolism using hyperpolarized ^{13}C-labelled cell metabolites. Nuclear spin hyperpolarization can increase sensitivity in the MR experiment by >10,000x. We have shown that exchange of hyperpolarized ^{13}C label between lactate and pyruvate can be imaged in mouse tumour models and that this flux is decreased post-treatment. We showed that hyperpolarized [1,4-^{13}C]fumarate can be used to image tumour cell necrosis post treatment and that both polarized pyruvate and fumarate can be used to detect early responses to anti-vascular and anti-angiogenic drugs. Fumarate can also be used to detect necrosis in other tissues, such as the kidney. Tissue pH can be imaged from the ratio of the signal intensities of hyperpolarized $H^{13}CO_3$- and $^{13}CO_2$ following intravenous injection of hyperpolarized $H^{13}CO3^-$ and tumour redox state can be determined by monitoring the oxidation and reduction of [1-^{13}C]ascorbate and [1-^{13}C]dehydroascorbate respectively. Related to this, we have shown that cytoplasmic lipid droplets, which give an intense 1H MR signal that can be detected *in vivo*, are a reflection of intramitochondrial oxidative stress. More recently we have shown that we can monitor tumour glycolysis by measuring the conversion of hyperpolarized [U-2H, U-^{13}C]glucose to lactate. Labelled lactate production was higher in the tumour than in surrounding normal tissue and was markedly decreased at 24 h after treatment with a chemotherapeutic drug.

Intra-operative assessment of transplant kidney function using optical methods

Presenter: Yu Chen
yuchen@umd.edu

Yu Chen, Peter Andrews, Hsing-Wen Wang, and Jerry Wierwille
A. James Clark School of Engineering, University of Maryland, College Park, MD, 20742
United States

The extent of acute tubular necrosis (ATN) present in the renal tubules may provide valuable prognosis regarding post-transplant function of donor kidneys. We use optical coherence tomography (OCT) to access the degree of ATN in donor kidneys. During ongoing clinical trials, we image harvested donor kidneys with hand-held OCT probe both while the kidney is being stored in sterile ice bath prior to its transplantation, and in situ following its reimplantation into the recipient. We are able to effectively image through the intact human kidney connective tissue capsule and see 4-5 underlying layers of uriniferous tubules and associated glomeruli. After transplantation and following revascularization of this same donor kidney, Doppler OCT was performed to detect renal blood flow as well as morphological features of the transplanted kidney. The status of the uriniferous tubules correlated well with the post-transplant renal function. That is, donor kidneys with the most patent (i.e., open) tubule lumens both prior to and following transplantation had the best post-transplant renal function. However, when the tubule lumens appeared shrunken or lost due to ischemic associated damage to the lining cells (i.e., ATN), post-transplant renal function either did not return to normal values or exhibited a delayed return to normal. This kind of timely, global, non-invasive, real-time histopathological perspective of donor kidneys is not possible when using the invasive, potentially damaging and artifact-prone procedure of excising biopsies. The foregoing observations suggest that OCT may provide important prognostic information regarding the status of donor kidneys.

Imaging of anti-angiogenic drug-induced transient shift in redox status and energy metabolism in tumor bearing mice

Presenter: Murali Krishna Cherukuri
murali@helix.nih.gov

Murali Krishna Cherukuri and James B. Mitchell
Radiation Biology Branch, Center for Cancer Research, NCI, NIH
Bethesda, MD, 20892-1002
United States

Anti-angiogenic therapies of solid tumors frequently proceed in two steps; transient normalization of structurally and functionally aberrant tumor blood vessels with increased blood perfusion, followed by pruning the tumor blood vessels and resultant shutdown of nutrients and oxygen delivery required for tumor growth. Conventional anatomic or vascular imaging is impractical or insufficient to distinguish the two steps of tumor response to anti-angiogenic therapies. Herein, we investigated that non-invasive imaging of tumor redox state and energy metabolism can be early surrogate markers for the transient vascular normalization process. Daily treatment of squamous cell carcinoma (SCCVII) tumor bearing in mouse with a multi-tyrosine kinase inhibitor sunitinib resulted in rapid decrease in tumor microvessel density and suppression of tumor growth. Electron paramagnetic resonance oxygen imaging showed transient increase in tumor oxygenation 2-4 days following sunitinib treatment, implying improved tumor perfusion. During this time window of vascular normalization, magnetic resonance imaging (MRI) of the redox state using an exogenously administrated nitroxide probe and hyperpolarized ^{13}C MRI of energy metabolic flux of pyruvate/lactate couple revealed oxidative shift in tumor redox state. Multimodal imaging of the particular redox sensitive metabolic couples in tumors could serve as non-invasive surrogate makers for distinguishing different stages in the course of anti-angiogenic treatment.

NIR spectroscopy of cytochrome *c* oxidase

Presenter: Chris Cooper
ccooper@essex.ac.uk

C.E. Cooper, Z. Rong, I. Tachtsidis, M. Tisdall, T. Moroz, B. Jelfs, M. Banaji,
J. Panovska-Griffiths, D. Highton, C. Kolyva, A. Ghosh, M. Smith and C.E. Elwell
School of Biological Sciences, University of Essex
Colchester, Essex, CO4 3SQ
United Kingdom

Mitochondrial cytochrome *c* oxidase (CCO) is responsible for over 95% of the body's oxygen consumption and is essential for the efficient generation of ATP. The redox state of CCO is thus a marker of cellular energetics that could potentially yield useful real time information about oxygen metabolism and hypoxia. Ever since the work of the late Frans Jöbsis in the 1970s there has therefore been great interest in the measurement of the CuA near infrared (NIR) signal of CCO, theoretically detectable in the human subject via a band centred at 830 nm. Britton Chance was a pioneer in the study of cytochrome redox states, his 1956 papers with Williams being the semninal contribution to the field. However, he was always sceptical about the ability to distinguish *in vivo* the small CuA signal from the much larger concentration changes in the hemoglobin NIR chromophores.Nevertheless the CuA 830 nm feature remains the only mitochondrial signal measurable in the adult human brain at the bedside. We have embarked on a research program to re-evaluate its importance using a combination of phase and mutliwavelenth multi-distance broadband CCD systems to optimise the optical signal. We then interprtet the measured redox state changes using a dynamic systems model. In this presentation we will report data from adult volunteers and patients who have suffered traumatic brain injury; we demonstrate that, when compared to hemoglobin signals, CCO changes are a more reliable measure of oxygen delivery and aerobic metabolism.

CBF as a biomarker of brain function

Presenter: John Detre
detre@mail.med.upenn.edu

John A. Detre, MD
Department of Neurology and Radiology, University of Pennsylvania
Philadelphia, PA, 19104
United States

The brain is a highly perfused organ, receiving approximately 20% of the cardiac output. Regional cerebral blood flow (CBF) is tightly coupled to regional brain function, though the precise mechanisms for this coupling remain unknown. Accordingly, CBF can be used as a biomarker of regional brain function at rest, in response to sensorimotor or cognitive tasks, in disease states, or to assess the effects of pharmacological therapies and other interventions. A variety of methods exist for monitoring of CBF *in vivo*, including noninvasive methods based on magnetic resonance and optical signals. This presentation will review the measurement of CBF, with a focus on arterial spin labeled perfusion MRI, and its applications in basic and clinical neuroscience.

Neonatal applications of advanced NIRS

Presenter: Maria Angela Franceschini
mari@nmr.mgh.harvard.edu

Harvard Medical School, Massachusetts General Hospital
Athinoula A. Martinos Center for Biomedical Imaging
Charlestown, MA 02129
United States

With the cause of perinatal brain injuries still unclear and the potential role of hemodynamic instability in their etiology, bedside monitoring ofneonatal cerebral hemodynamics with standard values as a function of age are needed. Because neurons are the primary consumer of oxygen, estimates of reduced cerebral oxygen consumption ($CMRO_2$) are also needed. Continuous wave near infrared spectroscopy, although now a common non-invasive measure of oxy- and deoxy-hemoglobin concentrations, neither allows absolute measurements nor measures cerebral blood flow, both of which are required for $CMRO_2$ estimates. We combined frequency domain near infrared spectroscopy (FD-NIRS) measures of hemoglobin oxygenation (SO_2) and cerebral blood volume (CBV) with diffusion correlation spectroscopy (DCS) measures of cerebral blood flow index (CBFi) and resulting estimates of $CMRO_2$ for a comprehensive hemodynamic assessment of the normal and injured developing brain.

Imaging redox state as diagnostic/prognostic biomarkers

Presenter: Lin Z. Li
linli@mail.med.upenn.edu

Lin Z. Li
Department of Radiology, University of Pennsylvania
Philadelphia, PA, 19104
United States

Redox state is a key mediator in many biological processes including metabolism, growth, survival, apoptosis, gene expression and signaling activities. In this presentation, I will review our work on developing and utilizing redox imaging techniques to probe the redox state *ex vivo* and *in vivo* to identify redox imaging biomarkers that may be useful for clinical diagnosis and prognosis of cancer. The key technique employed is the Chance redox scannerthat can image the mitochondrial redox state in tissue *ex vivo* at 3D submillimeter resolution. Redox scanning has demonstrated for the first time that cancer transformation and progression to metastasis are correlated with a more oxidized and heterogeneous mitochondrial redox state in various xenograft and transgenic mouse models of cancer including human melanoma, breast cancer, colon cancer, and pancreatic premalignancy. More recently we have obtained clinical data from breast cancer patients indicating redox indices may provide diagnostic/prognostic biomarkers. In addition, I will present our latest progress in developing NMR methods for non-invasive imaging of redox state *in vivo* including hyperpolarized ^{13}C-NMR and CEST-MRI (chemical exchange saturation transfer- MRI).

Multiphoton micro imaging

Presenter: Xingde Li
xingde@jhu.edu

Wenxuan Liang, Gunnsteinn Hall, Yuying Zhang, Kartikeya Murari, Jiefeng Xi,Meredith Akins, Ming-Jun Li, Zaver Bhujwalla, Kristine Glunde, Katherine Luby-Phelps, Mala Mahendroo, and Xingde Li
Biomedical Engineering, Johns Hopkins University
Baltimore, MD, 21295, United States

Nonlinear optical microscopy, such as two-photon fluorescence (TPF) and second harmonic generation (SHG) microscopy, is a powerful high-resolution imaging technology commonly used for basic and applied research. However, the scope of its *in vivo* clinical application is very limited due to the bulky microscope imaging platform and thus inaccessibility to many organs (except skin). Recent years have witnessed rapid advances in developing miniature TPF/SHG endomicroscopes. This talk will briefly review the development of the field. Since the first all-fiber-optic scanning TPF endomicroscope reported by our group in 2006, many technical and engineering challenges have been identified and overcome. The scanning head is the key component in the nonlinear endomicroscopy technology, and in our design, it consists of 1) a specially designed double-clad fiber for delivery the femtosecond excitation light and effective collection of the nonlinear signal, 2) a compact and fast 2D beam scanner, and 3) a micro compound objective lens. High-quality submicron endomicroscopy TPF/SHG imaging of biological tissues is possible without need for staining. Some representative TPF and SHG images related to GI tissue viability (under ischemia during transplantation), breast cancer detection, and preterm birth risk assessment etc. will be presented. The results suggest the potential of visualizing tissue histology in situ, *in vivo* and in real time with the nonlinear endomicroscopy technology based on intrinsic tissue metabolic (such as NADH and FAD) and structural (such as collagen) biomarkers. Other potential applications such as brain function imaging on live animals will also be discussed.

Brain atlas-guided volumetric diffuse optical tomography to study human cognitive functions

Presenter: Hanli Liu
hanli@uta.edu

Hanli Liu
Bioengineering, University of Texas at Arlington
Arlington, TX, 76012, United States

Functional near-infrared spectroscopy (fNIRS) is a non-invasive imaging technique which can measure cerebral oxygenation changes induced by brain activations. Diffuse optical tomography (DOT), a variant of fNIRS with multi-channel measurements, has demonstrated the ability to image or map human brain activities on to a 3D standard human brain atlas. The spatial resolution and image accuracy of volumetric DOT are significantly enhanced by combining brain atlas-guided DOT with voxel-based general linear model. Consequently, this emerging neuroimage tool provides researchers with unique opportunities to study human cognitive functions that may reveal particular cognitive deficits associated with specific neurological disorders. In this talk, we will report our recent development on implementing brain-atlas-based 3D DOT, followed by volume-rendered brain activation images of the prefrontal cortex (PFC) in response to several neuropsychological tests (Digit Span and Stroop test) and an established risk-decision making paradigm. The study with the latter paradigm allows us to conclude that the dorsal lateral prefrontal cortex acts differently between genders when they make risk decisions. While the results show a great promise of using 3D DOT to shed light on human cognitive functions, it is also of challenge since PFC is very complex and involves many cognitive and affective functions. It is difficult to isolate a particular cortical region when performing a given cognitive task. Also, interplay or interconnection between the PFC and other parts of the cortical areas may need to be carefully considered when we interpret the underlying meanings of the observed DOT images.

Glucose metabolism and perfusion in human breast cancer measured by imaging: an index of therapeutic resistance?

Presenter: David Mankoff
david.mankoff@uphs.upenn.edu

David A Mankoff
Department of Radiology, University of Pensylvania
Philadelphia, PA, 19104
United States

In most normal organs, metabolic demand and tissue blood flow are tightly coupled and closely regulated. This is not necessarily the case for cancer, where aberrant metabolism and a poorly regulated tumor vasculature may not provide the tight control of tissue perfusion and metabolism that is characteristic of normal organs. The development of quantitative imaging tools for measuring tumor perfusion and glucose metabolism provided the opportunity to study this phenomenon in patients with cancer undergoing treatment. The talk will review a series of observations regarding breast cancer blood flow and glucose metabolism made using quantitative ^{15}O-water and ^{18}F-fluorodeoxyglucose (FDG) PET in patients with locally advanced breast cancer undergoing pre-surgical chemotherapy. These studies uncovered patterns of pre-therapy blood flow and glucose metabolism that are highly predictive of therapeutic resistance and poor patient outcome, seen as a quantitative mismatch between tumor blood flow and glucose metabolism. These early findings have now been matched by similar findings in a variety of cancer types, and using a variety of quantitative imaging methods. Finding in cancer are also similar to patterns seen in hibernating myocardium. Recent work has identified a predilection for blood flow mismatch for certain subtypes of breast cancer, and ongoing work is seeking to identify mechanisms underlying these findings, including current and planned work with novel tracers of metabolism. This talk will review observations made by quantitative PET and discuss future studies directing to a better understanding of the associated biology and the therapeutic implications of the findings.

Real-time in-situ detection of microbes – from discovery to diagnostics

Presenter: Linda Powers
lsp@ece.arizona.edu

L. Powers and W. Ellis, Jr.,
Electrical and Computer Engineering and Biomedical Engineering
The University of Arizona
Tucson , Arizona, 85721
United States

Currently, methods do not exist for the real-time detection and quantification of microbes in the environment or the detection and identification of pathogenic organisms in clinical samples. We have developed technologies which overcome these limitations that are based inpart on the early work of Britton Chance [Chance, The Harvey Lectures, Series 49, 1953-54 (1955), 145 and Chance and Theorell, J. Biol. Chem. 2234 (1959), 3044]. The detection and quantification of microbes (total microbial load) is based on the intrinsic fluorescence of microbial metabolites and protein cofactors which provides an estimate of the total microbial load as well as the relative distribution of live cells, dead cells, and endospores. Detection limits of handheld instruments are as low as a few microbes per L in water, per cm^2 on abiotic surfaces, and per mL in body fluids. This technology has been applied to the in-situ measurements of sub-glacial (Svalbard, Norway), volcanic (Mount Kilimanjaro, Tanzania), and high desert (Atacama Desert, Chile) microbial communities, as well as the efficacy of disinfection of contact lenses, water quality, efficacy of surface sterilization, and food contamination. Recently, we have developed point-of-care disposable diagnostics for the identification of blood-borne pathogens from 1 mL of fresh whole blood with surface-tethered, small molecule ligands. Quantification is based on the intrinsic fluorescence of captured cells.

Receptor concentration imaging *in vivo*: imaging molecules not perfusion

Presenter: Brian Pogue
brian.w.pogue@dartmouth.edu

Brian W Pogue, Kim S. Samkoe, Kenneth Tichauer, Jason Gunn, Scott C. Davis
Engineering, Dartmouth College
Hanover, NH, 3755, United States

Cancer imaging is largely dominated by vascular perfusion and leakage, and the idea that molecular receptor/inhibitor imaging could be used to guide therapy is still largely unsuccessful. The idea that receptor expression could be used to guide more direct surgical intervention has not been all that successful to date, but will change with availability of clinical fluorescence imaging systems. Complementary approaches must also be developed to observe molecular reporter signals without the vascular delivery and lymphatic blockage effects dominating the image.The way forward in improving the evaluation of drug efficacy in preclinical studies is to quantify both drug delivery and drug binding in more expansive, realistic populations of tumor cell line xenografts. Recently we have shown that by imaging the uptake of a reference (untargeted) imaging agent along with a targeted imaging agent, it is then possible to calculate an image of the bound concentration of a molecular agent. Compartmental modeling studies show that with either static images or parametric temporal analysis allows recovery of images of just the receptor concentration *in vivo*. Imaging receptor concentration and the targeted uptake of molecular tracers provides direct *in vivo* assessment of new drug efficacy, and can allow imaging at early times after injection and at microdoses. This concept extends to human use as well and RCI could be used to guide surgery once targeted fluorescent agents gain FDA approval. The role of using molecular binding to guide surgery would open up the era of molecular-guided surgery in a meaningful manner.

Metabolic effects of ketosis on cerebral glucose consumption

Michelle Puchowicz
map10@case.edu

Michelle Puchowicz, Ph.D.
Department of Nutrition, Case Western Reserve University, Cleveland, Ohio, United States

The mammalian brain is completely reliant on a constant delivery of oxygen and glucose substrate through the coupling of cerebral blood flow to metabolic rate. Our complete understanding of the regulation and coupling of glucose consumption to oxidative metabolism in brain is important to discerning the pathophysiology of "metabolic related" diseases. Mammalian cells consume glucose as an oxidative substrate through glycolysis by producing pyruvate. Under aerobic conditions the entry of pyruvate into the citric acid cycle results in its complete oxidation to CO_2 and H_2O [via the electron transport chain]. The coupling of these processes to oxidative phosphorylation (OXPHOS) under the driving conditions of energy demand by the cell, results in the liberation of free energy as ATP. Dysfunctions in any of these processes result in pathology or cell death. Glucose is the major metabolic fuel for brain, but alternate energy substrates such as ketone bodies can serve as efficient metabolic fuel sources. This is especially important under certain nutritional conditions, such as with fasting, starvation, feeding of a ketogenic diet (high fat, carbohydrate restricted) and development. Clinicians and investigators have been interested in ketosis as a therapeutic regime for the treatment of hypoglycemia, seizure disorders, Alzheimer's, Parkison's, Freidreich's Ataxia and ALS, as well as part of cancer and post-ischemia treatment regimes.

We have previously shown neuroprotection in a rat model of ketosis following middle cerebral artery occlusion and continue to investigate the metabolic mechanisms related to the effects of ketosis on neuroprotection. We purport that ketosis plays two roles in neuroprotection, through the sparing of the glucose oxidation and the other through the stabilization of HIF1-alpha. Our rationale is that cerebral oxidation of ketone bodies is beneficial through the stabilization of energy metabolism by way of substrate partitioning of glucose and citric acid cycle intermediates while maintaining ATP turnover. Our studies using stable isotopomer analysis supports our rationale that ketosis reduces glucose consumption and partitions oxidative metabolism towards ketone body consumption. A shift in carbon flux via the citric acid cycle is a potential metabolic link between the effect of ketosis and neuroprotection. Using PET imaging analysis we have measured ~10% decreases in glucose consumption (CMRglc) for each 1mM increase of blood ketone bodies in brain of ketotic rats. It is not clear whether the decrease in CMRglc is due to a decrease in ATP demand ($CMRO_2$) or less oxygen efficiency. Developing a mathematical model of oxidative metabolism in brain might reveal that during complete oxidation of ketone bodies, total ATP production remains unchanged (relative to glucose oxidation) but the rates of O2 consumption increase. Future work on investigating the metabolic effects of ketosis on the partitioning of energy metabolism, as well as the mechanistic link between HIF1-alpha and neuroprotection is presented.

Simultaneously quantifying tumor oxygenation and glycolysis *in vivo* via quantitative spectroscopy

Presenter: Nimmi Ramanujam
nimmi@duke.edu

Nimmi Ramanujam, PhD
Department of Biomedical Engineering, Duke University
Durham, North Carolina, 27708
United States

An important hallmark of most cancers is enhanced glucose uptake. There is conclusive proof that certain tumors exhibit this enhanced glucose uptake even in the presence of oxygen. Such an aerobic glycolysis phenotype provides a growth advantage to tumors and causes tumor resistance to therapy and development of metastases. Although PET imaging of radiolabeled FDG is used clinically for detecting and staging cancers, it does not provide information regarding blood flow and oxygenation, both of which are required for determining the presence of an aerobic glycolysis phenotype and understanding tumor response to therapy. Our lab has developed a fast and portable optical spectrometer and a series of algorithms to perform quantitative optical spectroscopy of tumor oxygenation and blood volume *in vivo*. This talk will focus on the development of an optical spectroscopy-based toolbox for simultaneously measuring oxygenation and glucose uptake in tumors. Glucose uptake in tumors is measured using 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxy-d-glucose (2-NBDG), a fluorescent glucose analog. We will show that optical spectroscopy is capable of measuring turbidity-free intrinsic fluorescence *in vivo* which is linearly related to the underlying fluorophore concentrations and that a combination of 2-NBDG fluorescence and oxygen saturation as measured using optical spectroscopy is sensitive to changes in tissue metabolic demand.

Discovery in translation: near-infrared fluorescence lymphatic imaging

Eva Sevick-Muraca
eva.sevick@uth.tmc.edu

Center for Molecular Imaging, University of Texas Health Science Center
Houston, TX 77030
United States

In efforts to qualify the sensitivity of near-infrared fluorescence (NIRF) imaging instrumentation in humans prior to "first-in-humans" molecular imaging studies, we accidentally discovered the ability to dynamically image lymphatic function and architecture (Sevick-Muraca, Ann Rev. Med., 2012). More recently, we have begun to image patients with disorders in which lymphatics are suspected to play a role. Recently we used NIRFLI and confirmatory radiographic lymphangiography in a Parkes Weber Syndrome (PKWS) patient found to have an early frameshift deletion in RASA1 by whole exome sequencing (Burrows, et al., PNAS, 2013 in press). Abnormal lymphatic vasculature was imaged in the leg presenting with the vascular lesion as well as in the unaffected leg of the PKWS subject. Lymph that drained the legs was transported to the inguinal lymph nodes, but drained atypically into the abdomen and into dermal lymphocele-like vesicles on the groin. Dermal lymphatic hyperplasia and dilated vessels were also observed in Rasa1 deficient mice with subsequent development of chylous ascites and chylothorax (Lapinski, et al., JCI, 2012). These studies show that the RASA1 mutation is responsible for the aberrant lymphatic architecture and functional abnormalities visualized in the PKWS subject and in the animal model. Other lymphatic disorders involving different gene mutations in the same signaling pathways are under investigation. Our method to combine investigatory NIRFLI for accurate phenotyping and whole exome sequencing for unbiased genotyping may allow for the study of molecular mechanisms of lymphatic involvement in disorders not otherwise associated with the lymphatic circulatory system.

Repeated measurements of pO_2 in human subjects

Presenter: Harold Swartz
harold.m.swartz@Dartmouth.edu

Harold Swartz, Benjamin Williams, Lesley Jarvis, Bassem Zaki, Huagang Hou, and Nadeem Khan
Department of Radiology, Dartmouth College
Lebanon, NH, 3766
United States

The level of oxygen in a tumor is one of the most important factors that affect the response to therapy. Patients vary in their baseline tumor PO_2 and the level of tumor oxygen changes with disease progression and with therapy in a complex and unpredictable manner. Direct measurements are needed to follow it repeatedly. We have developed an approach, based on electron paramagnetic resonance (EPR). We aim to provide quantitative measurements which will aid physicians in the characterization of disease status and the effects of therapeutic measures, so that treatments can be applied with optimal effectiveness by taking into account the oxygen-dependent aspects of the therapy. The overall goal is to enhance clinical outcomes. Tumor oximetry measurements have been performed in tumor tissues of >12 patients during courses of radiation and chemotherapy. Tumor types include melanoma, basal cell, soft tissue sarcoma, and lymphoma, and measurement sites have ranged from the feet to the scalp. Very recent results and analyses indicate that using a simple clinically applicable approach with breathing carbogen, tumors can be characterized in regard to whether or not they respond to this hyperoxic treatment which does raise the pO_2 in the vascular system. Some tumors did not respond at all and some had only minimal changes while others had robust changes in tumor pO_2. These results indicate that it should be feasible to more adequately determine effectiveness of hyperoxic treatments and therefore both individualize therapy and develop more robust strategies for optimizing hyperoxic therapies.

Hypoxia in tumors: Pathogenesis-related classification, characterisation, and clinical implications

Presenter: Peter Vaupel
vaupel@uni-mainz.de

Peter Vaupel
Department of Radiooncology and Radiotherapie, University Medical Center
Mainz, Rheinland- Pfalz, 55131
Germany

Hypoxia is a hallmark of locally advanced tumors which can lead to adaptive processes (e.g., mostly mediated through the HIF- system), development of aggressive phenotypes, and treatment resistance. Depending on underlying mechanisms and their duration, two main types of hypoxia have been identified in tumors: chronic and acute, coexisting with complex spatial heterogeneities. Chronic or continuous hypoxia is preferentially caused by diffusion limitations due to enlarged diffusion distances and adverse diffusion geometries (e.g., countercurrent vs. concurrent microvessels, Krogh- type vs. Hill- type diffusion geometry) and -to a lesser extent- by hypoxemia (e.g., upon tumor- associated anemia, in primary or metastatic liver tumors supplied by the portal vein), HbCO formation in heavy smokers, and a compromised perfusion or flow stop due to sustained interstitial hypertension. Acute or fluctuating hypoxia mainly results from transient disruptions of perfusion (e.g., due to vascular occlusion by cell aggregates and/or fibrin clots), fluctuating red blood cell fluxes, transient reversal of flow directions, and -possibly- by short- term contractions of the interstitial matrix. In each of these hypoxia subtypes oxygen supply is critically reduced, but perfusion- dependent nutrient supply, delivery of anti- cancer drugs and repair competence can vary or may not be affected. The detailed differentiation of tumor hypoxia may impact on our understanding of tumor biology and may aid in the development of novel treatment strategies (e.g., hypo- vs. hyperfractionated radiotherapy), tumor detection by imaging and tumor targeting, and thus is of great clinical importance.

Imaging the gradients of oxygen in cells and tissues using GFP

Eiji Takahashi
eiji@cc.saga-u.ac.jp

Department of Advanced Technology Fusion, Saga University, Saga 840-8502
Japan

Diffusional gradients of oxygen concentration in tissues are of special importance in mitochondrial functions *in vivo*. Thus, they were also the big concern of BC. In this study, we will show a simple technique to establish gradients of oxygen concentration in a 2-D tissue model composed of cultured cells. In this model, we visualized oxygen level in individual cells using hypoxia dependent red shift of GFP fluorescence. We found that HIF-1α induction by a prolyl hydroxylase inhibitor DMOG significantly reduced oxygen gradients in this model; half maximal changes in the red shift of GFP fluorescence took place at 370 μm deep from the oxygen source in the control cell while it extended to 1250 μm deep in the DMOG treated cell. The result is consistent with that HIF-1α downregulates mitochondrial respiration. Then, we visualized the maximum depth in the tissue model at which mitochondrial membrane potential (ΔΦm) is sustained by diffusional oxygen delivery (the anoxic front, AF). In consistent with the shallow oxygen gradients in the DMOG treated cell, AF was extended from ~500 μm to 1500-2000 μm after treatment with DMOG. However, a question arises how mitochondria could sustain ΔΦm in cells located in otherwise oxygen depleted regions because reduced mitochondrial respiration (that causes shallow oxygen gradients) reflects reduced electron transport in the respiratory chain (reduced proton pumping from the matrix to the intermembrane space). Besides detailed demonstrations of the oxygen measurement using GFP fluorescence, we will also propose possible mechanisms for ΔΦm generation with significantly reduced respiration.

Photoacoustic tomography: Ultrasonically breaking through the optical diffusion and diffraction limits

Presenter: Lihong Wang
lhwang@biomed.wustl.edu

Lihong Wang
Biomedical Engineering, Washington University in St. Louis
St. Louis, MO, 63130-4899
United States

Photoacoustic tomography (PAT) provides *in vivo* multiscale non-ionizing functional and molecular imaging by combining optical and ultrasonic waves via the photoacoustic effect. High-resolution pure optical imaging (e.g., confocal microscopy, two-photon microscopy, and optical coherence tomography) offers rich tissue contrast but is limited to depths within the optical diffusion limit (~1 mm in the skin). In PAT, pulsed laser light penetrates the tissue and generates a small but rapid temperature rise, which induces emission of ultrasonic waves due to thermoelastic expansion. The ultrasonic waves, ~1000 times less scattering than optical waves in tissue, are then detected to form high-resolution images at depths up to 7 cm, breaking through the optical diffusion limit. Super-resolution beyond the optical diffraction limit has also been achieved. PAT is the only modality capable of imaging across the length scales of organelles, cells, tissues, and organs with consistent contrast. Such a technology has the potential to enable multiscale systems biology and accelerate translation from microscopic laboratory discoveries to macroscopic clinical practice. PAT may also hold the key to the earliest detection of cancer by *in vivo* label-free quantification of hypermetabolism, the quintessential hallmark of cancer The technology has been commercialized by several companies. The annual conference on this topic has been doubling in size approximately every three years since 2003 and has become the largest in SPIE's Photonics West as of 2009.

Time-resolved MRI oximetry for quantifying $CMRO_2$ and vascular reactivity

Felix Wehrli
wehrli@mail.med.upenn.edu

Felix W Wehrli
Department of Radiology, Laboratory for Structural NMR Imaging
University of Pennsylvania
Philadelphia, PA,19104
United States

Venous and arterial blood hemoglobin (Hb) oxygen saturation, along with blood flow to the brain, allows quantification of the cerebral metabolic rate of oxygen consumption ($CMRO_2$), one of the key physiologic parameters. Recent advances in quantitative MRI in the speaker's laboratory now allow simultaneous measurement of total cerebral blood flow (tCBF) and venous oxygen saturation (SvO_2), and thus $CMRO_2$, with a temporal resolution of a few seconds, therefore enabling the study of non-steady-state processes. The method exploits deoxyhemoglobin's inherent paramagnetism. The induced local magnetic field in a major vein such as the superior sagittal sinus or jugular vein, is measured by phase mapping and converted to blood magnetic susceptibility values by modeling the blood vessel as a long cylinder. Along with a phase-contrast measurement of arterial inflow through internal carotid and vertebral arteries, $CMRO_2$ is computed from Fick's law. Measurements were conducted in the human brain both at baseline and in response to vasodilatory stimuli providing results in agreement with those obtained by invasive techniques. Studies in neonates with congenital heart disease (hypoplastic left heart syndrome, transposition of the great arteries) leading to hypoxemia, show that in spite of their severe cardiac abnormalities these infants have normal vascular reactivity in response to transient hypercapnia. Lastly, venous SvO_2 can serve as a dynamic endogenous tracer following induced ischemia via transient occlusion of the femoral vein. Results show that the hyperemic response is impaired in patients with peripheral arterial disease, as well as in smokers without overt cardiovascular disease.

Optical cerebral blood flow and hemoglobin concentration monitoring in brain

Arjun Yodh
yodh@physics.upenn.edu

Arjun Yodh, Ph.D.
Laboratory for Research on the Structure of Matter (LRSM)
James M. Skinner Professor of Science, Department of Physics and Astronomy
University of Pennsylvania, Philadelphia, PA 19104
United States

An important application of diffuse optical methods is in the area of brain function and physiology. Indeed, the interplay between tissue oxygen consumption, vascular supply, and regulatory effects remains poorly understood. Therefore, comprehensive sets of hemodynamic data containing independent information about hemoglobin concentration, blood oxygenation, and blood flow are desirable. I will describe the use of combined Diffuse Correlation Spectroscopy (DCS) and Diffuse Optical Spectroscopy (DOS/NIRS) to monitor brain responses in both animal and humans.

Poster abstracts

Poster I.D.: #14
Display date: Tuesday, June 18

Functional analysis of *Drosophila* heart at different developmental stages using optical coherence microscopy

Presenter: Aneesh Alex
aneesh.alex@lehigh.edu

Aneesh Alex, Nicole Pirozzi, and Chao Zhou
Department of Eletrical and Computer Engineering, Lehigh University
Bethlehem, PA, 18015
United States

Drosophila melanogaster heart is an important model system for investigating cardiac development due to its simple tubular organization and similarities to vertebrate heart at early development stages. Identification of regulatory genes involved in *Drosophila* heart development and their impact on cardiac functions is important. In this study, a high-speed non-invasive optical imaging technique, known as optical coherence microscopy (OCM), was utilized to image the *Drosophila* heart at different development stages of its lifecycle. Three-dimensional and M-mode images of *Drosophila* heart was obtained from 20 wild-type flies at second instar, third instar, pupa and adult stages. In addition to heart rate, other functional parameters such as heart tube dimensions, fractional shortening and prevalence of arrhythmia were quantified. Heart rate, being the highest at the second instar stage (310 beats per minute, bpm), decreased at third instar stage to 253 bpm and further decreased to 74 bpm at early pupa stage. The heart stopped beating during mid-pupa stage and resumed to beat by late pupa stage (161 bpm). The average heart rate in an adult fly was 299 bpm. In addition to heart rate, other parameters also showed significant changes throughout *Drosophila's* lifecycle. In order to determine functional roles of the SOX102F gene (*Drosophila* ortholog of human SOX5 gene) in heart development, 20 transgenic flies silenced for SOX102F were also imaged. Morphological and functional changes of the mutant heart at different development stages were compared to that of age-matched control flies.

Poster I.D.: #15
Display date: Tuesday, June 18

NIR-fluorescent choline kinase inhibitors for cancer imaging and therapy

Presenter: Sean Arlauckas
sarl@mail.med.upenn.edu

Sean P. Arlauckas, Anatoliy V. Popov, and Edward J. Delikatny
Department of Radiology, University of Pennsylvania
Philadelphia, PA, 19104
United States

Choline Kinase (ChoK) catalyzes the conversion of choline to phosphocholine (PC), an important mitogenic second messenger and the first step in biosynthesis of phosphatidylcholine. The upregulation of ChoK in breast cancer has been correlated with aggressiveness, drug resistance, and overall poorer patient prognosis. Recent studies have shown ChoK inhibition to be a promising strategy for solid tumor treatment. Analogs of the bis-cationic choline mimetic hemicholinium-3 have been identified as specific ChoK inhibitors whose antitumor capabilities are being explored in Phase I clinical trials. There are several structural similarities between these ChoK-targeted inhibitors and a class of near infrared (NIR) fluorescent dyes known as the carbocyanines. We hypothesize that NIR-fluorescent ChoK inhibitors will bind ChoK and accumulate in regions of heightened expression, making possible the use of *in vivo* optical imaging to estimate ChoK status. We have synthesized multiple carbocyanine-based NIR-fluorescent ChoK inhibitors, the best candidate thus far being JAS239. This compound competitively inhibits ChoK in multiple breast cancer cell lines, resulting in substantial cell death. JAS239 rapidly enters cells independent of choline transporters, binds its cytosolic target, and is excluded from the nucleus where mutagenesis and non-specific cell death would otherwise be complicating factors. *In vivo* studies were used to demonstrate the biostability of JAS239, its ability to accumulate within non-necrotic portions of the tumor, and the feasibility of optical imaging for detection of targeted NIR-fluorophores. We are now translating JAS239 into murine tumor models with variable ChoK expression to better understand lipid metabolism in breast cancer.

Poster I.D.: #16
Display date: Tuesday, June 18

Neurovascular coupling varies with level of global cerebral ischemia in a rat model

Presenter: Wesley Baker
wbaker@sas.upenn.edu

Wesley B. Baker, Zhenghui Sun, Teruyuki Hiraki, Mary E. Putt, Turgut Durduran, Martin Reivich, Arjun G Yodh, and Joel H Greenberg
Department of Physics, University of Pennsylvania
Philadelphia, PA, 19104
United States

In this study, cerebral blood flow, oxygenation, metabolic, and electrical functional responses to forepaw stimulation were monitored in rats at different levels of global cerebral ischemia from mild to severe. Laser speckle contrast imaging and optical imaging of intrinsic signals were used to measure changes in blood flow and oxygenation, respectively, along with a compartmental model to calculate changes in oxygen metabolism from these measured changes. To characterize the electrical response to functional stimulation, we measured somatosensory evoked potentials (SEPs). Global graded ischemia was induced through unilateral carotid artery occlusion, bilateral carotid artery occlusion, bilateral carotid and right subclavian artery (SCA) occlusion, or carotid and SCA occlusion with negative lower body pressure. We found that the amplitude of the functional metabolic response remained tightly coupled to the amplitude of the SEP at all levels of ischemia observed. However, as the level of ischemia became more severe, the flow response was more strongly attenuated than the electrical response, suggesting that globalischemia was associated with an uncouplingbetween the functional flow and electrical responses.

Poster I.D.: #17
Display date: Tuesday, June 18

Laser speckle contrast imaging of resting-state functional connectivity in mice

Presenter: Karla Bergonzi
bergonzik@wustl.edu

Karla M. Bergonzi, Adam Q. Bauer, and Joseph P. Culver
Department of Biomedical Engineering, Washington University in St. Louis
St. Louis, Missouri, 63110
United States

We present the use of Laser Speckle Contrast Imaging (LSCI) to map resting-state functional connectivity (FC) in mice through an intact skull using cerebral blood flow (CBF). The CBF-based FC maps were found to be both robust and repeatable across mice and corroborate previously observed FC patterns in healthy mice using changes in oxyhemoglobin concentration in fcOIS. Spatial and temporal averaging was used to decrease the instantaneous noise in the inherently noisy LSCI measure. After averaging, the spatial resolution of the CBF-based FC maps was on the order of a single whisker barrel (0.5 x 0.5 mm) and the temporal resolution was 1 second, which fully resolves the hemodynamic response. Creating FC maps using spontaneous CBF in addition to oxyhemoglobin concentration could provide a more comprehensive hemodynamic assay, potentially clarifying mechanisms involved in FC disruption due to disease. We have successfully created a system using LSCI capable of acquiring resting-state physiological data with enough fidelity to allow not only for FC measures to be analyzed, but also for metabolic parameters to be calculated and the neurovascular coupling to be monitored.

Poster I.D.: #37
Display date: Wednesday, June 19

Cerebral oxygenation, blood flow, and oxygen metabolism during the first three days of life

Presenter: Erin Buckley
buckley@nmr.mgh.harvard.edu

Erin M. Buckley, M. Dehaes, P.Y. Lin, K. Hagan, A. Fenoglio, D.A. Boas, P.E. Grant, and M.A. Franceschini
Department of Radiology, Massachusetts General Hospital
Charlestown, MA, 02129
United States

Objective: Near infrared and diffuse correlation spectroscopies (NIRS and DCS, respectively)offer a means for non-invasive bedside quantification of cerebral oxygen saturations, blood volume, blood flow, and oxygen metabolism in critically-ill neonates. In order to interpret these measurements in sick infants, it is vital to understand the normal changes of these parameters in healthy neonates.

Methods: Longitudinal frequency domain NIRS (ISS, Inc) and DCS measurements were made daily for 3 days after delivery. Measurements of oxy-hemoglobin (HbO), deoxy-hemoglobin (HbR), total hemoglobin concentration (HbT), cerebral tissue oxygen saturation (SO_2), and an index of cerebral blood flow (CBFi) were made on seven different locations over the frontal, parietal, and temporal cortices. A non-invasive pulse cooximeter (Rad-87, Masimo Corporation) quantified arterial oxygen saturation and hemoglobin concentration. Combining these arterial parameters with FD-NIRS/DCS parameters, we also derived cerebral blood volume (CBV), oxygen extraction fraction (OEF), and an index of cerebral oxygen metabolism ($CMRO_2i$).

Results: Nine healthy, full-term neonates were recruited within 24 hours of delivery via caesarian section. SO2 increased significantly from age 1 to 2 d while CBFi decreased significantly on days 1 and 2 as compared to day 3. $CMRO_2i$ decreased over the course of 3 days of measurements, however the results did not reach statistical significance.

Interpretation: For the first time, we quantify longitudinal measurements of microvascular cerebral oxygen metabolism, blood flow, and blood volume over the first 3 postnatal days in healthy neonates. These results will be a valuable tool to understand how disease states alter normal hemodynamic development.

Poster I.D.: #32
Display date: Wednesday, June 19

Statistical tumor localization and monitoring in diffuse optics

Presenter: David Busch
drbusch@sas.upenn.edu

David R. Busch, Regine Choe, Saurav Pathak, Wensheng Guo, Turgut Durduran, Michael D. Feldman, Carolyn Mies, Mitchell D. Schnall, Mark A. Rosen, Brian J. Czernicki, Julie Tchou, Angela DeMichele, Mary Putt, and Arjun G. Yodh
Department of Neurology, The Children's Hospital of Philadelphia
Philadelphia, PA, 19143
United States

Diffuse optics permits measurement of multiple physiologically important parameters without invasive or ionizing procedure. We have applied statistical techniques to both extract the location of tumors from multi-parameter 3D tomograms and to track the evolution of tumors over the course of neoadjuvant chemotherapy treatment. Our results in small populations are encouraging and point the way towards future studies.

Poster I.D.: #13
Display date: Tuesday, June 18

Breast cancer redox heterogeneity revealed by chemical exchange saturation transfer (CEST) MRI

Presenter: Kejia Cai
kcflying@gmail.com

Kejia Cai, He N. Xu, Mohammad Haris, Anup Singh, Ravinder Reddy, and Lin Z. Li
Department of Radiology, University of Pennsylvania
Philadelphia, PA, 19104
United States

Predicting tumor metastatic potential to assist treatment strategies is of immense importance. Optical imaging of the redox state of freez-trapped ex vivo tissues has revealed tumor heterogeneity that differentiated tumor aggressiveness. In this study, chemical exchange saturation transfer magnetic resonance imaging (CEST MRI) has been investigated to characterize breast tumor heterogeneity and correlated with the redox state of two breast tumor mouse xenograft models with different metastatic potentials: the highly metastatic MDA-MB-231 and the less metastatic MCF-7. Similar to the redox scanning results, the CEST contrast imaging showed that the aggressive MDA-MB-231 tumors had higher degree of bimodal metabolic heterogeneity appearing as a distinct core-rim pattern than the MCF-7 tumors, whereas these heterogeneous patterns were not clearly observed by other conventional MRI methods. The mechanism on the correlation between the CEST contrast and the tissue redox state was validated through studies on *in vitro* redox reactions. We demonstrated that the reductants of redox reactions generally express CEST contrast more effectively than the oxidants. CEST MRI correlates with the cellular NAD(P)H level and the redox status based on the different contributions from the reductants and oxidants. CEST MRI may potentially provide a novel non-invasive imaging surrogate for the tissue redox status and a possible non-invasive diagnostic biomarker for predicting cancer metastasis in the clinic.

Poster I.D.: #34
Display date: Wednesday, June 19

MR spectroscopy of phospholipid metabolites as indicators of COX 2 activation

Presenter: Michael Chiorazzo
mchio@mail.med.upenn.edu

Michael G Chiorazzo, Emer M Smyth, and Edward J Delikatny
Department of Pharmacology, University of Pennsylvania
Philadelphia, PA, 19104
United States

Cyclooxygenase (COX) 2 is an inducible protein involved in the conversion of arachidonic acid to PGH2, a precursor to the signaling molecules prostanoids. COX2 has been shown to be upregulated in a variety of cancers and colocolizes with cytoplasmic phospholipase A2 (cPLA2), which is responsible for the cleavage of arachidonic acid from phosphatidylcholine. Alterations in cPLA2 activity can be measured indirectly using 1H NMR spectroscopy by measuring the levels of phosphatidylcholine metabolites: choline, phosphocholine (PC) and glycerophosphocholine (GPC). NMR spectra of shRNA COX2 knock down (KD) SMF mouse mammary tumor cells showed that PC and choline are elevated in COX2 KD cells relative to both wild type (wt) and non-target (nt) shRNA cells. This is consistent with a mechanism whereby the inhibition of cPLA2 activity causes increased flux through phospholipase C and phospholipase D resulting in higher levels of PC and choline respectively. In order to measure cPLA2 activity directly, an assay was developed utilizing 1-palmitoyl-2-14C -archidonyl-phosphatidylcholine (14C-PtdCho). Cells were incubated with liposomes containing 14C-PtdCho and cleavage was determined throughthin layer chromatography of cell extracts. Basal PLA2 activity of nt cells was significantlyhigher than COX2 KD cells. Lipopolysaccharides (LPS) were used to induce COX2, and cPLA2 activity was measured. Addition of LPS resulted in an increase of cPLA2 activity in both cell lines. Together, these data suggest a direct correlation between COX2 activity and cPLA2 activity which can be measured through changes in the choline metabolites visible with MR spectroscopy.

Poster I.D.: #18
Display date: Tuesday, June 18

Simultaneous diffuse optical and MR imaging for breast cancer

Presenter: Jeff Cochran
cochranj@sas.upenn.edu

Jeffrey M. Cochran, Li Lin, David R. Busch, David L. Minkoff, Thomas Connick, Han Y. Ban, Saurav Pathak, Madeline Winters, Mitchell D. Schnall, Mark A. Rosen, and Arjun G. Yodh
Department of Physics and Astronomy, University of Pennsylvania
Philadelphia, PA, 19104
United States

Diffuse Optical Tomography utilizes highly scattered near-infrared light to construct 3D maps of chromophores *in vivo*. We have applied this non-invasive and non-ionizing tool to image breast cancer simultaneously with MRI. This combination permits direct validation of DOT cancer imaging, co-registration of the two modalities, and simultaneous imaging of structural (MRI) and hemodynamic (DOT) contrasts. Recent instrument upgrades provide increased capabilities and robustness in both the optical and MR aspects of the system. Joint optical-MR phantom and human measurements are currently in the early stages.

Poster I.D.: #2
Display date: Tuesday, June 18

Optical microscopy of capillary oxygen transport

Presenter: Christopher Ellis
cgellis@uwo.ca

C.G. Ellis, S. Milkovich, G.M. Fraser, N.W. Ghonaim, and D. Goldman
Department of Medical Biophysics, University of Western Ontario
London, Ontario, N6K1X1
Canada

Dual wavelength intravital video microscopy (DIVVM) has been used to measure red blood cell dynamics and oxygen saturation in capillary networks in skeletal muscle *in vivo* (Japee *et al.*, *Microcirculation*, 2005) and to provide the three-dimensional geometric data to reconstruct these networks from the same video sequences for realistic oxygen transport models based on experimental data (Fraser *et al*., *Am J Physiol Heart Circ Physiol*, 2012; Fraser *et al*., *Microcirculation*, 2012). However, the original DIVVM systems were limited to thin tissues and to capillaries with red blood cell velocities < 0.5-mm/s due to the video technology (analog CCD, 8-bit frame capture, poor SNR). A new DIVVM system is presentedbased on digital video cameras (DualCam with two Rolera XR cameras mounted on an Olympus IX-81 inverted microscope) with 12-bit gray scale resolution, electronic shutter forshort exposure times and region of interest for higher frame rates when needed. The higher dynamic range makes it possible to use wavelengths with lower extinction coefficients (454-nm and 442-nm vs 420-nm and 432-nm) hence study oxygen transport in thicker tissues or older animals (e.g. 12-week diabetic vs 7-week prediabetic ZDF rats). Short exposure times eliminate blurring of high velocity red blood cells and potential artifacts in oxygen saturation calculations. The DIVVM system combined with microfluidic chambers for perturbing oxygen levels at the muscle surface make it possible to study the local regulation of microvascular oxygen supply *in vivo* (Ghonaim *et al*, *Microcirculation*, 2011).

Poster I.D.: #35
Display date: Wednesday, June 19

Simultaneous quantification of perfusion, venous oxygen saturation, and skeletal muscle T2* in response to cuff-induced ischemia in the leg

Presenter: Erin Englund
eenglund@mail.med.upenn.edu

Erin K. Englund, Michael C. Langham, Cheng Li, Emile R. Mohler,
Thomas F. Floyd, and Felix W. Wehrli
Department of Radiology, University of Pennsylvania
Philadelphia, PA, 19104, United States

A novel method to simultaneously measure perfusion, venous oxygen saturation, and skeletal-muscle T2* using an interleaved pulsed arterial spin labeling and multi-echo GRE sequence is presented. The technique, termed Perfusion, Intravascular Venous Oxygen saturation, and T2* (PIVOT), was evaluated compared to standard measurement methods in healthy subjectsduring a series of ischemia reperfusion paradigms. Time course data were analyzed to investigate the kinetics of recovery following cuff-induced ischemia. Results indicate that PIVOT is capable of faithfully measuring perfusion, venous oxygen saturation, and T2* at 2 second temporal resolution. No significant bias was introduced by using the combined methodcompared to individual measurement methods. PIVOT was also used to investigate a small cohort of peripheral artery disease patients. In these patients, a blunted and delayed hyperemic response was detected.

Poster I.D.: #5B
Display date: Tuesday, June 18

The metabolic change of biopsy samples from normal and tumor tissue

Presenter: Min Feng
minfeng8@gmail.com

Min Feng, He N. Xu, Lin Z. Li
Department of Radiology, University of Pennsylvania
Philadelphia, PA, 19104
United States

Previously we showed the metabolic information of clinical biopsy samples could differentiate between cancerous and normal breast tissue, where the biopsies were taken from the resected breasts. To standardize the biopsy sampling procedure it is desired to know how the metabolism of biopsy tissues changes over time. In the present study biopsies sizing 2×2 to 3×6 mm^2 were taken from the leg muscle of an anesthetized mouse and the Ramos tumor xenografted in the mouse. The Ramos tumors were largely uniform according to our previous studies. These biopsies were placed on PBS-moistened paper and exposed to air. At different time point within 0-20 minutes, they were snap-frozen in liquid nitrogen followed by redox-scanning using the Chance redox scanner. The fluorescence signals from the reduced nicotinamide adenine dinucleotide (NADH) and the oxidized flavorproteins (Fp) in the frozen tissues were collected from multiple sections at different tissue depth and further analyzed. The results showed that the muscle had very different metabolic behavior than the tumor tissue. For the muscle biopsies, both NADH and oxidized flavoproteins decreased over time and the Fp redox ratio Fp/(NADH+Fp) is positively correlated with time (R^2=.91, p=.003); whereas there is no apparent pattern of either NADH or Fp change with time and no correlation between the Fp redox ratio and time found for the tumor tissue. More repetitive tests shall be performed in future to validate the study.

Poster I.D.: #19
Display date: Tuesday, June 18

A near-infrared spectroscopic handheld wireless device for assessing infantile hemangiomas

Presenter: Christopher Fong
cjf2123@columbia.edu

Christopher J. Fong, Lauren Geller, Jennifer W. Hoi, Molly Flexman, Christine Lauren, Hyun-Keol Kim, Maria Garzon, and Andreas H. Hielscher
Department of Biomedical Engineering, Columbia University
New York, NY, 10027
United States

Infantile hemangiomas (IH) are common vascular growths that occur in 5-10% of neonates. Affecting mostly superficial skin layers, these hemangiomas can be disfiguring and even lead to life-threatening complications. Yet the current methods of assessment are not standardized and remain largely subjective to the individual physicians. An objective standardized method for diagnosis and assessment of IHs, which would provide reliable information about blood volume and saturation as well as lesion thickness, is highly desirable. To this end we have developed a low-cost, Bluetooth-compatible, handheld wireless device (HWD) containing two Si photodiodes that measures back-reflected light from 4 infrared laser diodes at distances between 0.6 and 2 cm. The data is used to determine oxygenated and deoxygenated hemoglobin concentration ([HbO_2] and [Hb]), as well as scattering within tissue. Values of these variables are computed with a multispectral evolution algorithm. The performance of the device and algorithm was validated by experimental studies involving well-characterized tissue phantoms. Furthermore, in an ongoing longitudinal pilot study with 15 children, the easy-to-operate HWD is being used to characterize the changes in optical properties of IHs in response to treatment as well as through their natural history. Preliminary findings show a decrease in oxy- and deoxy-hemoglobin concentrations as well as an increase in oxygen saturation in IHs in response to treatment. These findings correlate with the fact that lesions become less vascular with response to treatment and the hypothesis that IH lesions become less hypoxic during its involuting stage.

Poster I.D.: #27
Display date: Wednesday, June 19

Two-photon imaging of intracellular H_2O_2 with chemoselective fluorescent probes

Presenter: Hengchang Guo
hcguo@umd.edu

Hengchang Guo, Hossein Aleyasin, Scott Howard, Bryan C. Dickinson, Vivian Lin,
Renee E. Haskew-Layton, Jianting Wang, Christopher J. Chang, Chris Xu, Rajiv R. Ratan, and Yu Chen
Fischell Department of Bioengineering, University of Maryland
College Park, Maryland, 20742
United States

H_2O_2, a common reactive oxygen species (ROS), is recognized as a second messenger for cellular signaling that exerts diverse physiological and pathological effects. It is also an oxidative stress indicator related to cancer, diabetes, and neurodegenerative diseases. In addition, H_2O_2 is involved in therapeutic processes such as wound healing and an adaptive response in astrocytes that leads to neuronal protection. To monitor the production of intracellular H_2O_2 *in situ*, we used chemoselective fluorescent probes such as Peroxyfluor-6 acetoxymethyl ester (PF6-AM) and Mitochondria Peroxy Yellow 1 (MitoPY1). These fluorescent probes are based on boronate-switch mechanism for selective detection of intracellular H_2O_2 with fast response time. PF6-AM was designed with the intracellular acetoxymethyl ester functionalities allowing for cell membrane-permeability. MitoPY1 was designed with a mitochondrial-targeting phosphonium moiety for detection of H_2O_2 localized to cellular mitochondria. Two-photon absorption (TPA) spectra of the chemoselective fluorescent probes were measured with a mode-locked Ti:sapphire laser in the wavelength range of 720-1040 nm. The peak TPA cross section values of these probes are comparable to that of fluorescein, which is sufficiently large for TPF imaging to detect localized endogenous H_2O_2 production in living cells. Two-photon fluorescence (TPF) imaging was then demonstrated in brain cells to monitor cytoplasmic H_2O_2 production and localized mitochondrial H_2O_2 production. This study demonstrates that chemoselective fluorescent probes provide a novel opportunity for real-time two-photon imaging of H_2O_2 and oxidative stress evaluation in live cells and *in vivo*.

Poster I.D.: #20
Display date: Tuesday, June 18

Correlation of mitochondrial and mechanical dysfunction in fibroblasts following toxic exposure

Presenter: Judith Kandel
jkandel@seas.upenn.edu

Judith Kandel and David M. Eckmann, Ph.D, M.D.
Department of Bioengineering, University of Pennsylvania
Philadelphia, PA, 19104
United States

Both treatment and prevention of clinical disease can be advanced through the study of pathophysiology at the cellular and molecular levels. While bioengineers emphasize the importance of cellular and molecular mechanics in a variety of clinical pathologies, mitochondrial biologists view mitochondrial and bioenergetic impairment as a key component of disease development and progression. We make the novel proposition that mechanical and mitochondrial dysfunction that are both characteristic of many abnormal cellular conditions (typically considered "toxicity") are linked. A fundamental component ofour research is to demonstrate the direct interrelationship between mitochondrial dysfunction and abnormal mechanical characteristics arising in cells subjected to severely toxic conditions. We use an array of experimental tools, drawing on both classical biology and engineering, to interrogate the molecular mechanical and bioenergetic interrelationships which develop in intentionally distressed cells. The mechanical tools include atomic force microscopy to measure cell stiffness and fluorescence microscopy to quantify the integrity of cellular cytoarchitecture. For metabolic assessment, we use fluorescence microscopy to define the mitochondrial network structure. We process microscopy images and utilize MATLAB programming to quantify changes in mitochondrial dimensions following toxic exposure of cells. Such changes demonstrate, for instance, mitochondrial swelling and/or fragmentation, indications of cellular toxicity. We demonstrate that fibroblasts subjected to varying levels of toxic exposure (e.g. osmotic swelling) display corresponding levels of mechanical and mitochondrial disruption which increase with increasing severity of the exposure. This supports our hypothesis that cells respond to toxic stimuli on multiple levels, which include both mitochondrial and mechanical dysfunction.

Poster I.D.: #36A
Display date: Wednesday, June 19

Biomarker triggered NIR optical contrast agent with enhanced sensitivity

Presenter: Kyung Kang
kyung.kang@louisville.edu

Kyung A. Kang, Samuel Achilefu, and Jianting Wang
Departmet of Chemical Engineering, University of Louisville
Louisville, Kentucky, 40292
United States

Fluorophores are probably the most frequently used optical contrast agents for molecular imaging. Adding a capability of appropriately controlling the emission level of fluorophores will be even more valuable for increasing both their selectively and sensitivity. Since the mechanism of fluorescing is due to the change in the state of electrons of fluorophores, placing a localized electro-magnetic field at a controlled level near them will allow us to manipulate the emission level.Nano-sized gold nanoparticles (GNP) generate the localized electro-magnetic field upon receiving photonic energy. We were able to controlling fluorescence emission level from complete quenching to an extensive enhancement, by utilizing the field generated by GNPs. A safe Indocyanine Green (ICG) based near infrared (NIR) fluorophore was appropriately treated with GNPs so that there is little to no fluorescence emission under normal condition, but its emission was triggered by the presence of breast cancer secreting enzyme urokinase type plasminogen activator. The design also allows that, when it is triggered for the emission its level could be significantly enhanced. This particular method of controlling fluorescence is similar to the mechanism of molecular beacon. However, this method is not restricted only to the nucleotide detection and, in addition, this provides greater sensitivity. Adding targeting ability to this GNP/fluorophore complex of conditionally fluorescence emitting NIR fluorescence allows more accurate and sensitive disease diagnoses. Research for adding various targeting molecules including antibodies, aptamers, and nucleotides are currently in progress. This work was partially supported by the U.S. Army Breast Cancer Program.

Poster I.D.: #36B
Display date: Wednesday, June 19

Primo Vascular System: A newly discovered circulation system

Presenter: Kyung Kang
Kyung A. Kang and Kwang-Sup Soh*

*Nano Primo Research Center, Advanced Institute of Convergence Technology
Seoul National University, Suwon
Korea

Primo Vascular System (PVS) is a newly found organ, composed of small nodes (primo nodes; PNs) and thin vessels (primo vessels; PVs) branching out of PNs. The PVS is normally difficult to identify due to its small size and semi-transparent optical property. The diameter of PVs is in the range of only 20-50 micrometers and the size of the PN is 100-1000 micrometers. Because of its short history of this organ, much of its roles and functions in the mammalian body are still under investigation. Some of the important PVS properties already reported are:

- The PVS appears to be present in the entire body including inside blood and lymphatic vessels and some from the brain to the rest of the body via the spinal canal, indicating it to be an extensive communication network throughout the body.
- Some cells transported via the PVS present stem cell biomarkers and these stem-cell-like cells appeared to be stored in the PNs at a very high concentration.
- As tumors are formed the PVS is also formed at a high density around the tumor. Cancer cells are shown to be transported via PVS from the primary to the secondary tumors.
- There has been claim that the PV is meridian and PNs in the skin are acupoints.

From these, the PVS appears to have fundamental roles in maintaining mammalian lives including controlling metabolism, and therefore we believe that elucidating its functions is highly important for future health care.

Poster I.D.: #26
Display date: Wednesday, June 19

Noninvasive determination of the relationship between mitochondrial stimuli and O_2 diffusion rate during exercise

Presenter: Ryotaro Kime
kime@tokyo-med.ac.jp

Ryotaro Kime, Masako Fujioka, Shunsaku Koga, Takuya Osawa, Takuya Osada,
Norio Murase, and Toshihito Katsumura
Department of Sports Medicine for Health Promotion, Tokyo Medical University
Shinjuku-ku, Tokyo, 160-8402
Japan

Mitochondrial oxidative phosphorylation, which modulates resynthesis of PCr, depends in part on the availability of O_2 for the mitochondria in working muscle. When mitochondrial O_2 limitation is caused by reduced O_2 availability due to inadequate blood flow (ischemia), there is evidence that the manner in which the blood flow reduction is imposed may influence muscle metabolism and the degree of impairment of contractile function. Particularly during intense exercise, the induced lower O_2 availability affects mitochondrial oxidative phosphorylation. However, there are few studies which have reported the relationship between mitochondrial stimuli and oxygen diffusion rate from capillary to mitochondria (rDO_2) during varying-workload exercise including under severe acidosis conditions in humans. The purpose of this study was to investigate the relationship between muscle PCr, rDO_2, and muscle deoxygenation in human skeletal muscle during incremental dynamic exercise. The PCr during exercise was evaluated using 31-phosphorus magnetic resonance spectroscopy, the rDO_2 and the muscle deoxygenation level were monitored using near-infrared continuous wave spectroscopy, and the mean blood flow (mBF) of the brachial artery was measured using Doppler ultrasound. The PCr level subsequently decreased with higher workloads, and the rDO_2 above 10% MVC significantly increased from the resting, and was constant with higher workloads. The deoxygenation level was also significantly greater above 10% MVC, and the mBF increased linearly with higher workloads. These results suggest that rDO_2 is limited at higher workloads, although mitochondrial stimuli are increased. The constant rDO_2 with higher workloads may be caused by reduced O_2 gradient from capillary to mitochondria.

Poster I.D.: #9
Display date: Tuesday, June 18

Non-invasive evaluation of seizure-induced neuronal injury in organotypic brain cultures using optical coherence microscopy

Presenter: Fengqiang Li
fel211@lehigh.edu

Fengqiang Li, Alexandra Dryer, Michael D Feldman, Yevgeny Berdichevsky, and Chao Zhou
Department of Electrical and Computer Engineering, Lehigh University
Bethlehem, PA, 18015
United States

Organotypic brain cultures are increasingly used as a model system to develop better treatments for neurological conditions like epilepsy. Analysis of neuron morphology and number in organotypic brain cultures could evaluate the seizure neuronal activity which causes the neuronal death in epilepsy. Typical methods to evaluate neuronal viability require tissue fixation and staining. In this study, we present a non-invasive 3D optical imaging modality, optical coherence microscopy (OCM), which provides the evaluation of neuronal viability in organotypic brain cultures without tissue processing and staining. A spectral-domain OCM system was developed with 1.5 μm axial resolution in tissue, over 100 dB sensitivity, ~2.3 μm transverse resolution with a 10x objective, and ~200 μm extended depth of field with a 175-degree conical lens. Organotypic brain slices (~250-350 μm thickness) were dissected from the hippocampus of three 7-day old Sprague-Dawley rats. 3D-OCM images were performed from brain slices at 7, 14, 21, and 28 days *in vitro*. After imaging, brain slices were sent for H&E histology or confocal imaging. Morphological changes in the brain slices observed with OCM were compared with H&E histology and confocal images to identify features associated with neuronal injury. We observed a significant reduction in the neuron count from the brain slices as DIV increases. In summary, we demonstrated OCM as a promising non-invasive 3D optical imaging technique to evaluate morphological changes associated with neuronal injury in organotypic brain cultures, which opens up new possibilities to investigate treatment mechanism for various neurological conditions using organotypic brain cultures.

Poster I.D.: #21
Display date: Tuesday, June 18

Elastic properties imaging and application of thyroid hydatoncus diagnosis based on OCT elastography

Presenter: Hui Li
hli@fjnu.edu.cn

Xiaona Lin, Zhifang Li, Hui Li*, and Wei R. Chen
College of Photonic and Electronic Engineering, Fujian Normal University
Greenbelt, Maryland, 20740
United States

In this work, we present an optical technique to image elastic properties of the human thyroid with suspected cysts utilizing optical coherence elastography. The influences of kernel size and the dilation parameter had been investigated based on an experimental agarose phantom. The internal displacements were calculated by 2D normalized cross-correlation, and the corresponding displacement vectors were described graphically. Then thecontinuous wavelet transform was used as a much effective and stable method to improve the accuracy of estimation. Four types of images including axial/lateral displacement, axial strain elasogram, modulus and Poisson's ratio elastograms were obtained to characterize elasticity variations of the phantom. Images of elastic properties enable to distinguish the inclusion from background with the stiffness ratio of 12.0 0.3. In addition, elastic properties images of the human thyroid were obtained to characterize the elasticity difference between suspected cysts and normal tissue qualitatively by the herein presented method. With the stiffness ratio of 0.9 0.3, the suspected cyst founded could be considered as a benign nodule. It is expected that elastic properties images based on OCE can be used as a guide to preliminary diagnosis of human thyroid diseases, and shows great promise for the detailed characterization of lesions. Further studies including the estimation algorithm improvement and higher localization accuracy of lesion tissue are needed.

Display date: both days

Citation analysis of the scientific publications of Britton Chance in ISI citation indexes

Lin Z. Li,[1,2] Loet Leydesdorff,[3] Nannan Sun,[1,2,4] Shoko Nioka,[4] and Eugene Garfield[5]

[1]Department of Radiology; [2]Britton Chance Laboratory of Redox Imaging, Johnson Research Foundation, Department of Biochemistry and Biophysics, Perelman School of Medicine at the University of Pennsylvania, United States; [3]University of Amsterdam, Amsterdam School of Communications Research (ASCoR), Netherlands; [4]Britton Chance Center for Biomedical Photonics, Wuhan National Laboratory for Optoelectronics, Huazhong University of Science and Technology, Wuhan 430074, P. R. China; [5]Founder & Chairman Emeritus, Institute for Scientific Information, Thomson Reuters

In order to illustrate the scientific impact of Britton Chance on research, we employ scientometric analysis tools to analyze the publications of Britton Chance with data downloaded from the ISI Citation Indexes in April 2013. We included articles, reviews, and proceeding papers but excluded meeting abstracts. In total we obtained 1023 publication records with 1,236 authors in 266 journals with 17,114 citations from 1946 to 2013. We show the annual publications and citations that Britton Chance received from 1946 to 2013, and generate HistCite maps on the basis of the global citations (GCS) and local (self) citations (LCS) to show the citation relationships among the top-30 publications of Britton Chance. Furthermore, we generate the journal map and co-authorship map to show the broad scope of research topics and collaborators and the high impacts of the scientific oeuvre of Britton Chance ranging from physics, engineering, chemistry, and biology to medicine.

Poster I.D.: #22
Display date: Tuesday, June 18

Real-time monitoring of photo-immunotherapy using optical coherence tomography

Presenter: Chia-Pin Liang
cpliang@umd.edu

Chia-Pin Liang, Takahito Nakajima, Kazuhide Sato, Hisataka Kobayashi, and Yu Chen
BIOE, University of Maryland, College Park
College Park, MD, 20740
United States

Photo-immunotherapy (PIT) is a low-side-effect cancer therapy based on an armed antibody conjugate that induces rapid cellular necrosis after exposure to near infrared light. The conjugate consists of a hydrophilic photosensitizer phthalocyanine dye, IR700, which is covalently bound to a humanized monoclonal antibody. When exposed to near-infrared light, the conjugate induces highly selective and rapid cancer cell death which have been demonstrated both *in vitro* and *in vivo*. Following PIT, serial histology reveals dramatic changes in the appearance of cells within 20-30 minutes. However, the gross features of the tumor are much slower to resolve. Therefore, real-time monitoring methods that detect acute changes in the tumor micro-environment will be important for understanding the mechanism of PIT treatment. In our pilot studies, optical coherence tomography (OCT) imaging reveals dramatic vascular variation during PIT. We developed and applied several techniques, including speckle variance analysis, Doppler flow measurement, bulk motion removal and automatic ROI selection to quantify the size and the flow speed of tumor vessels *in vivo*. The data shows the blood flow speed slow down to beyond the detection limit in tenminutes. This phenomenon may be caused by the dramatic change of vessel wall permeability and interstitial pressure. Lastly we demonstrate that the needle-type OCT probecan acquire real-time imaging feedbacks, which could be used as surrogate biomarkers to modulate NIR intensity for optimizing the therapeutic efficacy.

Poster I.D.: #4
Display date: Tuesday, June 18

Fiber-optic multiphoton endomicroscopy for translational imaging of biological tissues

Presenter: Wenxuan Liang
wliang5@jhmi.edu

Wenxuan Liang, Gunnsteinn Hall, Yuying Zhang, Jiefeng Xi, Ming-Jun Li,
Katherine Luby-Phelps, Mala Mahendroo, and Xingde Li
Department of Biomedical Engineering, Johns Hopkins University
Baltimore, Maryland, 21205
United States

Multiphoton imaging technologies, including two-photon fluorescence (TPF) and second- harmonic generation (SHG) microscopy, are able to collect submicron-resolution structural and functional information based on exogenous or even purely intrinsic fluorophores (e.g. NADH and FAD) and structure proteins (e.g. collagen). To translate multiphoton technologies to clinical applications and realize non-invasive *in vivo* "optical biopsy", a flexible miniature endomicroscope with imaging capability comparable to standard bench-topmicroscopes is highly needed, and recent years have witnessed increasing interest in this field. Our newly-developed endomicroscope features a single customized double-clad fiber with a large inner-clad, a piezoelectric actuator-based fiber-optic micro-scanner, and a highly achromatic miniature objective lens. The system achieves high signal collection efficiency with low background noise, which enables intrinsic TPF and SHG imaging with an excitation power of 20~40 mW. TPF imaging using our endomicroscope can clearly visualize cellular structure of mouse small intestines. Moreover, TPF signals in NADH and in FAD band can be detected simultaneously to evaluate cellular redox ratio. SHG imaging using our endomicroscope can reveal the collagen structure in mouse cervical tissue and characterize its progressive remodeling during gestation, which can be potentially useful for preterm birth risk assessment. Furthermore, our endomicroscope can be supplied with a small-footprint femtosecond fiber laser of excellent portability and stability, thus the whole system can be easily moved to clinical practice and used either directly or through integration with commercial endoscopes. In summary our high-performance endomicroscopy system demonstrates a strong potential for translating multiphoton imaging modalities to various clinical applications.

Poster I.D.: #33
Display date: Wednesday, June 19

Intracellular oxygen: Evaluation by two methods

Presenter: David Lloyd
lloydd@cf.ac.uk

D. Lloyd, C.F. Williams, M. Kombrabail, K. Vijayalakshmi, N. White, G. Krishnamoorthy
Department of Biosciences, Cardiff University
Cardiff, Wales, CF10 3AT
United Kingdom

For a non-invasive approach of mapping intracellular O_2 tensions, two methods of phosphorescent lifetime imaging microscopy were examined. These were: 1. picosecond time-resolved epiphosphorescence microscopy (single 0.5 µm focused spot), and 2. two-photon confocal laser scanning microscopy with pinhole shifting. Both methods utilized nanoparticle-embedded Ru complex (45 nm diameter) as the phosphorescent probe, excited using pulsed outputs of Ti–sapphire Tsunami lasers (710–1050 nm). The former method used a 1 ps pulse width excitation beam with vertical polarization via a dichroic mirror (610 nm, XF43) and a 20X objective (NA 0.55, Nikon). Transmitted luminescence (>104 counts/s) was collected and time-correlated single photon counted decay times measured. Alternatively, an unmodified Zeiss LSM510 Confocal NLO microscope with 40X objective (NA 1.3) used successivelyshifted pinhole positions to collect image data from the lagging trail of the raster scan. Images obtained from two-photon excitation of a yeast (*Schizosaccharomyces pombe*) and a flagellate fish parasite (*Spironucleus vortens*), electroporated with Ru complex, indicated the intracellular location and magnitude of O_2 gradients, thus confirming the feasibility of optical mapping under different external O_2 concentrations. Both methods gave similar lifetimes for Ru complex phosphorescence under aerobic and anaerobic gas phases. Estimation of O_2 tensions within individual fibroblasts (human dermal fibroblast (HDF)) and mammary adenocarcinoma (MCF-7) cells was possible using epiphosphorescence microscopy. MCF-7 cells showed lower intracellular O_2 concentrations than HDF cells, due to highermetabolic rates in the former. Future work will provide higher resolution 3D maps of Ru coordinate complex lifetime distributions.

Poster I.D.: #23
Display date: Tuesday, June 18

Validation of optically measured cerebral venous oxygen saturations in humans

Presenter: Jennifer Lynch
jenlynch@sas.upenn.edu

Jennifer M. Lynch, Erin M. Buckley, Peter Schwab, Mary E. Putt, Brian D. Hanna,
Daniel J. Licht, and Arjun G. Yodh
Department of Physics, University of Pennsylvania
Philadelphia, PA, 19102
United States

Diffuse Optical Spectroscopy (DOS) is a well-established and widely accepted modality for non-invasively measuring concentrations of oxy- and deoxy-hemoglobin ([HbO_2] and [Hb]) in tissue. Specifically, it is well suited for measurement of cerebral tissue oxygen saturation. However, while cerebral tissue oxygen saturation provides some insight into how oxygen is being utilized by the brain, quantification of cerebral oxygen extraction requires separate measurements of arterial and venous saturations. Measures of cerebral arterial oxygen saturation are easily attainable, but cerebral venous oxygen saturation is much more difficult to measure, especially non-invasively and without potentially dangerous perturbations such as venous occlusion. To isolate the venous component of the DOS signal without a perturbation, a method has been proposed previously that utilizes the oscillations of the venous blood volume at the respiration rate. However, direct comparison against a gold standard measurement in humans has not been performed. To this end, we validate this method against the gold standard invasive measurement of central venous saturations. We compare the optically measured SvO_2 against an oxygen saturation measured from a blood sample taken from the superior vena cava (SVC) in a pediatric population (N=9) for which this invasive measurement is part of clinical care. The SVC saturation exhibits good agreement with the optical measurements (R_2=0.79, $p<0.01$, slope=1.1±0.5), thereby demonstrating the ability to non-invasively measure cerebral SvO_2 unambiguously with DOS.

Poster I.D.: #29
Display date: Wednesday, June 19

From isolated mitochondria to *in vivo* determination of oxygen and glucose consumption

Presenter: Gheorghe Mateescu
gdm2@case.edu

G.D. Mateescu[1], G. Yvars[1], T. Dular[1], J. LaManna[2], A. Ye[1], B. Erokwu[4], C. Flask[3,4], X. Yu[4], M. Griswold[3,5], and J. Duerk[3]
Departments of [1]Chemistry, [2]Physiology, [3]Biomedical Engineering, Chemistry
Case Western Reserve University, Cleveland, OH, 44106
United States

Inspired by the seminal papers of Britton Chance, *in vivo* determination of oxygen consumption was pioneered at Case Western Reserve University in the late 1980s. Recently, simultaneous determination of glucose and oxygen consumption has been implemented via deuterium MR following administration of deuteriated glucose. MRF (Magnetic Resonance Fingerprinting) will make it possible to diagnose mitochondrial function in times suitable for clinical imaging.

Poster I.D.: #24
Display date: Tuesday, June 18

CHOP therapy-induced mitochondrial redox state alteration in Non-Hodgkin's lymphoma xenografts

Presenter: Tahreem Mir
tahreemaman2008@hotmail.com

H.N. Xu, H. Zhao, T.A. Mir, S.C. Lee, M. Feng, R. Choe, J.D. Glickson, and L.Z. Lia
Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA
The Aga Khan University, Medical College Karachi, Sindh, 74800
Pakistan

The redox scanner that collects the fluorescence signals from both the oxidized-flavoproteins (Fp) and the reduced form of nicotinamide adenine dinucleotide (NADH) in snap-frozen tissues has been previously employed to study tumor aggressiveness and treatment responses. Cancer therapy may alter the mitochondrial redox state in cancer cells to inhibit their growth and survival. Here we investigated the effects of chemotherapy on mouse xenografts of a human diffuse large B-cell lymphoma cell line (DLCL2). The mice were treated with CHOP therapy, i.e., cyclophosphamide (C) + hydroxydoxorubicin (H) + Oncovin (O) + prednisone (P) with CHO administration on day 1 and prednisone administration on day 1-5. The Fp content of the treated group was significantly decreased ($p=0.033$) on day 5, and the mitochondrial redox state of the treated group was slightly morereduced than that of the control group ($p=0.048$). The decrease of the Fp heterogeneity (mean standard deviations) had a border-line statistical significance ($p=0.071$). The result suggests that the mitochondrial metabolism of lymphoma cells was slightly suppressed and the lymphomas became less ag-gressive after the CHOP therapy.

Poster I.D.: #38B
Display date: Wednesday, June 19

The redox imaging of mouse muscles of different ages

Presenter: Lily Moon
lilymoon88@yahoo.com

Lily Moon, David Frederick, Joseph A Baur, and Lin Z Li
Department of Radiology, University of Pennsylvania
Philadelphia, PA
United States

The redox state of mitochondria may reflect a number of parameters related to aging, including mitochondrial reserve, free radical damage and coupling efficiency. Oxidized flavoprotein (Fp) and NADH are intrinsic fluorescent indicators of oxidation and reduction status of tissue. We used the Chance redox scanner (NADH/Fp fluorescence imaging at low temperature) to study the effect of aging on the redox state of skeletal muscle mitochondria. Six elder (age13 months) and six young (age 14 weeks) mice were sacrificed by cervical dislocation and the hind limb muscles were immediately dissected. The whole quadricep muscle was removed from the anterior surface of the femur and cleaned of residual adipose, then the quadriceps were flash frozen in liquid nitrogen. The time from cervical dislocation to snap freezing was 10 to 16 minutes. We used the Chance redox scanner to obtain the images of Fp, NADH, and Fp redox ratio i.e. Fp/(Fp + NADH) . The mean of Fp ($p=0.01$), mean of NADH ($p=0.04$) and Fp ratio ($p=0.16$) of young mice were greater than those of the elder group. These data indicate that the mitochondria of young muscles are in a more oxidized metabolic state.

Poster I.D.: #38A
Display date: Wednesday, June 19

Redox state imaging of the oral cancer; working progress report

Presenter: shoko nioka
shoko@nioka.net

Hsin-Ru Hung, Teng Yi Huang, Shoko Nioka, Dar Bun Shieh, and Pau-Choo Chung
Department of Communication and Electrical Engineering, NCKU
Philadelphia, PA, 19104
United States

Taiwan's oral cancer incidence rate is the highest in the world. In the Taiwan's 2008 Cancer Report, oral cancer incidence and mortality rate in Taiwan ranks fourth as cause of death in men. Further, India reports the highest prevalence of oral cancers globally with 85% of the world. We developed a device to diagnose an early stage of oral cancer with minimum effort for patients and health care personnel. Redox state imaging has been known to show mitochondrial changes in the metabolism, as the glycolysis is enhanced with and without hypoxia, resulted in high NADH/FAD ratio. We used LEDs for NADH and FAD excitations and CCD camera with proper filters which imaged of the auto fluorescence from the mucosa of the oral cavity. Hamster xenograft was used to produce oral cancer with human oral cancer cell line. We observed the process of cancer growth from 1 week before the inoculation to the death. The results showed very significant decreases in intensities of the both auto fluorescence. There was an increase in the vascularity of the cancer, which contributed the fluorescence absorption. The cancer redox ratio (NADH/FAD) became elevated. We include hemoglobin imaging and relation to the redox ratio. Our question is that hypoxia causes the high redox ratio in the cancer.

Poster I.D.: #39
Display date: Wednesday, June 19

Mesoscopic fluorescence molecular tomography applied to engineered tissue construct and mouse skin tumor

Presenter: Mehmet Ozturk
ozturm@rpi.edu

Mehmet S. Ozturk, Vivian K. Lee, Lingling Zhao, Guohao Dai, and Xavier Intes
Department of Biomedical Engineering , Rensselaer Polytechnic Institute
Troy, NY, 12180
United States

Mesoscopic Fluorescence Molecular Tomography (MFMT) is a fluorescence imaging technique for deep tissue interrogation (~3-5mm deep) with relatively high resolution (~200um). Here we present the applications of MFMT to diverse biomedical imaging scenarios. First, we demonstrate the potential of MFMT to image both structure and function in thick tissue constructs. 3D image reconstruction of GFP and mCherry reporter gene expressing cells printed in a thick collagen matrix is performed. Far red fluorescent beads are perfused into one of the channels to image the structure of the printed channel. Second, MFMT system is used to image the bio distribution of a PhotoDynamic agent in preclinical skin cancer tumors. Mice were imaged 20 and 40 hours after intraperitoneal injection of HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a). Optical reconstructions were benchmarked against Ultrasound interpolated A-scan images. They demonstrated excellent agreement between both modalities. In summary, we have demonstrated the capabilities of MFMT with *in vitro* and *in-vivo* studies. This establish MFMT as a suitable imaging modality for deep tissue molecular imaging.

Poster I.D.: #40
Display date: Wednesday, June 19

Redox imaging distinguishes indolent and metastatic melanoma xenografts

Presenter: April Peng
penapril@seas.upenn.edu

April Peng, Lily Moon, Lin Z. Li
Department of Bioengineering
University of Pennsylvania School of Engineering and Applied Sciences, Philadelphia, PA, 19104
United States

Fluorescence images of snap-frozen mouse xenografts of two human melanoma tumor lines, A375P and A375M, were produced using the Chance redox scanner that gathered fluorescence signals from oxidized flavoproteins (Fp) and reduced nicotinamide adenine dinucleotide (NADH) and analyzed for biomarkers to distinguish tumor metastatic potentials. The A375M cell line originated from lung metastases of A375P cells and is known to be more invasive and metastatic. The resulting redox images of both tumor lines showed the existence of oxidized regions (core) and reduced regions (rim) in tumors with the metastatic A375M tumors being more heterogeneous than the A375P tumors. The redox imaging data were analyzed using section-average and core-and-rim methods. Section-average analysis obtained the average of each image section in its entirety while the core-and-rim analysis considered the distinguishable oxidized and reduced regions of an image section and obtained core-and-rim averages. All redox indices were averaged across multiple sections within a tumor, and then averaged across multiple tumors to obtain the mean values for each tumor line. Student's t-tests comparing tumor cores and rims determined a significant difference between redox ratios (Fp/(Fp+NADH)) of the oxidized cores and reduced rims for both tumor lines (A375P: $p=0.0015$; A375M: $p=0.0036$) while the difference among A375M tumors was greater than that among A375P tumors. The A375M line of higher metastatic potential consistently displayed greater oxidation than the A375P line. These results indicate that tumor heterogeneity is an important factor in tumor progression and that redox imaging may be useful for tumor diagnostics.

Poster I.D.: #31
Display date: Wednesday, June 19

Delivery rate affects uptake of a fluorescent glucose analog in murine metastatic breast cancer

Presenter: Narasimhan Rajaram
n.rajaram@duke.edu

Narasimhan Rajaram, Amy Frees, Mark Dewhirst and Nimmi Ramanujam
Department of Biomedical Engineering, Duke University
Durham, North Carolina, 27705
United States

We demonstrate an optical strategy using intravital microscopy of dorsal skin flap window chamber models to image glucose uptake, oxygen saturation (SO_2) and the effects of delivery and decay kinetics on glucose uptake *in vivo*. Glucose uptake was imaged using a fluorescent analog of [18F]-FDG, 2-[N-(7-nitrobenz-2-oxa-1,3-diaxol-4-yl)amino]-2-deoxyglucose (2-NBDG). SO_2 was imaged using the differential absorption properties of oxygenated [HbO_2] and deoxygenated hemoglobin [dHb]. This study was carried out on two sibling murine mammary adenocarcinoma lines, 4T1 and 4T07. Vascular and metabolic characteristics of both tumors were imaged at baseline and after breathing hypoxic gas to cause a reoxygenation-induced increase in blood flow. Breathing hypoxic gas significantly increased SO2 in the 4T1 tumors ($p = 0.03$). The increased SO_2 was due to an increase in [HbO_2] ($r = 0.87$; $p = 0.001$), indicating increased blood flow in the tumors. At low rates of delivery that did not exceed the glucose consumption rate (as measured *in vitro*), both 2-NBDG uptake by the tumor and the clearance rate from the tumor was increased. However, when the delivery rate exceeded the glucose consumption rates of the tumor, 2-NBDG-uptake decreased but the clearance rate continued to increase. In summary, our findings demonstrate that uptake of glucose tracers such as 2-NBDG is dependent on rate of delivery to the tumor. Because delivery rate is influenced by blood flow, it is essential to determine kinetics of tracer uptake as well as SO_2 to make an informed assessment of the metabolic demand of a tumor.

Poster I.D.: #41
Display date: Wednesday, June 19

Blood flow and oxygenation correlate with local PDT dose and response

Presenter: Daniel Rohrbach
daniel.rohrbach@roswellpark.org

Daniel J. Rohrbach, Mary Jo Bowman, Erin Tracy, Heinz Baumann, Nestor Rigual, Barbara Henderson, and Ulas Sunar
Department of Cell Stress Biology, Roswell Park Cancer Institute
Buffalo, NY, 14202
United States

Noninvasive optical spectroscopy can provide near real-time parameters related to therapy efficacy. Here we tested whether pre-treatment and early changes in blood flow and oxygenation will be indicative of PDT response in an animal model and a clinical study. C3H mice with subcutaneous SCCVII tumors were treated with 0.47 µmol/kg HPPH and 100J treatment light but at two fluence rates: low (14mW/cm^2) and high (75mW/cm^2). Tumor blood flow was monitored continuously during PDT using diffuse correlation spectroscopy (DCS). After treatment the tumors were removed to determine the percent crosslinking of Signal Transducer and Activator of Transcription 3 (STAT3), a molecular biomarker for photoreaction. We observed significant differences in blood flow changes between the two fluence rate groups. Blood flow showed a high correlation with STAT3 crosslinking (r2 = 0.87). Mice in the low fluence rate group showed higher average STAT3 crosslinking than those in the high fluence rate group (19.2 ± 6.1% vs. 7.0 ± 2.8% respectively). Continuous monitoring of blood flow changes can provide an *in vivo* marker related to local PDT dose indicative of PDT efficacy allowing real-time feedback which can lead to more effective PDT. We further investigated these parameters in clinical-PDT for head and neck cancer of the oral cavity. Preliminary results indicate that blood flow correlates with STAT3 crosslinking while the combination of multiple parameters including blood oxygenation, blood flow and photosensitizer content is the strongest predictor of response. RPCI startup support grant (P30CA16056) and NCI CA55791

Poster I.D.: #42
Display date: Wednesday, June 19

Characterization and stress tolerance assessment of bacteria from agricultural soils

Presenter: Saumyadip Sarkar
saumyadip.gis@gmail.com

Saumyadip Sarkar, Fenella Nongkhlaw, Dr. S. R. Joshi
Department of Microbiology, GITAM Institute of Science, GITAM University
Kolkata, West Bengal, 700028
India

Soil samples were collected from rice fields and plated on Brown's N-free medium. Isolated colonies (7 in number) were selected for study of heavy metal tolerance on Copper (Cu), Lead (Pb), Zinc (Zn) and Cadmium (Cd). The isolates were grown at a gradually elevated level of different heavy metal concentrations on low phosphate medium. Amongst 7 colonies sample D10 showed maximum resistance towards Zn at 80mM, for Pb sample D10 showed maximum resistance at 1.5mM, for Cd sample D3 at 1.5mM and Cu, sample D3 at 50mM respectively. Selected samples were tested for antibiotic sensitivity and their MIC were determined. Phosphate solubilization, chitin digestion, cellulase producing ability, pectindigestion, and indole acetic acid production was also studied. Samples were identified by 16S rRNA gene sequence. D1 was identified to be Pseudomonas sp.

Poster I.D.: #30
Display date: Wednesday, June 19

Optical measure of muscle oxygenation

Presenter: Ken Schenkman
ken.schenkman@seattlechildrens.org

Lorilee S. L. Arakaki, Wayne A. Ciesielski, Jeremy M. Shaver, and Kenneth A. Schenkman
Department of Pediatrics, University of Washington, Seattle, WA, 98105
United States

In shock, impaired cardiac output and decreased peripheral perfusion results in decreased oxygenation of muscle. Early recognition of shock is critical to timely treatment that would help prevent the cascade of events leading to long-term hospitalizations and/or death by multiple organ failure. We have developed a reflectance optical system that measures muscle oxygenation (Mox) noninvasively from the surface of the skin in the visible-NIR region. Low Mox measured from an extremity like the hand can identify low tissue perfusion early since during shock, blood is shunted from the extremities to preferentially perfuse and oxygenate core internal organs (e.g., heart, lungs, and liver) and the brain. The physical and biological differences between human subjects present a complicated problem when predicting Mox, a measure of the relative amounts of oxygenated and deoxygenated hemoglobin and myoglobin in the muscle. Using multiwavelength analyses, we have demonstrated correlation between Mox and hypoxia in animals subjected to sub-ambient FiO_2 and also in animals subjected to hemorrhagic shock and resuscitation. We have also demonstrated correlations between Mox and clinical severity in human trauma victims and humans with septic shock. These data indicate that our optical monitor of muscle oxygenation may be able to identify patients at risk for worsening shock and may be helpful in monitoring response to therapy in emergency departments and intensive care units.

Poster I.D.: #43
Display date: Wednesday, June 19

DCS and ASL measurements of CO_2 reactivity in children with HLHS undergoing staged surgical palliation

Presenter: Peter Schwab
schwab.peter.j@gmail.com

Peter J. Schwab, Jennifer M. Lynch, David R. Busch, Erin M. Buckley, Mary E. Putt, Daniel J. Licht, Arjun G. Yodh, Mark A. Fogel
Department of Neurology, The Children's Hospital of Philadelphia
Philadelphia, PA, 19104
United States

Depressed CO_2 reactivity has been shown to correlate with both short-term cognitive dysfunction and hypoxic-ischemic neurological injury in pediatric populations. We use concordance correlation to compare Arterial Spin Labeling MRI (ASL-MRI) and Diffuse Correlation Spectroscopy (DCS) measurements of CO_2 reactivity in children with hypoplastic left heart syndrome (HLHS). DCS is inexpensive, portable, and less intimidating for a child than MRI measurements like ASL. Longitudinal episodic optical measurements of cerebral blood flow with DCS are feasible, provide data comparable to ASL data, and may be clinically useful for tracking CO_2 reactivity in HLHS patients as they progress through staged surgical palliation, potentially informing the timing of each surgery.

Poster I.D.: #44
Display date: Wednesday, June 19

Distinguishing cortical bone bound and pore water by T2* at multiple magnetic field strengths

Presenter: Alan Seifert
aseifert@seas.upenn.edu

Alan C. Seifert, Suzanne L. Wehrli, Henry H. Ong, Cheng Li, Jeremy F. Magland, and Felix W. Wehrli
Department of Radiology, University of Pennsylvania
Philadelphia, PA, 19104
United States

^{1}H NMR signals arising from free and collagen-bound bone water can be differentiated based on their T2 relaxation times (bound T2~400µs, free T2>1ms), but due to the presence of severe susceptibility-induced field gradients at bone-water interfaces, the T2* of free water in small pores is reduced to near that of bound water. Because susceptibility-induced field inhomogeneities are more severe at high fields, there may be a limit above which differentiation based on T2* is impossible. To assess the separability of bone water fractions, we performed multi-exponential fitting of free-induction decays (FIDs) from eight cylindrical lamb tibial cortical bone specimen at 1.5T, 3T, and 7T. Custom PTFE transmit/receive solenoidal RF coils were used. Mono-, bi-, and tri-exponential functions were fit to each real-component FID. To measure actual bone water fractions, bones were immersed in 99.9% D2O-saline for 72hr at room temperature, then scanned at 9.4T using 2H inversion recovery spectroscopy.Mono-component T2* fits were of poor quality at 1.5T and 3T, but of better quality at 7T, where T2* of pore water approaches that of bound water. Bi-component T2* fitting significantly underestimates actual pore water at all field strengths, although fitted fractions do correlate with actual bone water fractions at 1.5T and 3T. Tri-component T2* fitting is not physically realistic, and leads to data overfitting. Although long-T2* component fraction at 1.5T and 3T may be a useful surrogate for porosity, T2* fitting is unable to accurately measure bone water fractions at clinical field strengths.

Poster I.D.: #8
Display date: Tuesday, June 18

Multiparametric monitoring of rat cortex based on NADH fluorescence in different causes of hypoxia

Presenter: Hua Shi
huashi@mail.hust.edu.cn

Hua Shi, Nannan Sun, Avraham Mayevsky, Zhihong Zhang, Qingming Luo
Britton Chance Center for Biomedical Photonics, Huazhong University of Science and Technology,
Wuhan National Laboratory for Optoelectronics
Wuhan, Hubei, 430074
China

According to the different stages of oxygen transport in body, hypoxia can be classified by the cause of the reduced brain oxygen: hypoxic, hypaemic, circulatory, and histogenous hypoxia. Current clinical hypoxia measurements utilize blood oxygen indices targeted to the global blood oxygenation properties of the first three stages, but the regional histogenous hypoxia is hard to be recognized. As Dr. Britton Chance concluded in 1973, NADH can be considered as an oxygen indicator in mitochondria and tissues. Several trials have been proceeded focused on the hypoxia models applied in rat cortex *in vivo* since 1962. We have tried to establish the four different pathological models caused from the four hypoxia types, monitored the change of NADH fluorescence, cerebral blood flow and other parameters during the course beginning from induced hypoxia to death, and summarized the multiparametric patterns for specific types of hypoxia. The results contributed to the possibility to introduce multiparametric monitoring based on NADH fluorescence to clinic application.Our study indicated the combination of NADH fluorescence and cerebral blood flow is sufficient to distinguish the four types of hypoxia death models, which is gratifying to support NADH fluorescence as one of the sensitive indices to clinic diagnosis of hypoxia. This method can be also applied in monitoring other organs.

Poster I.D.: #45
Display date: Wednesday, June 19

Changes of cerebral hemodynamics and metabolism in a rat model of severe hemorrhagic shock

Presenter: Nannan Sun
sunnan721@gmail.com

Nannan Sun, Lin Li, Weihua Luo, Qingming Luo
Wuhan National Laboratory for Optoelectronics, Huazhong University of Science and Technology and University of Pennsylvania
Philadelphia, Pennsylvania, 19104
United States

It is important to understand how the preservation of cerebral microcirculation works and how the irreversible damage of cerebral hemodynamic performance and mitochondrial metabolism of brain tissue happen during severe hemorrhage shock, especially the decompensatory stage. In this study, we used a multi-parameter cerebral cortex optical imaging system to obtain the long-lasting (4 hours) observation of cerebral hemodynamic change and metabolic alteration of exposed cortex of rats during severe hemorrhagic shock (rapid bleeding until blood pressure down to 40 mmHg, maintaining the level for two hours followed by fluid resuscitation). The observation parameters include blood pressure, cerebral blood flow (CBF), function vascular density (FVD), vascular perfusion, blood oxygenation and mitochondrial NADH signal. In compensatory stage, CBF decreased rapidly due to the deficiency in vascular perfusion but FVD and NADH can be well preserved. During the transition process from compensatory to decompensatory stage, NADH signal showed a visible rise as well as total hemoglobin, while FVD showed a marked decline in the meantime. In the decompensated stage, various parameters were abnormal and cerebral perfusion and metabolic state were impaired. In conclusion, we present for the first time simultaneous imaging of hematological dynamic and NADH signals *in vivo*. This novel multi-lever method provides clear result that the severe hemorrhagic shock suffers irreversible damage which cannot be compensated by the autoregulation mechanism, probably because of injured mitochondria. Signature changes of mitochondrial metabolic state may be used as a sensitive marker between compensatory stage and decompensatory stage in hemorrhage shock.

Poster I.D.: #6
Display date: Tuesday, June 18

Multimodal imaging of skin cancer for surgery and treatment planning

Presenter: Ulas Sunar
ulas.sunar@roswellpark.org

Ulas Sunar, Dan Rohrbach, Dan Muffoletto, Rolf Saager, Janet Morgan, and Natalie Zeitouni
Department of Cell Stress Biology and Oncology, Roswell Park Cancer Institute
PDT Center, Optical Imaging, Buffalo
United States

Nonmelanoma skin cancers (NMSCs) have increased dramatically, with more than a million new cases worldwide each year. Treatment is usually either by excision or Mohs micrographic surgery and alternatively may include photodynamic therapy (PDT). Any tool that can help to delineate the depth of the tumor and assess the margins would guide surgery or PDT and lead to better pre-treatment planning. PDT has shown variable responses depending on the operator and treatment protocol with much lower success rates in treating thicker tumors. For effective PDT with minimal damage to normal tissue, an appropriate treatment field has to be outlined. Incorrect treatment planning may result in under-treatment and ultimately recurrence or over-treatment of surrounding normal tissue. Thus, there exists a need for routine evaluation of tumor thickness and vascularity. Several noninvasive imaging modalities have been applied for skin cancer. Among them, high frequency ultrasound provides high resolution (~50 μm) as well as deep penetration depth (>2 mm). However, the technique relies on mechanical contrast rather than functional contrast. Optical imaging can complement high resolution ultrasound with its high functional contrast and sensitivity. Photoacoustic imaging, which is based on generating sound waves via optical absorption of laser pulses, can achieve resolution of ~50 μm at ~3 mm depth with vascular contrast. We will present preliminary results from our recently developed clinical multi-modal instrument. Our results indicate that multimodal approach can map optical and ultrasound contrasts to enable clinicians to better discriminate the tumors from normal tissue.

Poster I.D.: #46
Display date: Wednesday, June 19

Novel optical method for neural functions in deep brain *in vivo*

Presenter: Qinggong Tang
qtang@umd.edu

Qinggong Tang,Vassiliy Tsytsarev,Chia-Pin Liang,Chao-Wei Chen,Yu Chen
Department of Bioengineering, University of Maryland-College Park
College Park, Maryland, 20740
United States

Currently used fast CCD camera-based voltage-sensitive dye imaging (VSDi) can only provide two-dimensional information. We combined VSDi with gradient refractive index (GRIN) lenses to study neural functions in deep brain. Neural activities in mouse thalamus were imaged *in vivo* during whisker stimulation.

Poster I.D.: #10
Display date: Tuesday, June 18

Nanoparticles encapsulated polymeric microbubbles for multimodal imaging

Presenter: Nutte Teraphongphom
tnutte@gmail.com

N.T. Teraphongphom, P. Chhour, W. Witschey, D.P. Cormode, M.A. Wheatley
School of Biomedical Engineering, Science and Health Systems
Drexel University, Philadelphia, Pennsylvania, 19103
United States

Ultrasound Contrast Agents (UCA) are microencapsulated gas bubbles used to increase the overall contrast of the ultrasound (US) image. Novel multimodal polymeric UCA containing additional contrast agents that are active in multiple imaging modalities have been developed. Four platforms of loaded poly (lactic acid) (PLA) shelled UCA are presented. The first two platforms co-encapsulate aqueous or organic Quantum Dots (QD). The Third platform contains magnetic iron oxide nanoparticles (MNP). The fourth platform contains Gold Nanoparticles (Au-NP). All platforms showed that the properties of UCA are maintained as well as the properties of additional encapsulated contrast agent. This study explores the potential application for improving the screening of a subject using at least two different modalities, e.g. ultrasound and fluorescence, ultrasound and magnetic resonance imaging (MRI) and ultrasound and computerized tomography (CT).

Poster I.D.: #7
Display date: Tuesday, June 18

Regulation of oxidative and glycolytic metabolism by variation in O_2 availability: 2-photon imaging of NADH in cerebral cortex *in vivo*

Presenter: Hana Uhlirova
huhlirova@ucsd.edu

Hana Uhlirova, Sava Sakadžić, Krystal Nizar, Mohammad A. Yaseen, Payam A. Saisan, Qun Cheng, Kimberly Weldy, Lidia Reznichenko, Meryem A. Yucel, Gabriel A. Silva, Yuchio Yanagawa, Karl A. Kasischke, Anders M. Dale, Eliezer Masliah, David A. Boas, and Anna Devor
Department of Radiology, UCSD La Jolla, California, 92093
United States

Oxidative phosphorylation in isolated mitochondria responds to changes in partial pressure of O_2 (pO_2) within physiological limits (Wilson et al, 2012). Previously we demonstrated large variations in the baseline tissue pO_2 in cerebral cortex due to diffusion of O_2 from highly oxygenated arterioles (Devor *et al*, 2011). Using *in vivo* 2-photon imaging of nicotinamide adenine dinucleotide (NADH) in the mouse cerebral cortex, we asked if these differences could affect oxidative metabolism. Our results demonstrate that both the baseline and stimulus-induced NADH signals depended on the distance from diving arterioles and were modulated by breathing pure O_2. The baseline results confirmed (Kasischke *et al*, 2010). In subjects exhibiting stimulus-induced vasodilation, NADH signal rapidly decreased in proximity to diving arterioles. In contrast, the signal increased at distances >110 microns from diving arterioles probably reflecting limited pO_2. The same remote regions exhibited a more pronounced secondary signal decrease immediately after the peak of vasodilation, possibly due to (1) an increase in tissue pO_2 promoting oxidative metabolism and (2) restoration of extracellular lactate. This later NADH decrease was not present without the dilation response. In non-dilating animals, large-amplitude initial NADH decrease was observed both in the close and far regions possibly due to a low level of spontaneous activity, low baseline O_2 consumption, and higher tissue pO_2. As in the case of dilating subjects, an overshoot was detected only in the remote region. These results show that normal variation in O_2 availability affects the preference of cerebral tissue for oxidative or glycolytic pathways.

Poster I.D.: #25
Display date: Wednesday, June 19

Quantitative physiology and immunohistochemistry of oral lesions

Presenter: Hsing-Wen Wang
hwwang@umd.edu

Li-Tzu Lee, Po-Hsiung Chen, Chiou-Tuz Chang, John Wang, Yong-Kie Wong, and Hsing-Wen Wang*
Department of Bioengineering, University of Maryland, Arlington , VA, 22202
United States

Angiogenesis and hypoxia have been reported to correlate with tumor aggressiveness. In this study, we investigated the potential of optically estimated total hemoglobin concentration (THC) and blood oxygen saturation (StO_2) as a quantitative measure of angiogenesis and hypoxia in oral lesions by comparing with immunohistochemistry. 12 normal subjects and 40 oral patients (22 malignant oral squamous cell carcinoma (SCC), 11 verrucous hyperplasia (VH), and 7 hyperkeratosis/parakeratosis (HK)) were studied. The results showed that THC was correlated with microvessel staining in all lesions, but StO_2 was not correlated with Hif-1a. The high THC and StO_2 in all lesions were due to angiogenesis and inflammation induced neovascular formation resulting in no differentiation between lesions. By combining optical measurements of adjacent tissues, we found relative angiogenesis and hypoxia in SCC, but not in VH or HK patients. These two features allowed VH and SCC to be distinguished with a sensitivity of 91%.

Poster I.D.: #47
Display date: Wednesday, June 19

Molecular imaging of colorectal cancer in 3D by fluorescence laminar optical tomography

Presenter: Jianting Wang
wangjianting@gmail.com

Jianting Wang, Chao-Wei Chen, Anthony Fouad, Siddarth Plakkot, and Yu Chen
Fischell Department of Bioengineering, University of Maryland, College Park
College Park, MD, 20742
United States

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer-related mortality in the United States. Early detection is the key to patient survival. While conventional endoscopy is often able to detect the adenomatous polyps that can develop into CRC, many flat (non-polypoid) lesions are missed during routine exams up to 50%. Optical molecular imaging provides high sensitivity and resolution in detecting the molecular changes in the tissue. Here we have applied targeted, molecular fluorescent contrast agents to APCmin mouse model of colorectal cancer, and imaged the colon tissue using our angled fluorescence laminar optical tomography (aFLOT) system. The aFLOT system demonstrated the ability to provide depth-resolved molecular information of the CRC with 100-200 μm resolution over ~2 mm depth, showing the potential of providing real-time assessment of the morphology of the tumor simultaneously to the sensitive detection.

Poster I.D.: #11
Display date: Tuesday, June 18

Hyperspectral imaging to discern malignant and benign canine mammary tumors

Presenter: Chang-Hee (Andy) Won
cwon@temple.edu

Amrita Sahu, Cushla McGoverin, Nancy Pleshko, Karin Sorenmo, Chang-Hee Won
Electrical and Computer Engineering, Temple University
Philadelphia, PA, 19122
United States

Hyperspectral imaging is an emerging technology in the field of biomedical engineering which may be used as a non-invasive modality to characterize tumors. A hyperspectral imaging system was used to characterize canine mammary tumors of unknown histopathology and correlate these results with the post-surgical histopathology results. The system consisted of a charge coupled device camera, a liquid crystal tunable filter in the near infrared range and a controller. Spectral signatures of malignant and benign canine mammary tumors were extracted and analyzed. The reflectance intensities of malignant tumor spectra were generally lower than benign tumor spectra over the entire wavelength range. Previous studies have shown that cancerous tissues have a higher hemoglobin and water content, and lower lipid concentration with respect to benign tissues. The decreased reflectance intensity observed for malignant tumors is likely due to the increased microvasculature and therefore higher blood content of malignant tissue relative to benign tissue. Peaks at 700, 840, 900 and 970 nm were observed in the second derivative absorption spectra, these peaks were attributed to deoxy-hemoglobin, oxy-hemoglobin, lipid and water respectively. A 'Tissue Optical Index' was developed that enhances contrast between malignant and benign canine tumors. This index is based on the ratio of the reflectance intensity values corresponding to the wavelengths associated with the four chromophores. Preliminary results from 22 canine mammary tumors showed that the sensitivity and specificity of the proposed method is 85.7% and 94.6% respectively. These results show promise in the non-invasive optical diagnosis of canine mammary cancer.

Poster I.D.: #3
Display date: Tuesday, June 18

Spontaneous FAD dynamics reveal functional connectivity patterns in mice

Presenter: Patrick Wright
pwwright@wustl.edu

Patrick W. Wright, Adam Q. Bauer, Joseph P. Culver
Department of Biomedical Engineering, Washington University in Saint Louis
Saint Louis, Missouri, 63112
United States

Functional connectivity (FC) describes functional relationships within brain networks and has been recently mapped in mice using optical intrinsic signal (OIS) imaging. Here we extend FC imaging beyond hemodynamic contrasts to metabolite dynamics, in particular to that of flavin adenine dinucleotide (FAD). Whereas the hemodynamic response elicited by neural activity is indirect via a multi-step neurovascular coupling process, optical signals via metabolites (e.g. FAD) allow for imaging of cellular mechanisms known to be part of synaptic potential events. FAD is excited in the blue range of the visible light portion of theelectromagnetic spectrum and subsequently fluoresces green. The increased availability of calcium following neuronal action potentials allows for aerobic energy metabolism to occur, leading to the oxidation of flavoproteins and consequently, the potential for autofluorescence. Though previous studies have used FAD autofluorescence imaging to characterize metabolic activity in studies of cortical plasticity and somatosensory evoked responses, no studies have assessed the utility of it as an index for FC analysis. Wild-type Swiss Webster mice were imaged transcranially with sequential illumination provided by three collimated, collinear LEDs. Mechanical stimulation of the right hindpaw was used to quantitatively evaluate the spatial and temporal resolution of the FAD signal as compared to concurrently acquired OIS. Evaluation of spontaneous FAD signals demonstrated their ability in mapping FC patterns directly from metabolite dynamics. Mouse-specific FAD and OIS FC mapping of the neuronal metabolism and hemodynamic response, respectively, could provide a link between molecular level mouse models of disease and clinical human disease.

Poster I.D.: #5A
Display date: Tuesday, June 18

Is higher lactate production an indicator of tumor metastatic risk? – A pilot study using hyperpolarized ^{13}C-NMR

Presenter: He Xu
hexu3897@yahoo.com

He N. Xu, Stephen Kadlececk, Harrilla Profka, Ben Pullinger,
Jerry D. Glickson, Rahim Rizi, and Lin Z. Li
Department of Radiology, University of Pennsylvania, Philadelphia, PA, 19104
United States

Tumor metastatic risk determination remains one of the greatest clinical challenges due to the lack of reliable biomarkers of metastatic potential. Increased glycolysis resulting in higher lactate production under conditions of sufficient oxygen supply (the Warburg effect) has been demonstrated in tumor tissues in numerous studies including some that employed hyperpolarized ^{13}C-NMR. High grade metastatic tumors may or may not grow faster than low grade non-metastatic tumors. It is not entirely clear if the difference in levels of hyperpolarized lactate reflects differences in tumor growth rate or tumor metastatic potential or both. To answer this question, we examined two well-established breast tumor mouse models, the less metastatic but faster growing (MCF-7) and the more metastatic but slower growing (MDA-MB-231) tumor and quantitatively compared their metabolism using the hyperpolarized ^{13}C-NMR technique. The ratiometric analysis of the time course of the lactate to pyruvate ratio was performed to determine the apparent forward (k+) and reverse (k-) rate constants of LDH-catalyzed reaction. The high forward rate constant and production of 13C-lactate is proportional to the lactate pool size, thus the production of lactate in the tumor. The preliminary results showed that the less metastatic MCF-7 tumors had larger apparent forward rate constant k+ than the MDA-MB-231 tumors ($p=0.002$, unpaired t test), contradicting the assumption that lactate generation is positively associated with tumor metastatic potential.

Poster I.D.: #48
Display date: Wednesday, June 19

Quantitative redox imaging biomarkers for studying a wide range of biological questions

Presenter: He N. Xu
Email: hexu3897@yahoo.com

He N. Xu[1,2], Lin Z. Li[1,2]
[1]Department of Radiology, [2]Britton Chance Laboratory of Redox Imaging,
Johnson Research Foundation, Department of Biochemistry and Biophysics,
Perelman School of Medicine, at the University of Pennsylvania, Philadelphia, PA
United States

NAD^+/NADH redox has been implicated in many diseases such as cancer and diabetes as well as in the regulation of embryonic development and aging. To fluorimetrically assess the mitochondrial redox state, Chance and co-workers measured the fluorescence of NADH and oxidized Flavin-groups (Fp, i.e. molecules containing flavin groups that include riboflavins, FMN, FAD and flavoproteins) which served as an optical surrogate marker of non-fluorescent NAD+ and demonstrated Fp/NADH is a sensitive indicator for the mitochondrial metabolic states. The Chance redox scanner was built to measure NADH and Fp in tissue at submillimeter scale in 3D using the freeze-trap protocol. We further developed the redox scanning technique to measure the nominal concentrations (in reference to the freeze-trapped solution standards) of both the endogenous fluorescent analytes and the exogenous optical tracers in various biological tissues in the optical channels of NADH, Fp, and red light. This has enabled us to identify an array of the redox indices as quantitative imaging biomarkers (including [NADH], [Fp], [Fp]/([NADH]+[Fp]), [NADH]/[Fp], and their standard deviations) for studying the important biological questions with the following preliminary results. We found that the redox indices were associated with 1) tissue abnormality (cancer vs non-cancer of human breast tissue biopsies); 2) tumor metastatic potential; 3) tumor p53 status; 4) PI3K pathway activation; 5) therapeutic effects; 6) embryonic stem cell differentiation. Work is in progress to study the correlation of the redox indices with fasting and cancer drug side effect on the heart, tissue re-oxygenation, and organ aging. Together, our work suggests a good potential of the identified redox imaging biomarkers in disease detection and treatment strategy, developmental process, tissue metabolism, and aging. Future work includes more clinical biopsy applications.

Poster I.D.: #49
Display date: Wednesday, June 19

Reducing motion artifacts for long-term clinical NIRS monitoring using collodion-fixed prism-based optical fibers

Presenter: Meryem Yucel
mayucel@nmr.mgh.harvard.edu

Meryem A. Yücel, Juliette Selb, David A. Boas, Sydney S. Cash and Robert J. Cooper
Department of Radiology, MGH, Charlestown, MA, 2115
United States

As the applications of near-infrared spectroscopy (NIRS) continue to broaden and long-term clinical monitoring becomes more common, minimizing signal artifacts due to patient movement becomes more pressing. This is particularly true in applications where clinically and physiologically interesting events are intrinsically linked to patient movement, as is the case in the study of epileptic seizures. In this study, we apply an approach common in the application of EEG electrodes to the application of specialized NIRS optical fibers. The method provides improved optode-scalp coupling through the use of miniaturized optical fiber tips fixed to the scalp using collodion, a clinical adhesive. We investigate and quantify the performance of this new method in minimizing motion artifacts in healthy subjects, and apply the technique to allow continuous NIRS monitoring throughout epileptic seizures in two epileptic in-patients. Using collodion-fixed fibers reduces the percent signal change of motion artifacts by 90 % and increases the SNR by 6 and 3 fold at 690 and 830 nm wavelengths respectively when compared to a standard Velcro-based array of optical fibers. The collodion-fixed optical fiber approach has also allowed us to obtain good quality NIRS recording of three epileptic seizures in two patients despite excessive motion in each case.

Poster I.D.: #1
Display date: Tuesday, June 18

Non-invasive quantitative detection of transferrin receptor-mediated internalization using NIR FRET imaging in live mice

Presenter: Lingling Zhao
linglingzhao0121@gmail.com

Lingling Zhao, Ken Abe, Margarida Barroso, and Xavier Intes
Department of Biomedical Engineering, Rensselaer Polytechnic Institute
Troy, New York, 12180
United States

Current tumor targeting strategies use naturally existing proteins that show efficient cellular uptake at a targeted pathological site via receptor-mediated endocytosis. However, it is challenging to validate the efficiency of tumor targeting strategies *in vivo* due to the enhanced permeability retention effect. To overcome this critical issue, we developed a novel near infrared Förster resonance energy transfer fluorescence lifetime imaging (NIR FRET FLIM) technique with wide-field illumination strategies. Herein, we employed NIR FRET FLIM to validate and characterize cellular uptake of transferrin (Tfn) in both cancer cells and normal cells *in vitro* and *in vivo*. We have selected a NIR FRET pair (Donor: Alexa Fluor 700 conjugated to Tfn, Acceptor: Alexa Fluor 750 conjugated to Tfn) based on its brightness, stability and lifetime contrast. The quenched donor fractions estimated *in vitro* increased linearly as the A: D ratios increased, demonstrating that we can detect and quantify Tfn binding and uptake into cancer cells using NIR FRET FLIM. Accurate quantification of the quenched donor fraction was achieved *in vivo* in agreement with the *in vitro* studies. These results validated our method as a non-invasive and quantitative method to quantify internalization of Tfn within live small animals. This work, for the first time, establishes *in vivo* NIR FRET imaging in a relevant physiological system overcoming the limitation of penetration caused by visible FRET pairs. This work also provides the foundation for seamless translation from *in vitro* FRET assays to *in vivo* FRET studies in pre-clinical settings and potentially for clinical applications.

Call for papers

Call for Papers – Special Issue: Britton Chance 100th Commemorative

June 2013 marks the biennial symposium at University of Pennsylvania honoring the memory of Prof. Britton Chance, a prolific and legendary scientist in the field of metabolism of cells and tissue, who created pioneering contributions in the fields of radar, biomedical NMR and biomedical optics. Prof. Chance (1913-2010) dedicated his life to better understanding biological tissue function and disease through studies of advanced biophysics, imaging, and sensing techniques. His research activities spanned disciplines from physics, engineering, biology, and medicine with a high impact on health science and direct clinical translation. He published over 1800 journal papers and book chapters, out of which six have been cited for more than 1000 times in the ISI Citation Indexes.

This special issue of the journal *Academic Radiology* welcomes submissions with topics in this spirit, focused on translational or clinical imaging of tissue function and metabolism.

Submission deadline: To ensure a timely publication of this issue we require all authors to submit their articles online via the journal website (http://ees.elsevier.com/arad/), **ideally before July 31, 2013**. Authors should refer to formatting and submission guidelines in the online Guide for Authors. Submissions for this special issue should choose the Article Type "Research Corner" in the online submission process, and direct the paper to this special issue in their cover letter.
Publication date is planned for early 2014.

Special Issue Editors: Brian W. Pogue (Dartmouth College, USA), Huiming Zhang (National Institutes of Health, USA), Dar-Bin Hsieh (National Cheng Kung University, Taiwan), David R. Busch (University of Pennsylvania, USA).

Journal of Innovative Optical Health Sciences (JIOHS)

Call-for-Papers of Special Issue: Honoring the 100th Birthday of Professor Britton Chance

This year marks the centennial of Prof. Britton Chance one of the most prolific and legendary scientists in the world and the founder of the biomedical optics. Prof. Chance (1913-2010) dedicated his life to better understanding the physiology and metabolism of biological tissues through advanced biophysics, imaging, and sensing techniques including both optics and NMR. His research activities spanned from physics, engineering, and biology, to medicine with high impact on health sciences. He had published over 1800 journal papers and book chapters, out of which six have been cited for more than 1000 times in the ISI Citation Indexes.

Prof. Chance was one of the co-founders and the Advisor for *JIOHS*. He had set the best example for innovative optical research in health sciences. His innovations in spectroscopy spanning the full range from radiofrequency, infrared, visible, UV to X-rays had advanced many frontier research fields at the time with both the development of new methods/devices and the applications to key biological questions. For example, in early 1940s, he developed the rapid-flow method for studying fast enzyme-substrate kinetics with visible light. In 1950s, he invented the dual-wavelength spectrophotometer which has been widely used for studying biological samples and applied to extensive investigations on the electron transport in cellular respiration and redox cofactors, redox state, metabolic control, and the generation of reactive oxygen species in mitochondria. In the 1960s, he discovered electronic tunneling processes in biological systems. In the 1970s, he identified hydrogen peroxide released by the respiratory chain in mitochondria. From 1970s to early 1980s, he developed the 3D cryogenic redox scanner for imaging tissue redox state and its heterogeneity at submillimeter resolution. In the 1970-80s, he was also a key player in the development of in vivo NMR spectroscopy. Since late 1980s Prof. Chance and his collaborators had developed NIR spectroscopy and imaging methods for various biological applications including the measurement of blood oxygenation, volume and flow, brain activities, muscle functions, and cancer detections and diagnosis, which have been widely applied in both laboratory and clinic studies. His work in the last decade of his life includes developing novel molecular beacons for cancer detection and diagnosis, predicting cancer aggressiveness by redox scanning, and developing an oral optical metabolometer to detect nutritional status in human subjects.

Research papers in any areas of photonics in biology and medicine (basic, translational, and clinical) will be considered for inclusion provided that they are related to the research work by Prof. Chance. Reviews and/or reflections on the work and life of Prof. Chance are also welcome. With these special issues we hope to advance the scientific causes Prof. Chance has led us to.

Submission deadline: To ensure a timely publication of this issue we require all authors to submit their articles online via http://www.editorialmanager.com/jiohs/ as soon as possible **before July 15, 2013**. The authors are welcome to include a dedication clause in the manuscript. We plan to get the special issues/sections published in July and October.

JIOHS is now indexed by SCI. JIOHS becomes open-access this year and the publication fee is free for 2013.

Submission format: Authors should use the Latex or MS-Word style files. Please use the author instructions for further information on the submission process.

For more details, please visit http://www.worldscinet.com/jiohs/mkt/guidelines.shtml

CHAIRS:

Lin Z. Li
Assistant Professor, Molecular Imaging Laboratory, Department of Radiology
Britton Chance Laboratory of Redox Imaging, Johnson Research Foundation
Department of Biochemistry and Biophysics
Perelman School of Medicine at the University of Pennsylvania

Arjun G. Yodh
Director, Laboratory for Research on the Structure of Matter (LRSM)
James M. Skinner Professor of Science, Department of Physics and Astronomy
University of Pennsylvania, Philadelphia, PA 19104-6202

LOCAL ORGANIZING COMMITTEE:

David R. Busch
Neurovascular Imaging Lab
Department of Pediatrics, Division of Neurology, The Children's Hospital of Philadelphia
Department of Physics and Astronomy, University of Pennsylvania

Susan Colleluori
Associate Director, Center for Magnetic Resonance and Optical Imaging (CMROI) and
John S. Leigh Resource for Ultra-High Field Imaging, Department of Radiology
University of Pennsylvania

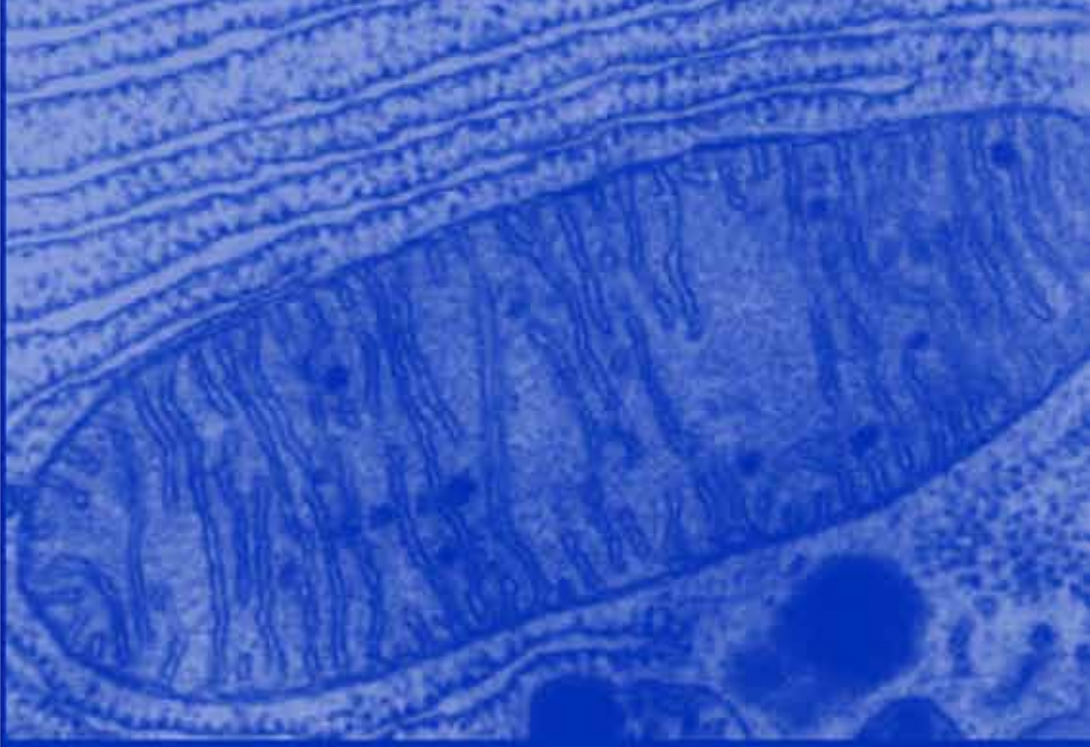
Mary A. Leonard
Biomedical Art & Design, Department of Biochemistry and Biophysics
University of Pennsylvania

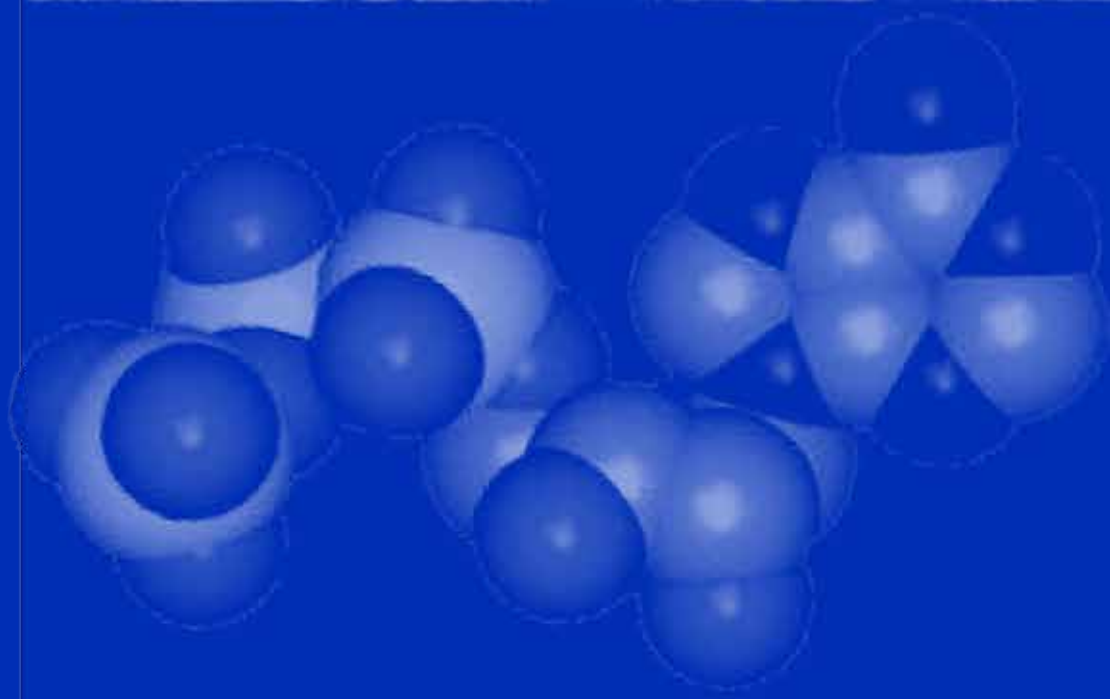
Shoko Nioka
Britton Chance Laboratory of Redox Imaging, Johnson Research Foundation
University of Pennsylvania

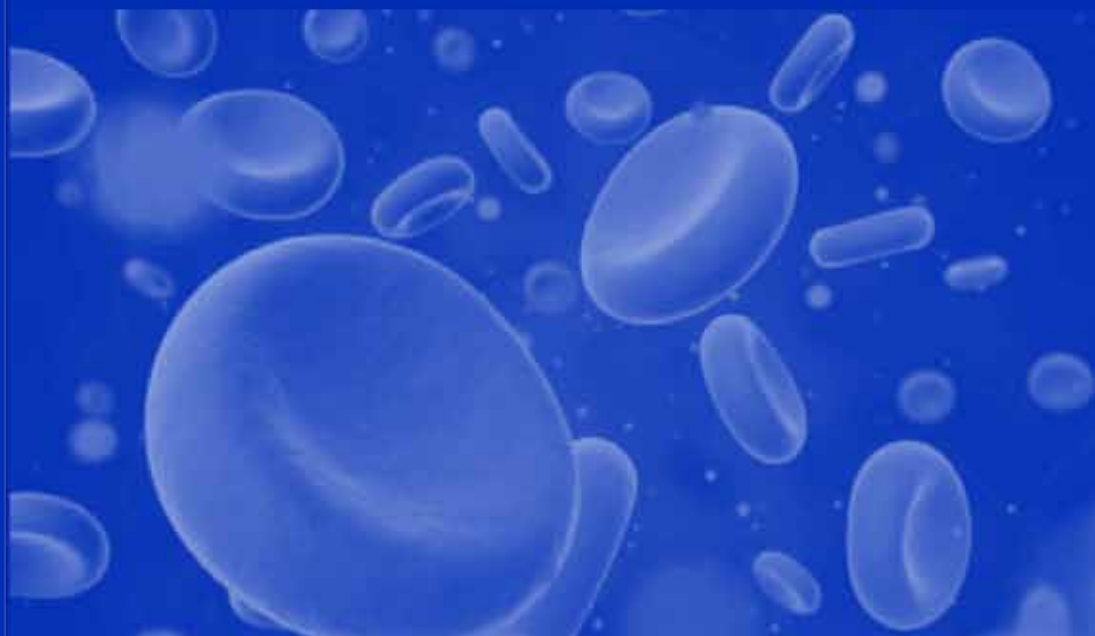
He N. Xu
Molecular Imaging Laboratory, Department of Radiology
Britton Chance Laboratory of Redox Imaging, Johnson Research Foundation
Department of Biochemistry and Biophysics, Perelman School of Medicine at the
University of Pennsylvania

PROGRAM COMMITTEE / FACULTY:

Abass Alavi, University of Pennsylvania
Robert Balaban, National Heart, Lung, and Blood Institute (NHLBI)
Morris Birnbaum, University of Pennsylvania
David Boas, Harvard Medical School, Massachusetts General Hospital
Kevin Brindle, University of Cambridge & Cancer Research UK
Yu Chen, University of Maryland
Murali Krishna Cherukuri, National Cancer Institute
Lewis Chodosh, University of Pennsylvania
Emily Conant, University of Pennsylvania
Chris Cooper, University of Essex, UK
Jeffrey Evelhoch, Merck Research Laboratories
Maria Angela Franceschini, Harvard Medical School, Massachusetts General Hospital
Jerry Glickson, University of Pennsylvania
Kyung Kang, University of Louisville
Stephen Kadlecek, University of Pennsylvania
John Kurhanewicz, University of California, San Francisco
Xingde Li, Johns Hopkins University
Hanli Liu, University of Texas Arlington
Qingming Luo, Huazhong University of Science and Technology, China
David Mankoff, University of Pennsylvania
Avraham Mayevsky, Bar Ilan University, Israel
Eva Sevick-Muraca, The University of Texas Health Science Center at Houston
Banu Onaral, Drexel University
Brian Pogue, Dartmouth College
Michelle Puchowicz, Ph.D. Case Western Reserve University
Nimmi Rammanujam, Duke University
Ravinder Reddy, University of Pennsylvania
Brian M. Salzberg, University of Pennsylvania
Harold Swartz, Dartmouth College
Eiji Takahashi, Saga University, Japan
Stephen Tang, University City Science Center
Bruce Tromberg, University of California, Irvine
Andrew Tsourkas, University of Pennsylvania
Peter Vaupel, University Mainz, Germany
Dah-Jyuu Wang, Children's Hospital of Philadelphia
Lihong Wang, Washington University St. Louis
Warren Warren, Duke University
Felix Wehrli, University of Pennsylvania
Rong Zhou, University of Pennsylvania







Penn Radiology

Provost
Interdisciplinary
Seminar Fund

ITMAT

50 science center
INVENTING THE FUTURE FOR FIFTY YEARS

National Cancer Institute

NIBIB

HAMAMATSU
PHOTON IS OUR BUSINESS