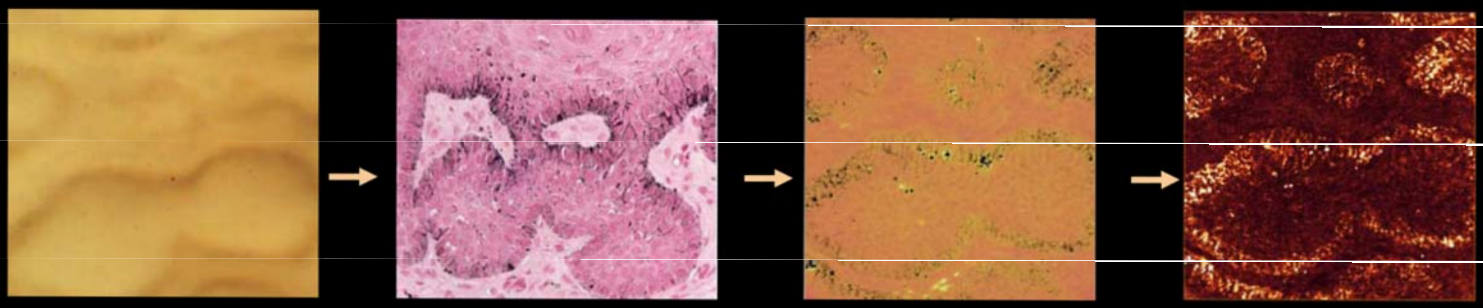

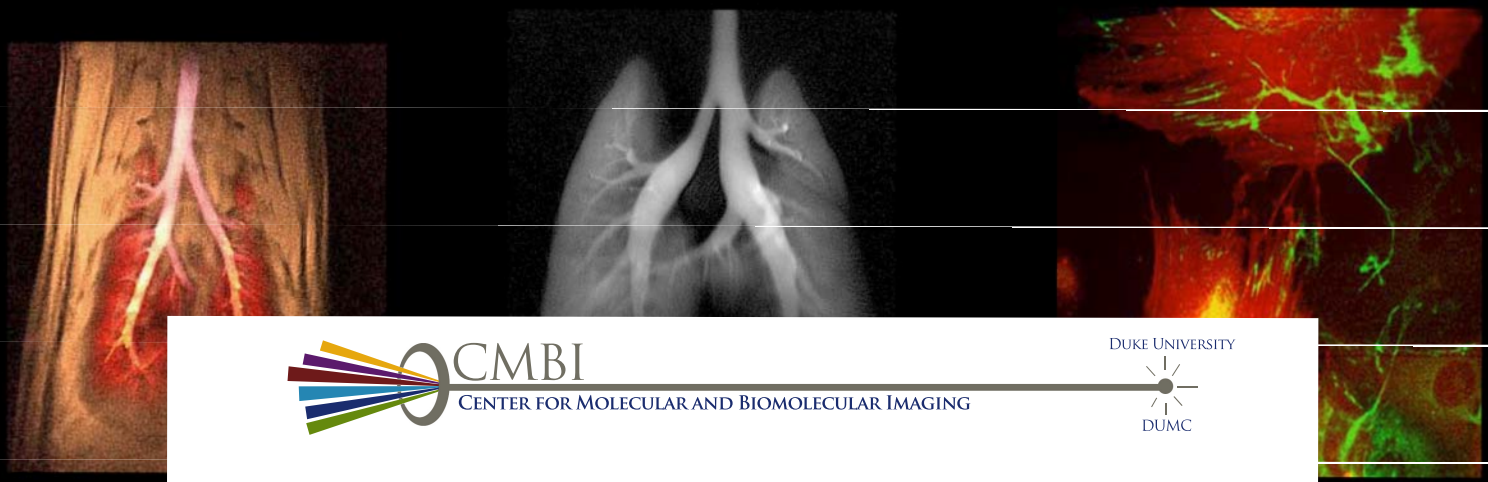

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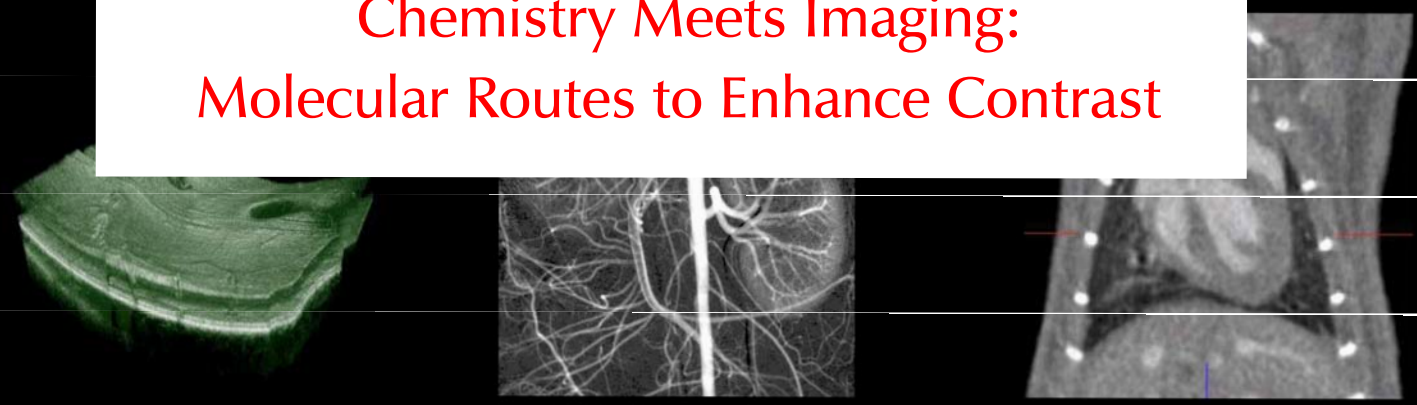
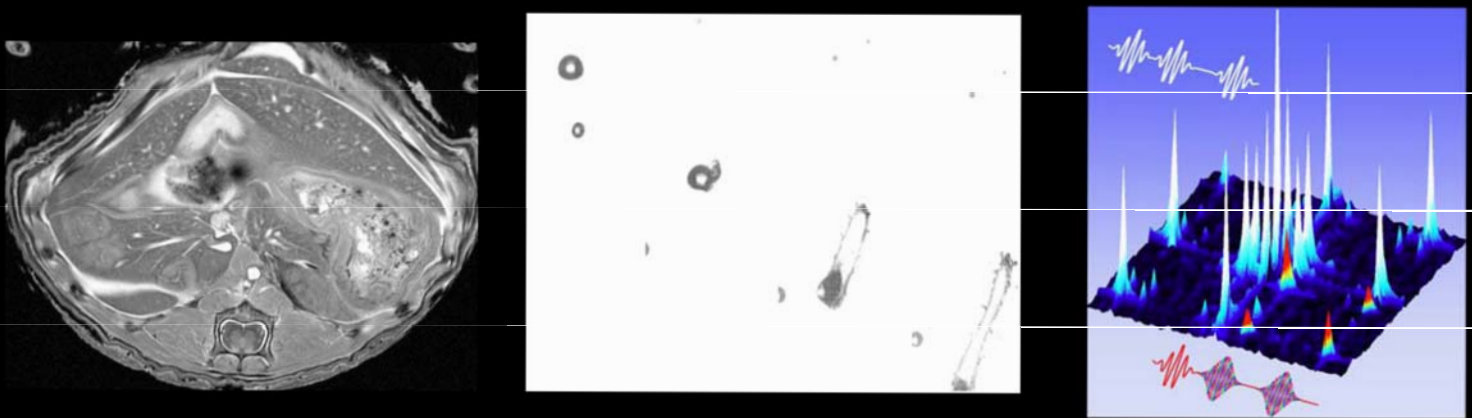
Chemistry Meets Imaging:
Molecular Routes to Enhance Contrast





French Family Science Center
Duke University
May 11, 2015

Warren S. Warren
James B. Duke Professor of Chemistry, Physics, Radiology, and Biomedical Engineering
Director, Center for Molecular and Biomolecular Imaging

May 11, 2015

Welcome to the Center for Molecular and Biomolecular Imaging 2015 conference, "Chemistry Meets Imaging: Molecular Routes to Enhance Contrast." This meeting will explore important new opportunities for the development of molecular agents to improve materials characterization and clinical diagnosis. One strong theme will be the use of hyperpolarization methods, which make it possible to transform magnetic resonance imaging (MRI) from a water-based, structural modality to a functional and diagnostic tool. New technology developments and hardware approaches will be presented which offer promise to drastically change the range of applicability of magnetic resonance techniques. Other talks will create context by comparison with other modern imaging and spectroscopic modalities.

CMBI is a Provost-level organization which unites several different schools at Duke (interconnecting Trinity College of Arts and Sciences, the Pratt School of Engineering, the Medical School, and the Nicholas School of the Environment) to support the transformative and inherently interdisciplinary nature of modern imaging science. This has a natural connection with one of Duke's greatest strengths, which can best be appreciated on *Google Maps*. If you locate the French Family Science center at 124 Science Drive, and go to the 200 foot scale, you will find all of physics, biology, chemistry, engineering, and computer science, and virtually all of the basic science buildings of the medical school. This extremely unusual proximity can, and does, foster strong connections between departments. It is the aim of this Center to support and strengthen these connections. To this end, our meetings have widely varying themes and foci that we hope will continue to intrigue the best and brightest across the imaging spectrum.

These meetings don't happen spontaneously. I am very grateful for the continuing efforts of Mike Conti (CMBI Manager), for helping to organize the meeting, and to the CMBI steering committee for their thoughts and guidance.

Sincerely,

Warren S. Warren

Chemistry Meets Imaging:
Molecular Routes to Enhance Contrast

May 11, 2015

French Family Science Center Room 2231

Morning Session

7:30AM	Breakfast – French Family Science Center Atrium	
8:30AM	Warren Warren Director, Center for Molecular & Biomolecular Imaging	Welcome and Introduction
8:50AM	Nan-kuei Chen Duke University Center for Brain Imaging & Analysis	Phase Reconstruction Algorithms for Challenging MRI Applications
9:20AM	Kayvan Keshari Memorial Sloan Kettering Cancer Center Department of Radiology	Interrogating Metabolism *in vivo* using Hyperpolarized Magnetic Resonance
10:00AM	Bastiaan Dreihuys Duke University Center for In Vivo Microscopy	Hyperpolarized 129Xe MRI – Insights from Beyond the Airspaces
10:30AM	Break	
11:00AM	Stephen Kadlecek University of Pennsylvania Functional and Metabolic Imaging Group	Molecular Imaging in the Lung Using Hyperpolarized 13C
11:35AM	Louis Bouchard University of California – Los Angeles Department of Chemistry & Biochemistry	Toward *in vivo* Applications: New Catalysts for Heterogeneous Phase PHIP in Water
12:10PM	Boyd Goodson Southern Illinois University Department of Chemistry & Biochemistry	Enhancing NMR and MRI with Hyperpolarized Xenon and Signal Amplification by Reversible Exchange

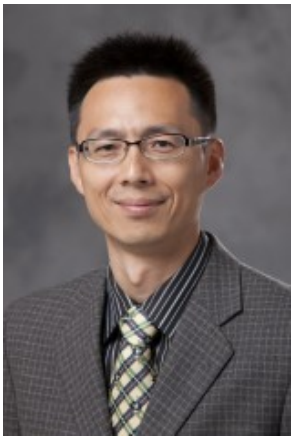
12:45PM	Lunch – French Family Science Center Atrium

Afternoon Session

2:00PM	Simon Duckett University of York Department of Chemistry	Using *Para*hydrogen to Sensitize MR Detection
2:35PM	Thomas Theis Duke University Department of Chemistry	Enhancing SABRE with Microstesla Fields
3:05PM	Hashim al-Hashimi Duke University Director, Center for RNA Biology	Redefining the Double Helix by NMR
3:35PM	Break	
4:00PM	Terry Wong University of North Carolina Biomedical Research Imaging Center	Molecular Imaging and Theranostics Using Radiopharmaceuticals
4:35PM	Francisco Robles Duke University Center for Molecular and Biomolecular Imaging	Improving Cancer Diagnosis with Nonlinear Optical Imaging

Chemistry Meets Imaging:
Molecular Routes to Enhance Contrast

Phase Reconstruction Algorithms for Challenging MRI Applications



Nan-kuei Chen, PhD
Associate Professor of Radiology
Brain Imaging & Analysis Center
Duke University

Prof. Chen is an MRI physicist with research interest in fast image acquisition methodology, pulse sequence design, MRI artifact correction, and application of MRI to studies of neurological diseases. He has been developing novel high-resolution imaging protocols and analysis procedures for mapping structural and functional connectivity of brains.

Abstract:

High-resolution and quantitative MRI are prone to various types of artifacts, which make it challenging to perform MRI based studies in many biomedical applications. In this talk I will discuss a series of improved MRI acquisition and reconstruction strategies, effectively addressing image distortions and signal loss artifacts resulting from phase inconsistencies in k-space data. Our improved phase reconstruction methods make it possible to generate high-quality images even for challenging applications. First, using a chemical-shift multiplexed sensitivity encoded (MUSE) algorithm, diffusion properties of multiple chemical species can be quantified from high-resolution multi-shot MRI, even in the presence of intra-scan subject motion. Second, using an inverse Double Echo Steady State (iDESS) pulse sequence, the phase contrast of interest (e.g., the susceptibility effect due to contrast agents or iron accumulation) can be separated from the undesirable phase induced artifacts (e.g., signal loss near the air-tissue interfaces). Third, using a k-space energy spectrum analysis algorithm, image-domain phase values can be reliably measured, even from data of very low signal-to-noise ratio (SNR).

Chemistry Meets Imaging:
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Interrogating Metabolism *in vivo* Using Hyperpolarized Magnetic Resonance

Kayvan Keshari, PhD
Department of Radiology
Molecular Pharmacology and Chemistry Program
Memorial Sloan Kettering Cancer Center

Dr. Keshari's research focuses on improving the biochemical understanding of cancer metabolism and using metabolic changes to develop imaging agents for diagnosis and treatment – specifically using hyperpolarized magnetic resonance to watch metabolic dynamics in real time.

Abstract:

Oncogenic transformation has been shown to have a dramatic impact on the metabolic state of the cell. Recent reports have demonstrated that specific alterations in oncogenes and signaling pathways results in increases in pathway flux as well as diversion of substrates. Interrogation though of these pathways in relevant systems has been hindered though by lack of versatile technologies capable of monitoring metabolism. Hyperpolarized magnetic resonance (HP MR) addresses a fundamental limitation of MRI for interrogating metabolic substrates, sensitivity. Using this approach, endogenous metabolic substrates can be prepared prior to infusion into a living system with dramatically increased signal. These probes can then be followed using spectroscopic imaging techniques non-invasively and inform on the metabolic state of the cell as well as the dynamics of metabolism in real time. In the setting of cancer metabolism, many probes have been developed which inform on multiple pathways. These include the measures of glycolytic flux to lactate (HP pyruvate) and redox state (HP dehydroascorbate) of the cell. Moreover, this approach has recently been shown to be safe in a first trial demonstrating the great promise of this approach for future interrogation of cancer metabolism *in vivo*. This talk will discuss the development and use of these probes and the road to translation of this approach into humans.

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Chemistry Meets Imaging:
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Hyperpolarized 129Xe MRI - Insights from Beyond the Airspaces

Bastiaan Driehuys, PhD
Faculty, Center for In Vivo Microscopy
Associate Professor of Radiology, Biomedical Engineering, and Medical Physics
Duke University

Professor Driehuys' research focuses on developing and applying hyperpolarized substances in MR imaging. His background is in the atomic physics of producing hyperpolarized noble gases 3He and 129Xe, not only in attacking the basic physics problems of these gases, but in their large-scale development and application to biomedical challenges

Abstract:

Pulmonary MRI using hyperpolarized noble gases has undergone a painful but critical transition from the rare isotope ^{3}He to more sustainable ^{129}Xe. ^{129}Xe MRI is now emerging as a powerful clinical research tool at Duke and other medical centers around the world. This inhaled agent provides a means to evaluate pulmonary function regionally, with sensitivity to the smallest airways where early disease originates. With this groundwork being completed, we are now positioned to exploit the most fascinating properties of ^{129}Xe – its solubility in biological tissues and accompanying range of chemical shifts. In this talk I will describe how these properties are being used to image gas exchange impairment in idiopathic pulmonary fibrosis, and pulmonary vascular disease. Moreover, we are finding that ^{129}Xe dissolved in pulmonary tissues generates a wealth of spectroscopic information beyond simple signal intensities. We find in patients, ^{129}Xe is sensitive to blood oxygenation levels, and in mouse models of cancer it exhibits unique spectral signatures related to disease progression.

Chemistry Meets Imaging:
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Molecular Imaging in the Lung Using Hyperpolarized 13C

Stephen Kadlecek, PhD
Research Assistant Professor of Radiology
Functional and Metabolic Imaging Group
University of Pennsylvania

Prof. Kadlecek's research focuses on the development of imaging techniques to probe organ structure and function, with particular emphasis on the use of hyperpolarized nuclear magnetic resonance. He examines the use of injectable, 13C-labeled hyperpolarized agents and their utility in identifying disorders of metabolism.

Abstract:

Lung MRI is well known to present significant challenges due to the low tissue density and rapid spin dephasing at air-tissue interfaces. Nonetheless, it is an appealing target for molecular imaging because in addition to its main function in gas exchange, the lung is involved in a variety of metabolic processes that are crucial for overall health. Furthermore, lung disease is highly heterogeneous, suggesting a heterogeneous metabolic origin in which imaging could yield important information. In the context of these goals, I will discuss general considerations in lung MRI and our progress in imaging both agent distribution and metabolism in the lung. This includes identifying and addressing challenges associated with the short agent T1 and the need to approximate physiological agent concentrations to get meaningful metabolic information. I will then summarize our initial work in the study of altered metabolism in ischemia, inflammation, mitochondrial dysfunction, and altered tissue redox state.

Chemistry Meets Imaging:
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Toward *in vivo* Applications:
New Catalysts for Heterogeneous Phase PHIP in Water

Louis Bouchard, PhD
Assistant Professor of Chemistry & Biochemistry
University of California – Los Angeles

Prof. Bouchard's research focuses on the development of measurement techniques and methodologies applied to chemical systems and condensed matter systems under the unifying theme of developing magnetic resonance technology. The measurement techniques, schemes and methodologies developed probe the properties of matter, their various phases and transformations.

Abstract:

Magnetic resonance imaging (MRI) has proven to be a powerful tool in the diagnosis and treatment of disease; however, MRI remains limited by the amount of signal needed to generate adequate resolution. Parahydrogen induced polarization (PHIP) techniques can turn biomolecules into molecular tracers through hyperpolarization. Hyperpolarization can increase MRI signal by up to 10,000-fold. Following injection into a subject, tracer molecules can be used to monitor the tracer molecules as they undergo transformations.

PHIP reactions necessitate a catalyst to produce hyperpolarized substrates. Previous experiments used a homogeneous phase, rhodium-based catalyst. However, this catalyst remains in solution with the hyperpolarized substrate prior to human injection, thus raising concerns of toxicity.

Metal-based nanoparticles capped with biocompatible and water-soluble ligands can also produce hyperpolarized substrates, where they can be filtered from the hyperpolarized substrate prior to injection. In this talk I will present results concerning the development of novel water-soluble heterogeneous catalysts that yield significant nuclear-spin polarizations sufficient for *in vivo* use.

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Enhancing NMR and MRI with Hyperpolarized Xenon and Signal Amplification by Reversible Exchange

Boyd Goodson, PhD
Professor of Chemistry & Biochemistry
Southern Illinois University

Professor Goodson's research focuses on the development and application of techniques for enhancing NMR/MRI sensitivity and information content, with particular emphases on (1) the development of hyperpolarized contrast agents for in vivo molecular imaging; and (2) studies of the fundamental physical and chemical processes that lead to hyperpolarization.

Abstract:

NMR and MRI enjoy wide applicability but often suffer from poor detection sensitivity due to low nuclear spin polarization. To combat this problem, we are pursuing two methods for generating nuclear spin hyperpolarization: (1) spin-exchange optical pumping; and (2) parahydrogen induced polarization via SABRE (signal amplification by reversible exchange). For (1), our "consortium" has recently created clinical-scale open-source xenon "hyperpolarizers". The devices can endow ^{129}Xe with near-unity polarization and imaging of human subjects has begun. For (2), we are investigating polarization enhancement via SABRE; SABRE utilizes an organometallic catalyst that transiently binds both parahydrogen (pH_2, a spin isomer of ordinary molecular hydrogen and a source of pure spin order) and the target substrate molecule, thereby allowing the target spins to be hyperpolarized. In collaboration with others, we are studying SABRE with heterogeneous catalysts, in aqueous environments, and in variable magnetic fields in order to create hyperpolarized agents for in vivo NMR and MRI.

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Chemistry Meets Imaging:
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Using *Para*hydrogen to Sensitize MR Detection

Simon Duckett, PhD
Director, Center for Hyperpolarisation in Magnetic Resonance
Professor of Chemistry
University of York

Prof. Duckett's works on the design, development and implementation of nuclear magnetic resonance methods and the application of them to the study of chemical processes. His research focuses on the development of parahydrogen induced polarization methods and exploiting molecular symmetry in NMR.

Abstract:

While magnetic resonance is used widely in chemistry and biochemistry it has also revolutionised the field of clinical diagnosis by providing non-invasive access to molecular-scale information. MR is, however, limited by low sensitivity when compared to other spectroscopic methods. This low sensitivity results from the fact that < 0.001% of the nuclei interrogated in a standard MR experiment contribute positively to the observable signal. Hyperpolarisation seeks to change this percentage in order improve the detection limits of MR and thereby facilitate an extension in the range of MR applications. In the Centre for Magnetic Resonance (CHyM) in York, we are seeking to develop hyperpolarised MR methods that use *para*hydrogen as a latent source of hyperpolarization (Duckett et al. Acc. Chem Res. 2012).

Recently, we have developed a pump-probe time-resolved technique to track rapid chemical change by following a hyperpolarised MR signal (Torres et al. JACS 2014). We do this by employing a metal dihydride complex which undergoes photochemical reductive elimination of H2. This is followed by the addition of parahydrogen which acts to prepare a reaction product in a precisely defined hyperpolarized nuclear spin-state. We then investigate the time-evolution of this state as a function of a delay that is introduced between the initial laser excitation step and the final NMR observation set. As a result we see signal oscillations that encode the magnetic properties of the complex and the rate of the product forming step. I will discuss the basis of these results and link them through to the signal amplification by reversible exchange (SABRE) processes (Adams et al Science 2009). SABRE hyperpolarises a target molecule (the contrast agent) using a reversible exchange reaction involving the contrast agent, parahydrogen and a polarization transfer catalyst. I will describe the basis of SABRE and illustrate how it can be optimised. Our aim is to inject a SABRE polarised agent in a patient in order to enable the tracking of the fate of agent which should shed light on disease. I will finish by discussing our progress towards achieving viable MRI contrast agents through SABRE.

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Enhancing SABRE with Microtesla Fields: Broadly Applicable, >10,000 Fold Direct Heteronuclear Signal Enhancement with >20 Minutes Signal Lifetimes

Thomas Theis, PhD
Center for Molecular and Biomolecular Imaging
Duke University

Dr. Theis is a postdoctoral associate at Duke University and Visiting Professor at RWTH Aachen University. His research focuses on the dynamics and characterization of molecular targets supporting long-lived singlet states for hyperpolarized MRI.

Abstract:

The current surge in hyperpolarized magnetic resonance (MR) is fundamentally shifting the long held paradigm labeling MR as a relatively insensitive detection modality. With the advent of increasingly more general hyperpolarization schemes, MR now combines 10^4 to 10^5 times lower detection limits with its well-known and unmatched sensitivity to chemical transformations. This paradigm shift opens entirely new application in, both, NMR and MRI.

The two largest challenges facing the most widespread hyperpolarization technology (dissolution Dynamic Nuclear Polarization) are relatively large costs (>$1M for a commercial hyperpolarizer) and relatively short hyperpolarized signal lifetimes (typically seconds and up to 1 min in favorable cases). Here we report significant progress in overcoming both of these challenges. We use the low-cost and versatile SABRE method (Duckett, Science 2009) which uses parahydrogen as the source of hyperpolarization to directly hyperpolarize long-lived states on ^{15}N spin pairs with lifetimes >20 min. Specifically, we target $^{15}N_2$ diazirines that can be incorporated into a wealth of biomolecules as small molecular tags. These breakthroughs promise hyperpolarized MR experiments with diazirines and other molecular motifs on truly biologically relevant timescales.

Furthermore, SABRE has mostly been used to hyperpolarize protons. Here we show that in order to target heteronuclei, such as ^{15}N or ^{13}C, all that is required is to conduct the SABRE hyperpolarization process at microTesla fields, which are easily established by a magnetic shield reducing the Earth's magnetic field by about 200 fold. At these low fields the hyperpolarization is easily transferred from parahydrogen to the heteronuclei. These findings are particularly significant for two reasons. First, heteronuclei have much longer lifetimes in general, and second, entirely new classes of molecules become possible SABRE substrates: We observe highly efficient heteronuclear SABRE in new molecular classes that exhibit very little to no ^{1}H-SABRE.

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Redefining the Double Helix by NMR

Hashim Al-Hashimi, PhD
Director, Center for RNA Biology
Professor of Biochemistry
Duke University

Prof. Al-Hashimi's research is focused on the development and application of NMR and computational methods to visualize dynamic biological processes at the atomic level within living cells and to develop a fundamental biophysical understanding to aid the design of therapeutics.

Abstract:

NMR spin relaxation in the rotating frame (R1rho) experiments are described for characterizing transient excursions in nucleic acid duplexes that are directed toward short-lived (lifetimes of milliseconds to seconds) and low populated (10%-0.001%) 'excited states'. The NMR chemical shifts are used to infer the structure of the excited states, and chemical modifications are used to trap, stabilize or destabilize a suspected excited state structure. Computational approaches, including density functional theory calculations, are also used to predict chemical shifts of the proposed excited state structure and to evaluate whether the transitions are stereochemically feasible. With this approach, we have uncovered two basic modes of base pair dynamics in nucleic acid duplexes. In one mode, canonical A-T and G-C Watson-Crick base pairs transition toward non-canonical Hoogsteen base pairs in which the purine base adopts a syn rather than anti conformation. Such transitions occur in B-form DNA but are highly unfavorable in A-form RNA. In a second mode, non-canonical G-T mispairs transition toward canonical Watson-Crick like base pairs through ionization and tautomerization of the bases. These transitions occur equally in B-form DNA and A-form RNA duplexes. The roles of these two dynamic modes in maintenance of genomic stability, sequence-specific recognition, damage induction and repair, and spontaneous mutations will be discussed.

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Molecular Imaging and Theranostics Using Radiopharmaceuticals

Terence Wong, MD, PhD
Chief of Nuclear Medicine
Director of Molecular Imaging, Biomedical Research Imaging Center
Professor of Radiology
University of North Carolina, Chapel Hill

Dr. Wong's primary interest is in the development and application of functional/anatomic imaging biomarkers to guide and evaluate therapeutic decisions.

Abstract:

Imaging physiologic processes with radiotracers has been applied clinically in nuclear medicine for decades. Radioisotopes can be selected in terms of half life and photon energy to match the clinical application. In addition, radiotracers labeled with corresponding beta- or alpha-emitting isotopes may be used for therapy. One of the major shortcomings of traditional nuclear medicine studies has been the lack of anatomic information. The development of hybrid SPECT/CT, PET/CT, and PET/MRI scanners has revolutionized combined radiopharmaceutical/anatomic imaging and has had a substantial impact on patient management. More importantly, this technology provides new opportunities for the development of novel molecular probes and imaging biomarkers to diagnose and guide therapy.

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Improving Cancer Diagnosis and Staging with Nonlinear Optical Imaging

Francisco Robles, PhD
Center for Molecular and Biomolecular Imaging
Duke University

Dr. Robles is a postdoctoral fellow at Duke. His research focuses on novel microscopy methods for functional and molecular contrast in order to achieve earlier and better diagnoses.

Abstract:

Pump-probe microscopy, a nonlinear optical imaging technique, possesses the unique ability to identify differences in the biochemical composition of melanins with subcellular spatial resolution, which yields novel insight into the progression and aggressiveness of melanocytic melanomas. The technique uses two ultrafast laser pulses of different colors to measure pigmented molecules' electronic excited state dynamics. Our work demonstrates that the molecular information can be used to quantify differences between invasive melanoma, melanoma in-situ and non-malignant melanocytic proliferations. This information can be used to provide a more informed decision regarding the need for surgical intervention (e.g., wide excision), which is particularly important for sensitive areas such as the eye and genitalia (both cases will be discussed). The melanin profile also reveals differences between metastatic invasive melanomas and non-metastatic invasive melanomas with much better sensitivity than the clinical gold standard (invasive sentinel lymph node biopsy), suggesting pump-probe microscopy can help better identify patients who need addition treatments beyond excision.