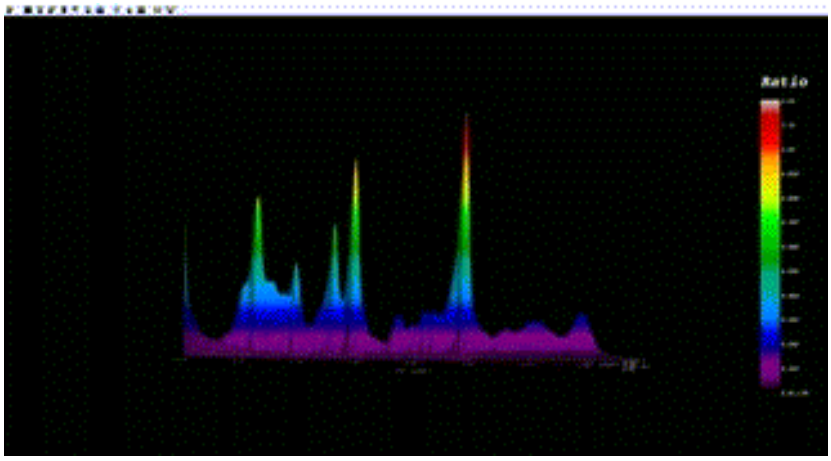
Center for Clinical Spectroscopy

The Center for Clinical Spectroscopy is comprised of a multidisciplinary team of scientists and collaborating clinicians whose goal is to translate magnetic resonance spectroscopy (MRS) into the clinic through technical development, clinical applications, and advocacy. Novel hardware and software advances in multinuclear spectroscopy and multidimensional spectral and spatial encoding enables non-invasive, objective, and quantitative 'virtual biopsy' measures of brain and body chemistry that provide biomarkers for early diagnosis and treatment monitoring across a broad range of diseases. Our current studies include traumatic brain injury, neurodegenerative disorders, cancer, psychiatric disorders, metabolic and immune disorders, chronic pain, diabetes, and continued expansion to additional clinical applications through funding from the National Institutes of Health, Department of Defense, and industry. The ultimate goal of the Center is to bridge the gap between research and clinical practice for MRS through promotion of this powerful technique at the local, national, and international levels via mentorship, training, education, and advocacy.



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- James Balschi, PhD
- Brian Ross, DPhil (Oxon), FRCS

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Fatah Adan

Announcements:

- Recruiting military service members and veterans for research study. Please click here for more details.
- Check out our current news

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About the Center:

Program History

The Center for Clinical Spectroscopy, founded by Dr. Carolyn Mountford in 2006 and established with Drs. Saadallah Ramadan and Peter Stanwell. Bringing three decades of experience in two dimensional MRS, Dr. Mountford and her team, with an industry-sponsored award from Siemens Medical Solutions, helped develop the 2D-correlated spectroscopy (COSY) method for use on Siemens clinical MRI scanners. The 2D-COSY method allows for the disambiguation of chemicals that typically overlap in conventional methods, thereby increasing the number of potential biomarkers for inspection from five to more than 35 different metabolites. This method was developed and applied in the brain, breast, and muscle at both 3T and 7T.

In 2009, Dr. Alexander Lin, joined the Center and, with his long-time mentor, Dr. Brian Ross brought extensive experience with clinical spectroscopy, particularly in the brain. Dr. Lin's research primarily focuses on brain injury, including studies in military veterans and professional athletes. In collaboration with the Psychiatric Neuroimaging Laboratory and Boston University Medical Center, there are several ongoing studies in both of these fields. Preliminary results of this study recently highlighted on a local CBS program on concussion and in articles in the New York Times, CNN, and other media reports on sports-related head injury, has gained national recognition for the work that is being done at Brigham and Women's Hospital.

Future Goals:

The mission statement for the Center for Clinical Spectroscopy describes several research focuses within each of our major goals: technology development, clinical translation and advocacy.

Technology Development

We continue to develop novel methods for MR spectroscopy in both hardware and software. In anticipation of the completion of the Brigham Building for the Future and the new MR facilities that will be available, we are currently developing hardware and software to take advantage of this rich resource that will enable significant improvements to conventional MR spectroscopy by increasing signal to noise and spectral dispersion for the improved detection of chemicals, and enhancing multinuclear spectroscopy methods such as ^{13}C, ^{23}Na, and ^{31}P.

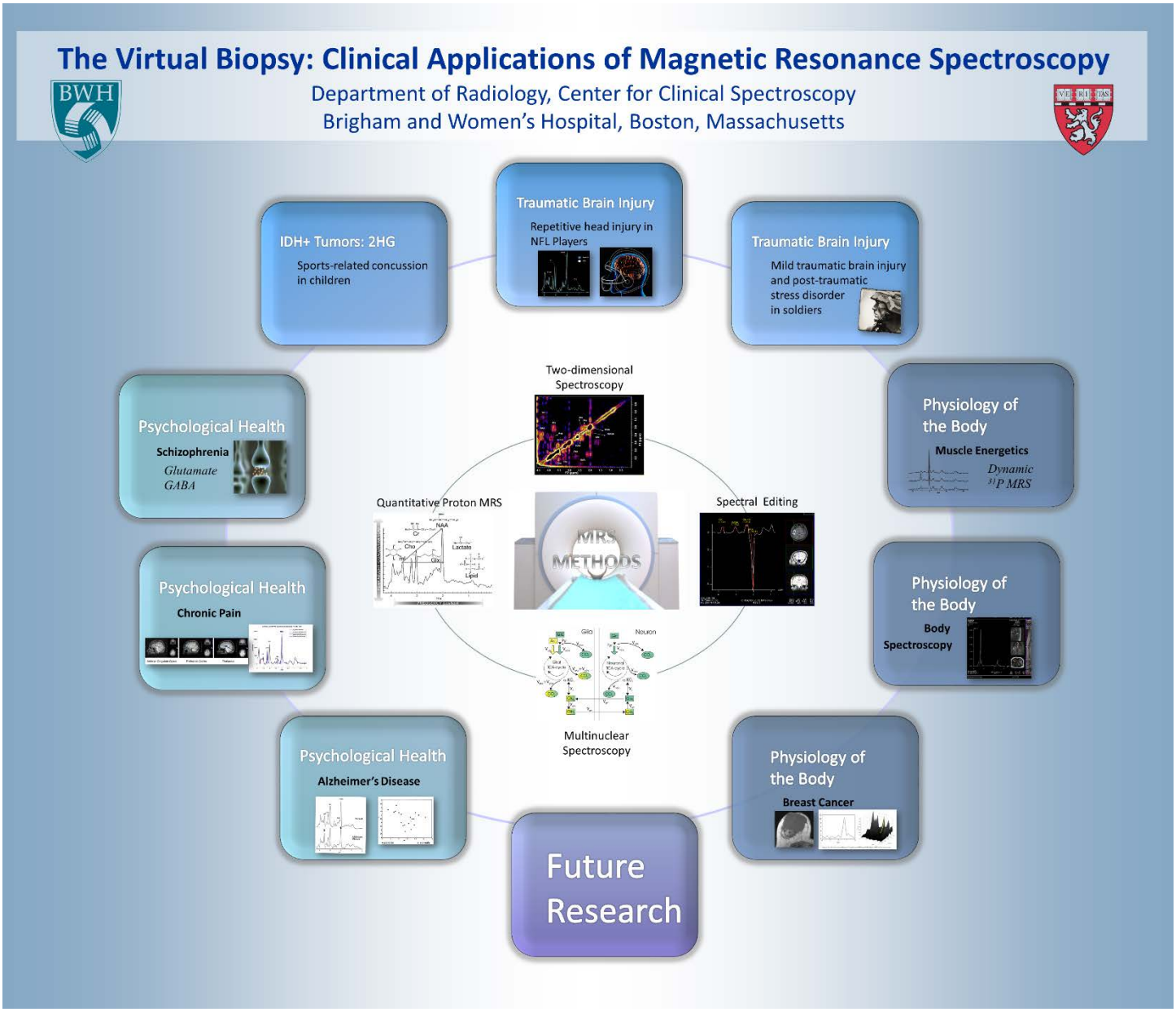
Clinical Translation

Each of the research projects has potential clinical applications that need to be translated into clinical use. We will continue to foster cross-disciplinary collaborations that will help identify clinical needs that can be met with MRS technology. Cross-institutional collaborations with local institutes such as the Martinos Center at MGH, Childrens Hospital Boston, and international sites, such as Tongji Medical School in Wuhan, China where we are establishing an exchange program, will help to further translate our technology for multi-center studies and greater outreach.

Advocacy

Complete translation of MRS into the clinic has been hampered by the lack of consensus on methodology and a paucity of evidence of utility and patient benefit. One of the goals at the Center will be to advocate for MRS by participating in international consensus efforts. This effort has resulted in a recent publication in the journal, Radiology, in which consensus was reached for clinical applications for MRS. We continue to promote spectroscopy at a local level by providing educational lectures to medical students, residents, and fellows, mentorship of students from high school through medical school, and the organization of medical education courses at Brigham and Women's and internationally.

Current Studies:



- U.S. Army Medical Research Acquisition Activity, W81XWH-10-1-0835, Identifying Biomarkers that Distinguish Post-Traumatic Stress disorder and Mild Traumatic Brain Injury Using Advanced Magnetic Resonance Spectroscopy (PI: Alexander Lin)
- Osher
- NIH, R01 NS 078337-01A1, Chronic Traumatic Encephalopathy: Clinical Presentation and Biomarkers (PI: Robert Stern)
- American Diabetes Association, 7-13-CE-17,Bedside to Bench and Back: Cardiometabolic Effects of Betaine Supplementation (PI: Allison Goldfine)
- U.S. Army Medical Research Acquisition Activity, Tau Imaging of Chronic Traumatic Encephalopathy (PI: Martha Shenton/ Robert Stern)

- VA Merit Award, 1-I01-RX000928-01A2, Development of MR Biomarkers of Brain Injury in Acute and Chronic mTBI (PI: Martha Shenton)
- BWH Institute for the Neurosciences. 2-Hydroxyglutarate as Biomarker of Tumor Response in IDH1-Mutant Gliomas Using Magnetic Resonance Spectroscopy (PI: Nils Arvold)
- Biomarin. The Brain, Neurological Features and Neuropsychological Functioning in Adults with Phenylketonuria: A Pilot Study (PI: Susan Waisbren)
- Gilead/Merck. Advanced neuroimaging evaluation of the central nervous system biological changes associated with efavirenz therapy (PI: Nina Lin)
- VA Merit Award, 2-I01-CX000157-06, Neurophysiological and MRI Studies of Schizophrenia (PI: Robert McCarley)

Collaborators:

To achieve our goal of expanding MR spectroscopy to other disciplines, we have established multiple collaborations across departments and with almost all Harvard institutions. This work includes improved diagnostics for brain cancer with BWH Neuro-oncology and Dana-Farber Cancer Institute, measuring treatment effects in the liver with the Joslin Diabetes Center, biomarkers for metabolic disorders with Boston Children's Hospital, HIV research with Massachusetts General Hospital, and schizophrenia with Harvard Medical School and Veterans Administration Boston. Our research portfolio is diversified across multiple disciplines and we received funding from NIH, DOD, and through several industry agreements and awards. We continue close collaboration with industry leaders such as General Electric Healthcare and Siemens Healthcare.

- Nils Arvold, MD. Assistant Professor of Radiation Oncology, Harvard Medical School; Radiation Oncologist, Dana-Farber Cancer Institute, Brigham and Women's Hospital
- Allison Goldfine, MD. Associate Professor of Medicine, Harvard Medical School; Head of the Section of Clinical, Behavioral & Outcomes Research, Joslin Diabetes Center
- John Irvine, PhD. Laboratory Technical Staff, Information and Decision Systems Charles Stark Draper Laboratory
- Nina Lin, MD. Assistant Professor, Boston University School of Medicine. Internist, Infectious Diseases
- Robert McCarley, MD. Chair and Professor of Psychiatry Harvard Medical School and the VA Boston Healthcare System; Director, Laboratory of Neuroscience, VA Boston Healthcare System, Brockton
- Srinivasan Mukundan, MD, PhD. Associate Professor of Radiology, Harvard Medical School; Chief of Neuroradiology, Brigham and Women's Hospital
- Carmen Sceppa, MD PhD. Professor and Director, Graduate Programs in Exercise Science, Department of Health Sciences, Northeastern University
- Martha Shenton, PhD. Professor of Psychiatry Harvard Medical School and Director, Psychiatry Neuroimaging Laboratory; Director, Clinical Neuroscience Division, Laboratory of Neuroscience, VA Boston Healthcare System, Brockton
- Robert Stern, PhD. Professor of Neurology and Neurosurgery, Director, ADC Clinical Core, Boston University School of Medicine
- Susan Waisbren, PhD. Associate Professor of Psychology, Harvard Medical School, Clinic for Inborn Errors of Metabolism and Phenylkeotnueria.
- Patrick Wen, MD. Professor of Neurology, Harvard Medical School; Director, Center for Neuro-Oncology

In the News:

2014: BWH BRIght Futures Finalist

2013: Chronicles of Higher Education article

2012: PBS Newshour American Graduate program

BWH Clinical & Research News Feature

2011: "I Am Harvard Catalyst" Feature

2010: NY Times: Scans Could Aid Diagnosis of Brain Trauma in Living

The Scientist: Vital Signs: Imaging Trauma

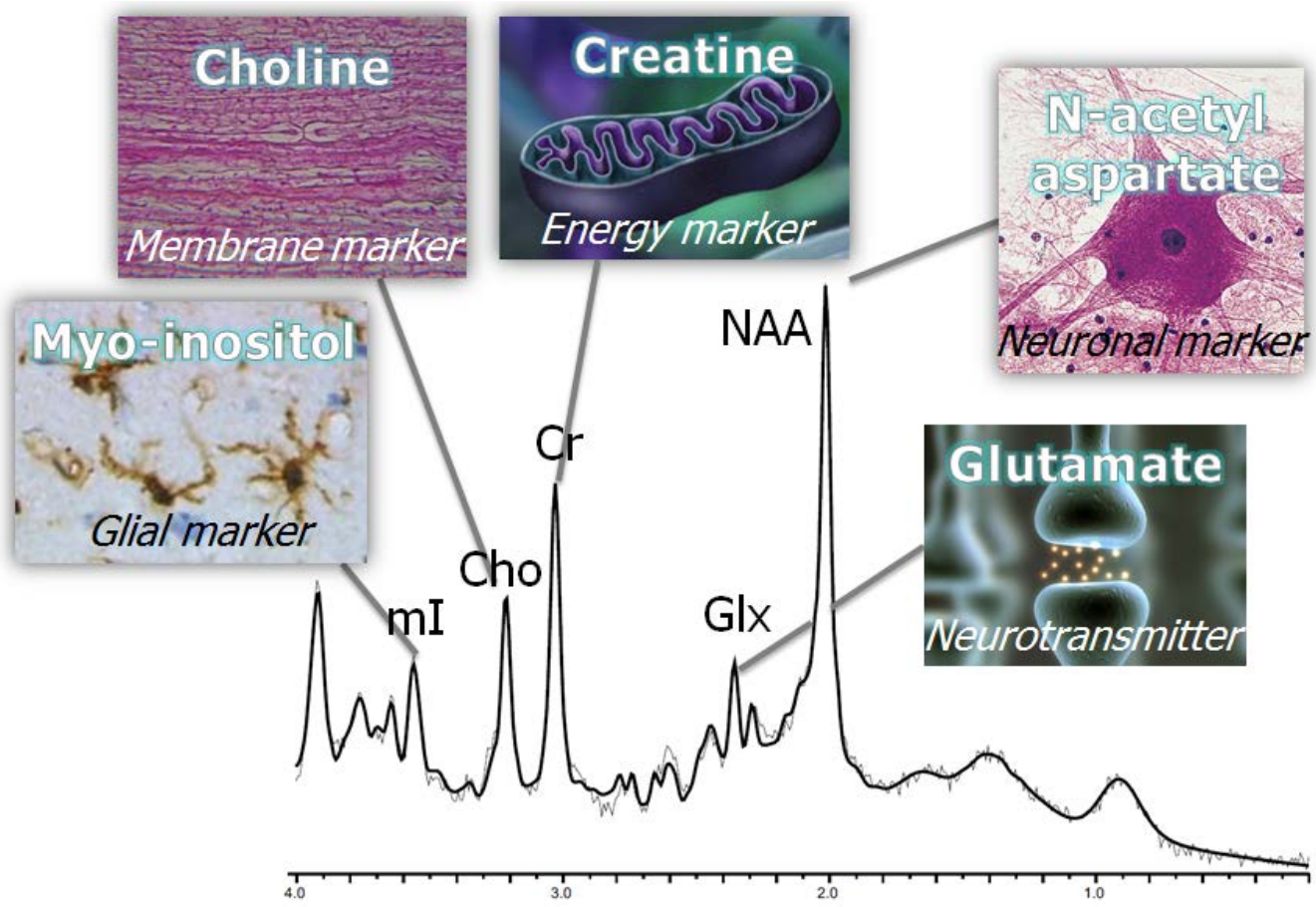
Boston Globe: Virtual Biopsy may detect athlete's brain injury

US News: Imaging May Reveal Sports-Related Brain Disorder at Early Stage

WebMD: Virtual Biopsy Diagnoses Brain Disorder

https://www.youtube.com/embed/xFxsUbQ3o20

About Spectroscopy



Magnetic resonance spectroscopy (MRS) is a powerful tool that examines brain metabolism using standard clinical MR scanners. A non-invasive and quantitative technique, MRS is ideally suited for repeated measurements and for measuring therapeutic outcomes. Often described as a “virtual biopsy”, MRS obtains chemical signals, or metabolites, from a region of interest (ROI or voxel). A spectrum of peaks is generated whereby each peak is reflective of a chemical that resonates at a specific frequency; the height of the peak reflects the concentration of that chemical in the brain (Figure above). The roles of these chemicals or metabolites are described below:

Lactate: Lactate is generally seen as a doublet (two peaks close together) at a frequency of 1.33 ppm. Again, healthy tissue does not have sufficient lactate to be detectable with MRS. However, CSF contains some lactate so that if the voxel is placed entirely in the ventricle, lactate may appear in the spectrum. Lactate, as a product of anaerobic glycolysis, is detected in diseased brain when oxygen starved. It is of great diagnostic value in cases of hypoxia, brain injury, and stroke. It is also elevated in some tumors where it is suggestive of aggressiveness as well as abscesses.

N-acetyl aspartate (NAA): At 2.0 ppm, NAA is an amino-acid derivative synthesized in neurons and transported along axons. It is therefore a "marker" of viable neurons, axons, and dendrites27. The diagnostic value of NAA lies in the ability to quantify neuronal injury or loss on a regional basis and therefore, decreased NAA plays a diagnostic role in brain tumors, head injury, dementias, and many other neurological disorders in which neuronal loss is expected. Increased NAA is observed only in recovery and in Canavan disease that is due to a specific genetic disorder that reduces NAA-deacyclase activity resulting in net accumulation of NAA.

Glutamate—Glutamine—Gamma-amino butyrate (Glx): A mixture of closely related amino acids, amines and derivatives involved in excitatory neurotransmission lie between 2.1 and 2.4ppm. Glx is a vital marker(s) in MRS of stroke, lymphoma, hypoxia, and many metabolic brain disorders.

Creatine (Cr): The primary resonance of creatine lies at 3.0ppm. It is the central energy marker of both neurons and astrocytes and remains relatively constant. For that reason, it is often used as an internal reference for comparison to other metabolites. While some studies have found Cr reduced, it is only in inborn errors of metabolism that significant reductions of Cr occur.

Choline (Cho): Choline includes several soluble components of brain myelin and fluid-cell membranes that resonate at 3.2ppm. Because by far the majority of choline-containing brain constituents are not normally soluble, pathological alterations in membrane turnover (tumor, leukodystrophy, multiple sclerosis) result in a massive increase in MRS-visible Cho.

Myo-inositol (mI): A little known polyol (sugar-like molecules) that resonates at 3.6ppm, mI is mostly a diagnostic "modifier" in those diseases that affect Cho (tumor, MS, etc). As an astrocyte marker and osmolyte, mI contributes specificity in dementia diagnoses106, and an almost absolute specificity to hepatic encephalopathy and hyponatremic brain syndromes.

Additional resonances: A number of additional brain metabolites can be measured with MRS, such as gamma-amino butyric acid (GABA), scyllo-inositol, glutathione, etc.; however, specialized editing sequences or additional software is required to detect and measure them and, therefore, they are beyond the scope of typical clinical practice. However, as MRS methods mature, they may soon be available to clinicians for assaying.

Alexander P. Lin

Alexander P. Lin, PhD is the director of the Center for Clinical Spectroscopy at Brigham and Women's Hospital and Assistant Professor of Radiology at Harvard Medical School. Dr. Lin is a graduate of the California Institute of Technology, where he completed his Masters degree in Bioengineering and his doctoral degree in Biochemistry and Molecular Biophysics. He began his training as a research associate in 1997 and was appointed Director of Clinical Services and Senior Scientist at the Magnetic Resonance Spectroscopy Unit at the Huntington Medical Research Institutes in 2003. Since that time, he has been a visiting research associate at the Center of MR Research at the University of Illinois Chicago. From 2007 to 2009, Dr. Lin had a research fellowship at the National Heart, Lung and Blood Institute at the National Institutes of Health in Bethesda, MD. Dr. Lin arrived at Brigham and Women's Hospital in 2009.

Dr. Lin's research interests include clinical applications of multinuclear magnetic resonance spectroscopy in the brain, breast, and liver, and cardiovascular magnetic resonance imaging. He was awarded the Young Investigator's Award in 2003 for his work in ^{13}C spectroscopy in Alzheimer's disease and an NHLBI Fellows Research Award for his work in strain mapping of the carotid arteries in 2007. He was recently awarded a Congressionally Directed Medical Research Program grant from the Department of Defense to study mild traumatic brain injury and post-traumatic stress disorder in soldiers returning from the Iraq/Afghanistan wars. In addition, he has ongoing collaborations with the Boston University Center for Study of Traumatic Encephalopathy to examine the long-term effects of repetitive head injury using magnetic resonance spectroscopy. He has co-authored more than three dozen peer-reviewed publications, five book chapters, and 75+ conference abstracts.

Finally, Dr. Alexander Lin has also been recognized through awards and media reports for his efforts in supporting mentorship, particularly of students of diversity through the laboratory's involvement in the Student Success Jobs Program and Harvard Catalyst summer research studies. He actively mentors Harvard Medical School students and received a Young Mentor Award from Harvard Medical School. Further, he is involved in education and training in several international workshops for MR spectroscopy.

Awards:

- BWH Biomedical Research Institute Clinical Research Excellence Award (2011)
- Partners in Excellence Team Award (2011)
- Harvard Medical School Excellence in Mentoring Award (2014)

James Balschi, PhD

Dr. Balschi is the director of the Physiological NMR Core Laboratory in the Department of Medicine at Brigham and Women's Hospital and an Associate Professor of Medicine at Harvard Medical School. He is an Associate editor of Circulation.

Jim completed his PhD in Chemistry at SUNY Stony Brook. He began at Harvard Medical School as Technical Director of the HMS NMR Laboratory and, a post-doctoral associate in myocardial metabolism. After which he was a faculty member at the Center for Nuclear Imaging Research at the University of Alabama Birmingham. He has been in BWH Cardiology since 1998.

Dr. Balschi has developed and applied novel NMR tools, *e.g.*, shift reagents for cations, magnetization transfer measurements, as well as, ^{1}H and ^{23}Na MR relaxography, to address biomedical questions. He has extensive experience in the use of multinuclear MRS to the study cellular energetics, oxygen consumption, and metabolism. He has been an integral part of the Center for Clinical Spectroscopy efforts to develop ^{31}P MRS of exercising skeletal muscle at BWH.

Brian D. Ross, DPhil (Oxon), FRCS

Brian D. Ross earned his D.Phil. degree in biochemistry at Trinity College, University of Oxford with Sir Hans Krebs, and M.D. at University College Hospital in London and University of Southern California. He is an accredited surgeon, pathologist, radiologist, and neurologist. Introduced to NMR by Ray Freeman and Sir Rex Richards, Dr. Ross has been a pioneer in developing clinical magnetic resonance spectroscopy, conducting his first MRS studies with Sir George Radda in Oxford in 1981. He has authored more than 200 publications and instituted the first comprehensive clinical MRS service in the United States at Huntington Medical Research Institutes where he was director from 1988 to 2014. He was awarded a Gold Medal by the International Society of Magnetic Resonance in Medicine in 1995 in recognition of his work in this field. He has also trained hundreds of physicians, scientists, and technologists in the acquisition and interpretation of data in this essential diagnostic technique. He is currently a visiting associate at the California Institute of Technology and lecturer at Harvard Medical School.

Benjamin Rowland, DPhil (Oxon)

Dr Rowland received his D.Phil. in quantum physics at Worcester College, University of Oxford, where he was also a tutor in mathematical methods. He then transitioned to MR spectroscopy as an Experienced Researcher in the prestigious Marie Curie fellowship program, investigating pioneering radiotherapy techniques for treating brain tumours at the Institut Claudius Regaud, Toulouse. Ben is a recent addition to the Center for Clinical Spectroscopy, working as an MR physicist with the primary role of developing new processing methods for data analysis.

Huijun "Vicky" Liao, BS

Huijun "Vicky" Liao joined the Center for Clinical Spectroscopy in May 2012 as a clinical research study coordinator. She graduated from Boston University with a degree in Human Physiology. She has more than two years' experience in clinical spectroscopy and continues receiving professional training using MR spectroscopy in the clinic and for research. She helps coordinate the study of mild traumatic brain injury both in sports related concussion and military blast injury. She also assists with studies in brain cancer, multiple sclerosis, and schizophrenia. In addition to neurospectroscopy, she is involved in MRS studies of the liver and leg muscle, including multinuclear ^{31}P spectroscopy.

Joshua Ladner, BS

Josh is a research trainee at the Center for Clinical Spectroscopy. He is directly involved with the DOD funded research using MR spectroscopy to differentiate mild traumatic brain injury and post-traumatic stress. He graduated from the United States Military Academy at West Point in 2006 with a BS in Mechanical Engineering. His honors included the Superintendent's List and the Brigadier General Clifton Carrol Carter Memorial Award for Excellence in Mechanical Engineering. Josh served two tours of duty in Iraq and one in Afghanistan with the 3rd Brigade of the 4th Infantry Division; he was awarded three Bronze Stars for his service. Josh is currently a first year student at Harvard Medical School, and will serve as a physician in the US Army upon graduation.

Xi 'April' Long, MD

Xi Long is a clinical radiologist from Department of Radiology at Union Hospital in Wuhan. Dr. Long completed her master degree and is a Ph.D. candidate in Radiology at Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China. She is a visiting fellow at the Center for Clinical Spectroscopy of Radiology department at Brigham and Women's Hospital, under the supervision of Dr. Alexander P. Lin. She studies 2-hydroxyglutarate detection by magnetic resonance spectroscopy in patients with brain tumors.

Praveen "Dev" Merugumala, BS

Dev Merugumala is a research trainee at the Center for Clinical Spectroscopy. He is a graduate of Baylor University with a Bachelor of Science in Biology. He was recently accepted by the Texas Tech University School of Medicine program and will be attending medical school in June.

Fatah Adan

Fatah Adan is a senior at New Mission High School and a research assistant through the BWH Student Success Jobs Program. He plays an important role at the Center for Clinical Spectroscopy by assisting with data processing of spectroscopy data including our brain injury studies. He has been accepted into prestigious universities such as Yale and Princeton Universities.