



Laser Biomedical Research Center
George R. Harrison Spectroscopy Laboratory
Massachusetts Institute of Technology

From the Director

With summer finally arrived to Boston, we are happy to report that Laser Biomedical Research Center (LBRC) has received funding support from NIH NIBIB for a five-year cycle. We continue to serve the biomedical community for the 33rd year, and are pleased to have made two major infrastructural changes in our center. The most significant improvement involves an ambitious expansion of the center's core competency by welcoming four new co-investigators with very complementary expertise: Dr. Ishan Barman (Mechanical Engineering/Oncology, Johns Hopkins University) an alumnus of the LBRC and an expert in spontaneous Raman spectroscopy; Dr. Conor Evans (Wellman Center, Massachusetts General Hospital), an expert in nonlinear Raman spectroscopy and contrast agent synthesis; Dr. Gabriela Schlau-Cohen (Chemistry, MIT) an expert in single molecule biophysics and ultrafast spectroscopy; and Dr. Zahid Yaqoob (Chemistry, MIT), who has been leading the center's interferometric imaging effort for many years and is aptly now recognized as a co-investigator. Expansion was recommended by our External Advisory Committee and our team has their support.



*Dr. Peter T.C. So, Professor of
Mechanics and of Biological Engineering,
directs the LBRC*

These additions to the leadership team strengthen the three research areas of the center, which focus on developing fluorescence, phase and Raman spectroscopy, and imaging instruments and techniques. This expansion also allows the LBRC to foray into an important new research area in which we plan to develop a nanoprobe toolkit for many biomedical applications. Within this toolkit, Dr. Mounji Bawendi (MIT) will continue to innovate his world-leading quantum dot probes and sensors for applications ranging from cancer to metabolic diseases. His development of quantum dots in the short-wave infrared regime promises to allow imaging and sensing in tissues and animals down to an unprecedented depth. With our two new co-investigators Dr. Barman and Dr. Schlau-Cohen, we gain new expertise in the synthesis and application of plasmonic nanoparticles and nanolipoproteins.

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Professor Mildred S. Dresselhaus: A Lifetime of Spectroscopy on Carbon

Professor Mildred S. Dresselhaus pioneered the fields of carbon science, nanotechnology, and thermoelectrics, and established the fundamental science underlying the technological advances that followed. In her experimental work, Professor Dresselhaus – known even to her children and grandchildren as “Millie” – employed many spectroscopic tools that used electric and magnetic fields to probe the properties of challenging new materials, well before they were commonly used. By combining data from new and old techniques, she was able to show important and unique properties of materials and to establish several optical and spectroscopic techniques as standards. This allowed Millie to guide generations of scientists and spectroscopists – including me, her granddaughter and a graduate student studying ultrafast imaging here at MIT.

Raman spectroscopy has been used to study carbon materials for decades, but Millie and her team were the first to apply it to carbon nanostructures. Her work in the late 1990s established Raman spectroscopy as the industry standard to characterize carbon nanostructures and differentiate between carbon nanotubes and graphene. This work developed the theory to understand the underlying interactions between the nanotubes and the probing irradiation, clarifying the origin of the spectroscopic signals. Her team showed how Raman spectra could differentiate between different chiralities of nanotubes, could resolve the coupling between the electronic and phononic bands, and showed how it characterized the defect density of the sample. These foundational studies established Raman spectroscopy as a key characterization tool to develop carbon nanotube samples and have enabled nanotubes to be applied to numerous fields of technology.



Professor Mildred S. Dresselhaus

Millie solidified the impact of Raman spectroscopy by training students and colleagues in the technique. She once recalled that a “student found me at one of the nanotube conferences, and she showed me that she had this kind of material and asked me what to do with it. So, I said, ‘Come up to MIT and we’ll do some spectroscopy!’” (The Zurich Physics Colloquium, 2012) Hundreds saw this side of Millie, as she taught colleagues to use the technique and see its impact.

Millie also specialized in helping others to get insights from spectroscopy: her students, her colleagues – and not surprisingly, her family. When I was a child, Millie taught me that we could use light to learn important things about materials. As I got older, I learned that this was called spectroscopy, and eventually I started to learn how different types of spectroscopy could differentiate between a material’s properties. When I started as a graduate student at MIT, Millie and I often attended the Modern Optics and Spectroscopy seminar series together, where I continued to learn about spectroscopy. But Millie always took me, and her students, a step beyond the seminars. She included us in conversations afterwards – sometimes including the speaker – about the science in the talks. Inspired by this, I eventually began my own research, which develops optical techniques to study shock waves.

Millie’s career in physics spanned 64 years – from 1953 to 2017. Throughout that time, by getting down to the fundamentals both of the experimental techniques and of the material properties, she was able to extend her results beyond our conventional understanding. By making her findings so easily accessible to students and colleagues, she was able to contribute significantly to science and society. And by making spectroscopy an ongoing conversation, always leaving extra time to talk with people about the work, Millie guided a new generation of scientists to use spectroscopy in important and meaningful ways. ~ by **Dr. Leora E. Dresselhaus-Cooper**

Spotlight on: Dr. Conor L. Evans

The LBRC is pleased to bring on several new collaborators, one of whom is Dr. Conor L. Evans, an Assistant Professor at Harvard Medical School and a researcher at the Wellman Center for Photomedicine at Massachusetts General Hospital. Dr. Evans, who is also an affiliate of the Harvard University Biophysics program, brings both teaching and research expertise to the LBRC. He completed his undergraduate work in Chemical Physics at Brown University, where he was a classmate—and later, labmate—of current LBRC researcher Dr. Gabriela Schlau-Cohen (MIT). While at Brown, Dr. Evans received numerous awards in acknowledgement of his undergraduate work in the lab of Dr. Peter Weber, among them a Goldwater Scholarship and Royce Fellowship.



Dr. Conor L. Evans

In 2002 Dr. Evans began his graduate studies under the mentorship of Professor Sunney X. Xie, leading to research focused on the development and application of coherent anti-Stokes Raman scattering (CARS) microscopy in biology and medicine. Additionally, he investigated new technologies including interferometric and frequency modulated CARS microscopy, and in collaboration with Dr. Charles Lin at MGH led the first use of CARS microscopy *in vivo*. A recipient of an NSF Graduate Fellowship, Dr. Evans received his Ph.D. from Harvard University in 2007 and immediately began a two-year postdoctoral stint at the Wellman Center, where he was mentored by Drs. Johannes de Boer and Tayyaba Hasan. During this time Dr. Evans performed research dealing with optical microscopy and cancer therapeutics, including specific work on ovarian cancer metastases. In 2009, he was hired at the Wellman Center as an instructor, and after receiving an NIH R21 Grant and Director's New Innovator Award, he began his lab the following year.

The Evans lab is driven to solve problems in clinical medicine through the use of imaging, spectroscopy, and chemical innovation. Dr. Evans notes that the “three pillars of his lab” are advanced microscopy, oxygen sensing, and ultrasensitive detection of molecular factors. More specifically, these fundamentals of Evans lab research deal with areas such as cancer diagnostics using Raman imaging systems. The Evans lab is also looking at wearable oxygen sensing devices, and has developed “smart bandages” which change color depending on tissue oxygen concentration; clinical trials are being performed in support of the latter. Dr. Evans and his research are supported by various federal and private funding agencies and he looks forward to expanding his research through collaborative work with the LBRC. ~ by **Christine Brooks**

Research Report: Non-Invasive Blood Glucose Monitoring

Diabetes Mellitus is a chronic disorder, affecting 415 million patients worldwide (2015), which requires careful monitoring of blood glucose levels. Failure to adequately monitor and regulate glucose levels may lead to severe complications in multiple organ systems such as the retina, nerves, kidneys and the circulation. Given the necessity for repeated daily measurements of blood glucose levels, development of noninvasive glucose monitoring devices is essential to improve the quality of life in the diabetic population. These devices can also be very useful in the development of new technologies like an artificial pancreas to help diabetic persons automatically control their blood glucose level. An artificial pancreas provides the substitute endocrine functionality of a healthy pancreas and requires a closed-loop system that links glucose measurement with computer-driven insulin infusion so that no input is required from the user. To this end, Non-invasive measurement technologies such as Raman will be an ideal solution.

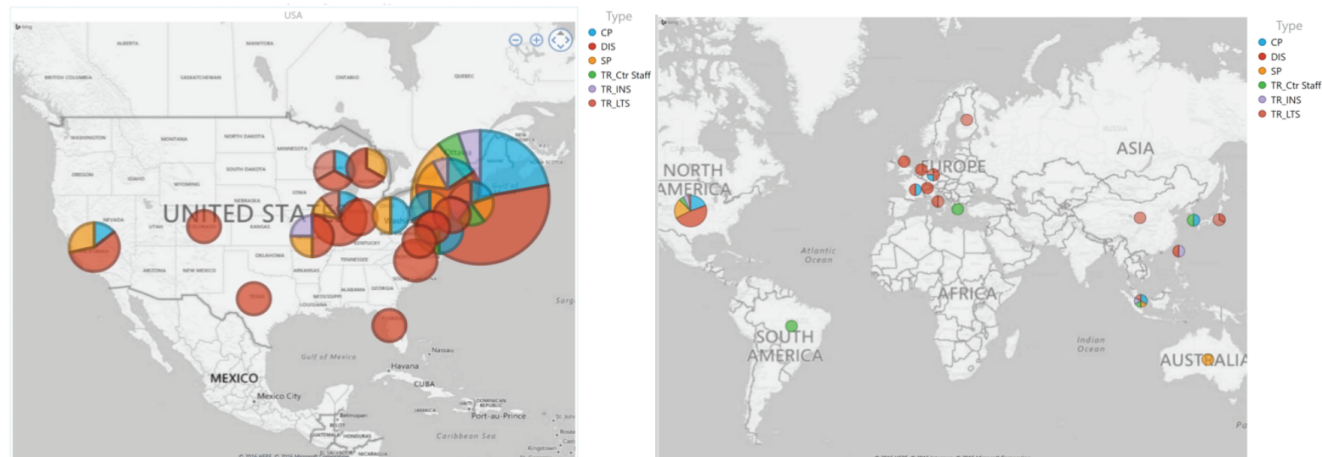
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Over the past decade, the LBRC has made significant advances in developing instrumentation and methodologies for non-invasive measurement of blood glucose using Raman spectroscopy. In 1996, accurate concentration measurements of glucose, lactic acid, and creatinine in saline solution were achieved with NIR Raman spectroscopy and a partial least-squares analysis. A root-mean-squared prediction error of 1.2 mM for glucose concentration was achieved. In 2000, concentrations of multiple analytes were simultaneously measured in whole blood with clinical accuracy using an instrument employing non-imaging optics, designed using Monte Carlo simulations of the influence of blood on the excitation and emission of Raman light in turbid medium. In 2005, we performed the first human volunteer study and in 2011 performed a second human volunteer study with upgraded instruments. We developed a novel, non-imaging optics-based portable Raman instrument with enhanced light collection efficiency for glucose-related studies.

In 2015, the collaboration between Samsung Advanced Institute of Technology and LBRC started as a Global Research Outreach (GRO). The GRO Program is Samsung’s academic research collaboration platform which calls for innovative research proposals on an annual basis, open to universities to foster collaborative research relationships. The goal of the project was to develop high-throughput Raman instrument and validate the system in the live animal experiments. After promising results, this collaboration was recently expanded as Technical Collaboration Program (TCP). Our goal in the following year is to further improve the system and validate it in the practical measurement conditions. ~ by **Dr. Jeon Woong Kang**

From the Director [continued from page 1]

Custom-designed plasmonic nanoparticles and assays have shown promise for analyte detection, based on surface enhanced Raman scattering showing better sensitivity than the industrial standard fluorescence ELISA approach with promising results in cancer research area. Nanolipoprotein are protein discs that encase a bilayer lipid membrane where transmembrane protein receptors can be selectively inserted. This allows Dr. Schlau-Cohen to study the activation mechanisms of many transmembrane receptor proteins that are critical for the development of the next generation of pharmaceuticals. The LBRC now spans three major academic/medical institutions: MIT, Massachusetts General Hospital, and Johns Hopkins University. We view the LBRC as a hub and a meeting-place connect the biophotonics community in the broader sphere by our broad range of dissemination activities. In the last cycle, we engaged in over 60 collaborative projects, with investigators utilizing cutting-edge technology under development in the center, as well as existing unique instruments that we maintain for service. In the past year, we hosted 10-15 long-term visitors who worked in the center for several months. We also hosted seminars and two named lectures, inviting roughly 25 researchers each year to visit. This figure shows the impact of our center on the research of institutions worldwide. ~ by **Dr. Peter T.C. So**

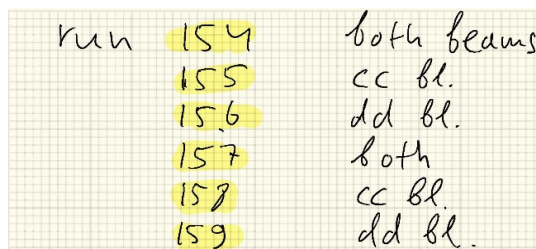


LBRC national and international interactions. Captions: CP: collaborative projects, SP: service projects, TR Ctr. Staff: trained center staffs, TR_LTS: trained long term stay visitors, TR_INS: training through instrument loan, DIS: dissemination through expert speakers.

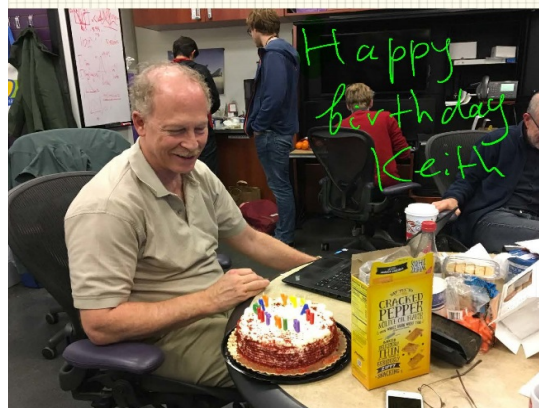
Prof. Keith A. Nelson Presents 2017 Dasari Lecture

The title of Professor Keith A. Nelson's 11th Annual Dasari Lecture on November 14, 2017 fit perfectly with the holiday season: "Light Interactions with Matter: The Gift that Keeps on Giving". He described not only career-highlights of his scientific achievements based on light-matter interactions, but also "gifts" he hopes to receive from future experimental endeavors. Nelson joined the MIT faculty in 1982 after receiving his Ph.D. in Physical Chemistry for his work in Professor Michael Fayer's group at Stanford University in 1981, followed by a postdoctoral stint at UCLA.

In his remarkable career, Nelson has discovered new light-matter interactions and exploited them for spectroscopy and control of coherent acoustic waves, lattice and molecular vibrations, excitons, spins, and their admixtures with light. He has devised novel methods for the study of solid-state chemical reactions, crystals near a phase transition, glass-forming liquids, electronic excited-state dynamics, thermal transport, and matter far from equilibrium. He is famous for his pioneering work in the field of ultrafast pulse shaping for coherent spectroscopy and quantum control, and for the development of impulsive stimulated Brillouin and Raman scattering. In particular, he was leader of a group that, in 1985, made the first direct observation of molecular vibrations in the time domain using femtosecond light pulses. Moreover, he is world-renowned for tabletop generation of strong terahertz-frequency fields and nonlinear terahertz spectroscopy. He is an author of more than 400 scientific publications, holds 30 US patents, and has commercialized a technology in which laser-generated acoustic waves are used to measure metal interconnect thickness during the fabrication of semiconductor chips. Nelson has been recognized as a Fellow of the American Association for the Advancement of Science, the Optical Society of America, and the American Physical Society and is a Member of the American Academy of Arts and Sciences. He has received the Coblenz, Lippincott, Zewail, Bomem-Michelson, and Isakson Awards from the Coblenz Society, the Optical Society of America, the American Chemical Society, and the American Physical Society.



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This photograph from a lab notebook shows Keith 3 weeks after the Dasari lecture, celebrating his 63rd birthday with members and collaborators during a shift at the Stanford Linac Coherent Light Source.

Professor Robert Field chose an unusual approach for his introduction of Nelson to the large and attentive audience. Instead of reading Keith's C.V. and listing scientific achievements and honors, he presented a video of Nelson giving a passionate speech at the 2009 Latke-Hamantaschen debate at MIT (for interested readers: https://www.youtube.com/watch?v=YLFp_KdP_-8). The snippet highlighted Keith's uniquely intense speaking style, supercharged with outrageous humor, a format clearly in evidence in his Dasari lecture.

Nelson began his lecture presenting diverse aspects of light-matter interactions in examples from different regions of the electromagnetic spectrum. In particular, he explained how he and his group uses light to drive a wide range of molecular and collective degrees of freedom, involving electrons, ions, and spins as well as motions of entire micro-particles. In addition to his group's achievements, Nelson introduced pioneering work in the field of light-matter interactions from other researchers at MIT. After that, Nelson turned his focus to the spectral domain of his most intense current interest: the terahertz region. Only recently, technological and scientific improvements, many pioneered in the Nelson lab, made strong fields in the terahertz region widely available. His passion

for light-matter interaction in the THz-domain can probably only be matched by his passion about Mexican hot chocolate – a spicy and sweet drink every student in his class or group has had the pleasure to taste. Nelson introduced the basics of lithium-niobate based generation of high-field single-cycle THz pulses, an explanation even non-experts could easily follow. He illustrated further how THz electric fields could drive lattice vibrations, electronic responses, and molecular rotations, all enabling interesting new spectroscopic applications.

The high electric fields of the THz pulses were crucial to enabling the investigation of nonlinear effects in diverse materials. One example is the structural phase transition in ferroelectric materials, like barium titanate (or strontium titanate, which is often used as an inexpensive replacement for a real diamond, which is appropriate to mention since we have been discussing *gifts* here...). The THz electric fields can drive large-amplitude displacements of the titanium atoms along the ferroelectric polarization axis. This THz-driven effect is associated with switching a dynamic rotation of the ferroelectric polarization on and off on a picosecond time scale, followed by long-lived vibrational heating effects driven by resonant excitation of the ferroelectric soft mode. In addition to these ultrafast structural changes, which are probed by femtosecond x-ray scattering, it is also possible to study the electronic responses of such materials in the THz domain.

As one of the pioneers of multidimensional optical spectroscopy, Keith Nelson also brought this technique into the THz domain by measuring the first-ever two-dimensional molecular rotational spectrum. The method, demonstrated on acetonitrile, can also be applied to polar molecules in flames and other reactive conditions in which light-enhanced control over molecular motions is still entirely possible. 2D spectroscopy was demonstrated not only with THz electric fields, but also THz magnetic fields. Nelson showed the first 2D THz EPR spectrum, recorded from collective spin waves (magnons) in an antiferromagnetic crystal. He then showed how THz magnetic fields enable facile EPR measurement of transition metal zero-field splittings.

Nelson ended his lecture with an outlook toward future directions of his research, THz-driven Bose-Einstein condensates as well as x-ray two-dimensional spectroscopy of nuclear transitions. The recently available coherent x-ray source is especially important to him. This becomes obvious from this pictorial excerpt from a group member's lab notebook: *how many PIs are still actively participating in beam time in a night shift at a national user facility x-ray source?*

The Dasari lecture was followed by a Question and Answer session, unfortunately, without Keith Nelson *as a member of the audience*. Keith is widely known for his constant typing on his laptop during a lecture. But at the end of the lecture, he typically asks several prescient questions, often to the great surprise and pleasure of the speaker. It turns out he is not multi-tasking: he is typing notes on the lectures, which he often consults later on. Alas, Keith could not ask himself post-talk questions! Fortunately, other audience members stepped up to the plate.

Prof. Field thanked Keith Nelson for the extraordinary talk and expressed, for all the audience, gratitude and pleasure for Nelson's work and his passion for science. ~ by **Prof. Robert W. Field**

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announcements, please email cbrooks@mit.edu and request to be added