



George R. Harrison Spectroscopy Laboratory Massachusetts Institute of Technology

Devices Could Help Diagnose Precursors To Cancer

Deborah Halber, News Office

Note: The following is based on an article that appeared in the September 17, 2003 issue of TechTalk. The original can be located at <http://web.mit.edu/newsoffice/tt/2003/sep17/spectroscopy.html>. Brief introductions to the Principle Investigators begin on page 2.

An MIT interdepartmental laboratory has received \$7.2 million from the National Institutes of Health (NIH) to further its work on devices that can detect and image precancerous cells as noninvasively as shining a tiny beam of light onto a patient's tissue.

The George R. Harrison Spectroscopy Laboratory in the School of Science has been awarded a Bioengineering Research Partnership grant to develop and implement spectroscopic techniques for imaging and diagnosing dysplasia—the precursor to cancer—in the uterine cervix and the oral cavity.

Cervical and oral cancer account for approximately 11,000 deaths in the United States each year and billions of health care dollars in screening costs. Detection of the precancerous state of human tissue is crucial for ease of treatment and greatly improved survival, but it is often invisible and difficult to diagnose. The new techniques provide a method for visualization and accurate diagnosis based on spectroscopic detection and imaging.

Clinical screening for cervical and oral precancer are multibillion-dollar industries which currently rely on visual detection of suspicious areas followed by invasive biopsy and microscopic examination. Given that visually identified suspicious areas do not always correspond to clinically significant lesions, spectroscopic imaging and diagnosis could prevent unnecessary invasive biopsies and potential delays in diagnosis.

Furthermore, real-time detection and diagnosis of lesions could pave the way for combined diagnosis and treatment sessions, thus preventing unnecessary follow-up visits.

Michael S. Feld, professor of physics and director of the Spectroscopy Lab, says the laboratory has developed a portable instrument that delivers weak pulses of laser light and ordinary white light from a thin optical fiber probe onto the patient's tissue through an endoscope. This device analyzes tissue over a region around 1 millimeter in diameter and has shown promising results in clinical studies. It accurately identified invisible precancerous changes in the colon, bladder and esophagus, as well as the cervix and oral cavity.

The second device, which has not yet been tested on patients, can image precancerous features over areas of tissue up to a few centimeters in diameter.

The researchers hope that these new methods, which can provide accurate results in a fraction of a second, may one day replace tissue biopsies in diagnosing certain types of cancers.

Feld predicted that in a couple of years, these devices will lead to a new class of endoscopes and other diagnostic instruments that will allow physicians to obtain high-resolution images. These easy-to-read images will map out normal, precancerous and

Laboratory Affiliated Faculty Receive Awards

Prof. Stephen J. Lippard, one of the core investigators of the Laser Research Facility, received the "2004 Alfred Bader Award in Bioinorganic or Bioorganic Chemistry" from The American Chemical Society.

Prof. Stanley Shapshay, BRP PI, received the Charles W. Vaughan, M.D. Award for Excellence in Clinical Teaching (Boston University, Department of Otolaryngology) and the 2003 Presidential Citation, The Triological Society (Southern Section Meeting, Naples FL, January 11, 2003). Additionally, Dr. Shapshay was the Guest of Honor at The American Bronchoesophagology Association, Annual Meeting, Nashville TN, May 3, 2003.

We congratulate our colleagues on these significant honors. ❖

Also this issue:

- * **BRP Investigators:**
A brief introduction to the Principle Investigators and their work
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Proton Coupled Electron Transfer: The Engine of Bioenergy Conversion by Prof. Daniel Nocera
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Rainbows by Stephen R. Wilk
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Modern Optics and Spectroscopy

BRP Personalities - Following are biographical sketches of the Principle Investigators of our new Bioengineering Research Partnership program.

Irene Georgakoudi
Massachusetts General Hospital

Irene Georgakoudi is an Instructor at the Wellman Laboratories of Photomedicine, at the Massachusetts General Hospital and Harvard Medical School. She received her bachelor's degree in Physics from Dartmouth College. Early on she became interested in the study of interdisciplinary problems involving physics, biology and medicine, and in particular the use of light as a means to treat and diagnose human diseases. As a Biophysics doctoral student at the University of Rochester, she worked in the field of photodynamic therapy (PDT), a treatment involving the combined use of photosensitive drugs followed by light irradiation. Under the supervision of Professor Tom Foster, she examined the effects of drug localization and photobleaching on the production of singlet oxygen, the major PDT cytotoxic agent. For her postdoctoral research, Irene worked under the guidance of Professor Michael Feld at the MIT Spectroscopy Laboratory. There, she demonstrated that the combined use of three spectroscopic techniques, intrinsic fluorescence, diffuse reflectance and light scattering spectroscopy, results in improved detection of pre-cancerous lesions in the uterine cervix and Barrett's esophagus. At Wellman Laboratories, she is working in the groups of Tayyaba Hasan and Charles Lin on the development of in vivo flow cytometry as a tool for detecting and quantifying circulating cancer cells and their role in tumor metastasis. As a project leader in the recently funded Bioengineering Research Partnership grant with Michael Feld as the PI, she plans to examine the intrinsic fluorescence and light scattering spectroscopic signatures of events associated with apoptosis, loss of cell cycle control and genomic instabilities in the context of neoplastic development. At home, she loves spending time with her husband and two great kids. Dancing and family trips to beautiful Greek beaches or scenic New England mountains are her favorite ways to have fun and relax. ❖



Irene Georgakoudi

THE SPECTROGRAPH

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GEORGE R. HARRISON SPECTROSCOPY LABORATORY

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Jeffrey I. Steinfeld
Associate Director:
Ramachandra R. Dasari

The Spectroscopy Laboratory houses two laser research resource facilities. The MIT Laser Research Facility, supported by the National Science Foundation, provides shared facilities for core researchers to carry out basic laser research in the physical sciences. The MIT Laser Biomedical Research Center, a National Institutes of Health Biomedical Research Technology Center, is a resource center for laser biomedical studies. The LBRC supports core and collaborative research in technological research and development. In addition, it provides advanced laser instrumentation, along with technical and scientific support, free of charge to university, industrial, and medical researchers for publishable research projects. Call or write for further information or to receive our mailings. (617) 253-4881
<http://web.mit.edu/spectroscopy/www/>

Michael Feld, MIT

Michael Feld is Professor of Physics at MIT and heads the George R. Harrison Spectroscopy Laboratory there. He is active in the application of lasers, light and spectroscopy to a variety of problems in biology and medicine. He directs the MIT Laser Biomedical Research Center, an NIH-supported center that he founded in 1985, which pursues research on the use of fluorescence, reflectance, elastic light scattering and Raman spectroscopy to characterize biological tissues and image disease via endoscopy and optical tomography.



Michael Feld

In 1985 Professor Feld showed that fluorescence could be used to diagnose atherosclerosis, laying the basis for the field of spectral diagnosis of disease. In 1991 he demonstrated that Raman spectroscopy can be used for histochemical analysis. In 1998 his group developed the technique of light scattering spectroscopy for measuring the size distribution of epithelial cell nuclei to characterize pre-cancerous change, and in 2001 the method of trimodal spectroscopy, a clinical technique which combines fluorescence and reflectance for spectral diagnosis. He and his colleagues are currently developing methods of low-coherence optical interferometry to measure nanometer length changes and small-scale dynamical processes in biological systems, with the aim of studying fractal structure and nonlinear dynamics in tissues, cells and nuclei. Professor Feld has deeply held beliefs in the importance of affirmative action in science and has received several awards for his activities in this area. His 1979 article in *Scientific American* on the physics of karate broke new ground, and you can see photos of him there breaking boards and concrete blocks. ❖

BRP Personalities

Karl Münger, Ph.D.
Harvard Medical School

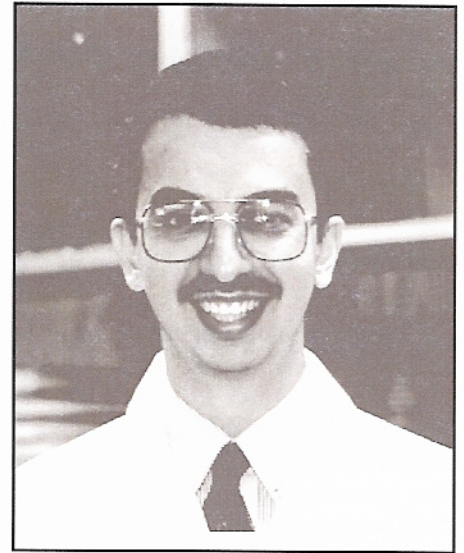
Karl Münger is Associate Professor of Pathology at Harvard Medical School. His current research is supported by grants from the National Institutes of Health and several pharmaceutical companies. His laboratory's main interest is to study the mechanisms of cervical carcinogenesis, a disease that is highly associated with infections by "high-risk" human papillomaviruses (HPVs). The HPV E7 oncoprotein is one of only two HPV proteins that are consistently expressed in cervical cancer, and continued expression of E7 is necessary for the induction as well as the maintenance of the transformed state. The main thrust of currently ongoing studies is to use proteomics to define molecular targets of E7, to delineate the cellular consequences of E7-mediated inactivation of these regulatory proteins, and to develop novel in vitro systems to study cervical carcinogenesis. His research has shown that high-risk HPV E7 proteins can subvert multiple cellular regulatory circuits, including those controlling cellular proliferation, differentiation, apoptosis and maintenance of genomic stability. Recent work has shown that HPV E7 can act as a "mitotic mutator" by subverting centrosome homeostasis, which causes the formation of excess mitotic spindle pole bodies. The resulting mitotic anomalies lead to asymmetric chromosome segregation, genomic destabilization and aneuploidy. ❖



Karl Münger

Kamran Badizadegan
Massachusetts General Hospital

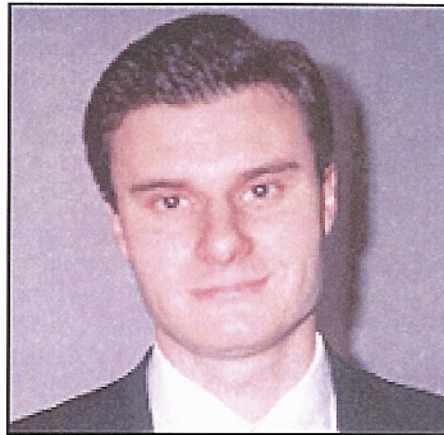
Kamran Badizadegan is an assistant professor of pathology at the Harvard Medical School and a staff pathologist at the Massachusetts General Hospital, where he practices gastrointestinal pathology and is the head of pediatric pathology. Dr. Badizadegan's research interests include epithelial cell biology, as well as diagnostic pathology, and he has been involved in a variety of clinical and basic science projects at the Spectroscopy Laboratory since 1997. Dr. Badizadegan is also a faculty of the Harvard-MIT Division of Health Sciences and Technology, where he currently teaches a course in human pathology and serves on the admissions committee. ❖



Kamran Badizadegan

Vadim Backman
Northwestern University

Vadim Backman is an Assistant Professor of Biomedical Engineering at Northwestern University, Evanston, IL. He received his Ph.D. degree in Medical Engineering and Medical Physics from Harvard University and Massachusetts Institute of Technology, Division of Health Science and Technology in 2001 under Prof. Michael S. Feld. His research interests include biomedical optics, spectroscopy, development of theoretical approaches to describe light propagation in biological media, and optical diagnostic imaging. ❖



Vadim Backman

Stanley M. Shapshay, M.D. Boston University School of Medicine

Stanley M. Shapshay, M.D. was born in Brooklyn, New York in 1942. Dr. Shapshay graduated from Brooklyn College with a Bachelor of Science degree and went on to receive his M.D. at the Medical College of Virginia in Richmond, Virginia. His surgical internship and residency were completed in the Tufts New England Medical Center system, and he completed his otolaryngology residency at the Boston University School of Medicine. He did his surgical fellowship at the Serafimer Hospital of the Karolinska Medical School in Stockholm, Sweden.

In 1975-77, Dr. Shapshay began his academic career as a clinical instructor in the Department of Otolaryngology at the University of Washington. Since that time, Dr. Shapshay has held numerous concurrent clinical, teaching, and administrative appointments at the Boston University School of Medicine, Tufts University School of Medicine, the Lahey Clinic Medical Center, Boston City Hospital, the Veterans Administration Medical Center, and the New England Medical Center Hospitals. From 1994-2001, Dr. Shapshay served as Professor of Otolaryngology and Chairman of the Department of Otolaryngology at Tufts University School of Medicine. He is a past chairman of the Department of

Shapshay continued on next page

Column: Spectral Lines

Dr. Wilk, a Visiting Scientist in the Spectroscopy Laboratory, will contribute columns to The Spectrograph on a regular basis. Dr. Wilk's interests range from optics to gargoyles, and he recently published a book, "Medusa: Solving the Mystery of the Gorgon" (Oxford University) on the latter subject.

Rainbows

by Stephen Wilk

Theories about the rainbow prior to the work by Johannes Kepler (yes, the one who formulated the Three Laws of Planetary Motion. I'll bet you didn't know he was a seminal figure in the history of the rainbow) were characteristically far off the mark. There were some notable successes in the early days, with good observations and reasoning by Thales of Miletus, Aristotle, Claudius Ptolemy, and Alexander of Aphrodisias. Some people have derided some of their theories, such as the idea that the rainbow is really a "reflection of the sun in a cloud", but I think the real problem here is simply a lack of modern terminology. The reasoning behind the theories is logical, and I suspect that the ancients didn't mean exactly what we conceive of by the terms "image" and "reflection". Be that as it may, the immense prestige of Aristotle tended to stifle original thought in many areas of inquiry, including this one, for a very long time. When people started to grope for a theory of the rainbow after the so-called "Dark Ages", their ideas were incredibly far from reality....

...except for two independent researchers, working some 2,000 miles apart, for one brief moment in the history of science, and whose work was quickly forgotten.

The earliest credit must go to a third man. Qutb al-Din al-Shirazi (1236-1311) was one of the most noted Persian scientists. Al-Shirazi was following in the footsteps of Abu Ali al-Hasan ibn al-Hasan ibn al-Haitham (c. 965-1039), usually called Alhazen. His **Treatise on Optics** was a seminal work in the study of optics. Curiously, it did not even mention the rainbow, and al-Shirazi set out to remedy that omission.

Al Shirazi knew about earlier theories of the rainbow, and must have been aware of their limitations. His innovation was to bring the study of the rainbow into the laboratory by using a glass globe filled with water as a model raindrop. Al-Shirazi's work was carried on by his student Kamal

al-Din al-Farisi (fl. 1300-1310), who wrote a commentary on Alhazen that contained their combined work.

They placed the sphere in a darkened room, with a thin shaft of light to illuminate it. They then studied the spectrum formed, blocking parts of the path and moving the beam. They studied the halo formed by light that refracted on entering the drop, then refracted again upon leaving it. They studied the Primary Rainbow that is formed by refraction upon entering the drop, reflection from the inner surface of the drop, then refraction as it exits, and they studied the case of the secondary rainbow, where the light reflects twice inside the drop before exiting. They even tried to study the case of light reflecting three times inside the drop before exiting – thus becoming the first people to ever see the Tertiary Rainbow. As Al-Farisi admitted, however, the light from such triply reflected ray is very weak. Al Farisi attempted an explanation of the colors, but there was nothing like a proper color theory available to him.

No illustrations, if any were ever published, survive. Al Shirazi's work is summarized in the **Nihayat**, a work on astronomy with some material on optics. Al Farisi's works contained in his commentary of Alhazen.

At exactly the same time that al-Farisi was composing his work, a German monk working at Toulouse in France was doing almost precisely the same thing. Theodoric of Freiburg flourished from 1285 to about 1310. He was less profoundly called Dietrich (the French called him Thierry). A member of the Order of Preachers, he earned a degree in Theology at Paris in 1297, occupied several administrative offices in his native Germany, and was eventually sent to Toulouse as German elector to the General Chapter of the Order. There, his Master-General, Aymeric de Plaisance, suggested he set down his ideas about the rainbow. The result was **De Iride et Radialibus Impressionibus**, a work of several hundred pages that has survived.

Like al-Shirazi and al-Farisi, Theodoric studied the rainbow through careful and original experimentation. He used a spherical glass flask filled with water as his model raindrop. Like Al Shirazi and Al Farisi, he traced the path of light moving through the drop, noting that rainbows resulted from cases where light refracts into the drop, reflects once or twice, and then exits. Unlike the Persians, Theodoric didn't observe the tertiary rainbow.

He did observe that the order of colors is reversed in the secondary rainbow. And, most striking, his drawings survive in his printed text. They look almost like the illustrations for a modern text on rainbows. The angles of refraction and reflection are as correctly drawn, as if a protractor was used, both for the primary and for the secondary rainbow. Theodoric also shows the reflection and refraction for different colors of the rainbow, showing how reflections from different drops are responsible for the different colors the eye observes at any instant. The only problem with the drawings is that the sun appears as a spot on a hemispherical heaven, not an almost infinitely distant source.

What is remarkable is that the work of Theodoric and that of al Shirazi and al Farisi should have arisen simultaneously (al Farisi and Theodoric both wrote their works in the decade 1300-1310) and so widely separated in space. There does not appear to have been any communication between them. Boyer ascribes the similarity to the common heritage – both groups were familiar with Aristotle's work on the rainbow, and with Alhazen's *Treatise on Optics*.

But each group also broke free of old ways of thinking. Theodoric freed himself from a slavish subservience to the authority of Aristotle, and justified it in his book on Aristotelian terms. Both groups recognized the authority of experiment over outdated theories, and used the same equipment in their studies. They independently conceived the notion of using the flask of water not as a miniature cloud, but as a magnified raindrop. All of these coincidences are remarkable.

Unfortunately, both groups were alike in being almost completely forgotten by those who followed. The history of the study of the rainbow for the next few centuries is a jumble of nonsense, until the work of Johannes Kepler, Rene Descartes, and Isaac Newton.

References

I recommend C.B. Boyer's **The Rainbow from Myth to Mathematics** for history, R.A.R. Tricker's **An Introduction to Meteorological Optics** for a good basic grounding in the math and physics, Jearl D. Walker's **The Flying Circus of Physics** (and the many references therein) for depth, and Van de Hulst's **The Scattering of Light by Small Particles** to relate all of this to the work being done here at the Spectroscopy Laboratory. ❖

BRP Personalities

Shapshay continued from page 3

Otolaryngology at the Lahey Clinic and former Chief of Ambulatory Surgery, Otolaryngology, at Boston City Hospital.

Currently, Dr. Shapshay is Professor of Otolaryngology at the Boston University School of Medicine and an active member of the clinical otolaryngology staff at Boston Medical Center. He is a Past-President of the American Laryngological Association (2001) and former Vice-President of the Eastern Section of the Triological Society. His research interests include the use of lasers for treatment and early diagnosis of head and neck cancer. His clinical interests include the subspecialty areas of laryngology, bronchoesophagology, rhinology, and head and neck surgery. ❖



Stanley Shapshay

Devices continued from page 1

cancerous tissue the way a contour map highlights elevations in reds, yellows and greens.

The optical fiber probe instrument employs a method called trimodal spectroscopy, in which three diagnostic techniques—light-scattering spectroscopy (LSS), diffuse reflectance spectroscopy (DRS) and intrinsic fluorescence spectroscopy (IFS)—are combined.

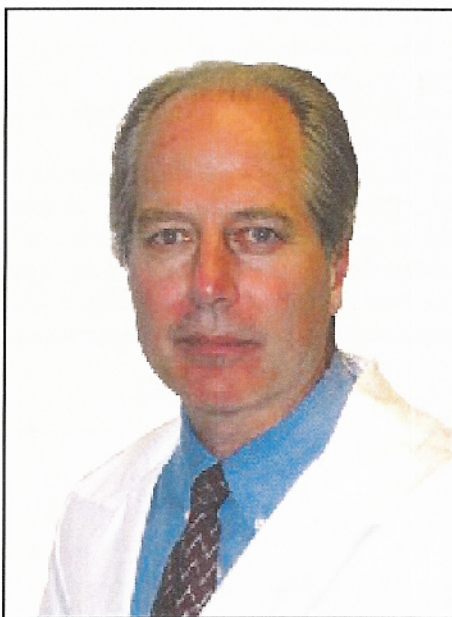
IFS provides chemical information about the tissue, LSS provides information about the cell nuclei near the tissue surface and DRS provides structural information about the underlying tissue. The information provided by the three techniques is complementary and leads to a combined diagnosis, though the imaging technique is based on LSS alone.

These techniques have been developed over the past few years at the MIT Laser Biomedical Research Center of the Spectroscopy Lab, both directed by Feld. The center, an NIH resource for laser-related medical research, is at the forefront for research using light and spectroscopy for analyzing biological tissue.

The LSS optical technique has long been used to study the size and shape of small spheres such as water droplets. For cancer detection, the method is applied to the cell's spheroid nucleus. Physics theory predicts that scattered light undergoes small but significant color variations when bouncing back from spheres of a certain size and refractive index.

Light is delivered through the probe onto the patient's tissue. The probe collects the light that bounces back and analyzes its colors. The color content is

Devices continued on page 13



Dr. Chris Crum

*Dr. Chris Crum
Brigham and Women's Hospital*

Dr. Crum is Professor of Pathology at Harvard Medical School and Director of Women's and Perinatal Pathology at Brigham and Women's Hospital. Dr. Crum has been working in the field of papillomaviruses and lower genital tract neoplasia for over 20 years and was among the first to draw a relationship between cancer causing papillomaviruses and advanced preinvasive cervical neoplasia. This work validated the proposed relationship between preinvasive and invasive cervical neoplasia and laid the groundwork for a two stage histologic classification for early cervical neoplasia that is currently used throughout the world. He currently directs the Division of Women's and Perinatal Pathology at

Brigham and Women's Hospital, which an active diagnostic, training and research group devoted to studying the pathobiology of female genital tract neoplasia. ❖

*Kristin Ann Keefe, M.D.
Brigham and Women's Hospital*

Dr. Keefe received her medical education at the Dartmouth Medical School and graduated in 1992. Her internship and residency were at Brigham and Women's Hospital in Obstetrics and Gynecology. Dr. Keefe's fellowship in Gynecologic Oncology was at the VCI Medical Center.

As the BRP PI on the cervical neoplasia project, Dr. Keefe will be primarily responsible for the research entitled "Early detection and monitoring of cervical neoplasia by in vivo spectroscopic techniques." As such, the Brigham and Women's Hospital involvement includes the recruitment and enrollment of at least 100 patients per year with various cytological abnormalities, including ASCUS, LSIL, HSIL and squamous cell carcinoma. In addition, Dr. Keefe will provide clinical guidance during the development of new imaging and diagnostic instruments and protocols, and participate in analysis and interpretation of the data gathered.

The overall goal of this research is to develop spectroscopic detection and imaging methodologies for diagnosing pre-invasive neoplasia and monitoring its progression.. ❖



Kristin Keefe

Research Report

Proton Coupled Electron Transfer: The Engine of Bioenergy Conversion.

Daniel Nocera, MIT

Introduction

The coupling of proton motion to electron transfer is the basis for bioenergetic conversion. Mitchell first recognized the importance of electron/proton coupling in biology with his proposal of proton translocation driven by electron transfer [1]. Since this seminal work, PCET has been recognized as a critical component in small-molecule activation, redox-driven proton pumps as well as radical initiation and transport processes in biology. Notwithstanding, a mechanistic description of how an electron is coupled to a proton did not exist prior to experiments that I describe below. Perhaps even more astounding, the timing of an electron and a proton in even the simplest chemical or biological reaction has never been measured! By examining PCET networks in biomimetic and natural systems, our group seeks to understand how PCET regulates: (i) bioenergy storage and (ii) the structure/function relationship in enzymes and proteins.

The coupling between the electron and the proton may be grouped into two general categories, which I designate as indirect and direct coupling. In the indirect coupling mechanism, electron and proton transport are driven by a thermodynamic gradient that is established by the flow of electrons prior to proton motion or vice versa. Here, the transport of an electron is not tied to a specific proton. A different situation arises for a direct coupling mechanism. The electron and the proton are linked to each other during transport. For this case, electron and proton movements do not need to be synchronous. As will be described below, the proton can affect the electron transport even when the electron and proton do not move together. Furthermore, the same electron and proton do not have to be coupled throughout an entire transformation. As the electron moves, it may encounter different protons along a transport chain. All that is required for direct coupling is that the kinetics (and

thermodynamics) of electron transport depends on the position of a specific proton or set of protons at any given time. It is direct coupling of the electron and proton that is the most elementary characteristic of a PCET event.

The need to account for the effect of proton motion on electron transfer in the PCET problem requires new experiments and theoretical efforts. PCET has emerged only recently as a field of study, first launched at a mechanistic level by my group using the approach shown in Figure 1 [2,3]. In this scheme, PCET is photoinitiated between a donor and an acceptor juxtaposed by a hydrogen-bonding interface, $D-[H^+]-A$. The initial $D-[H^+]-A$ construct exploited the propensity of carboxylic acids to form cyclic dimers ($[H^+] = [(COOH)_2]$) in low-polarity, non-hydrogen bonding solvents [4]. Measurement of the isotope effect for charge separation and recombination revealed the coupling between electron and proton. Within the $-(COOH)_2-$ interface, proton displacement on one side of the dicarboxylic acid interface is compensated by the concomitant displacement of a proton from the other side. Because charge redistribution within this interface is negligible, the only available mechanism for PCET arises from

the dependence of the electronic coupling on the position of the protons within the interface [5-6, 7]. Similar results have been obtained for donors and acceptors separated by guanine-cytosine base pairs [8-9, 10] and related interfaces [11] where net proton motion within the interface is minimal. Yet such cases are unusual in Nature, where proton displacement almost always accompanies the oxidation-reduction (i.e., redox) process. Mechanistic studies were therefore extended to include salt-bridge interfaces formed from the association of amidinium and carboxylate moieties [12-13, 14, 15, 16]. The movement of a proton from the amidinium toward the carboxylate may accompany electron transfer from D to A. The effect of this proton motion on ET has been demonstrated by a comparative kinetics study of a $D-[amidinium-carboxylate]-A$ complex and its inverted interfacial $D-[carboxylate-amidinium]-A$ counterpart [12, 16]. Differences between the charge transfer rate of the former is 10^2 slower than that of the latter.

A subsequent theoretical description of PCET [3, 17] has developed around these data to explain the pronounced rate differences. Most treatments are based on the four-state model shown in Figure 2: D is the electron donor, B is the proton donor,

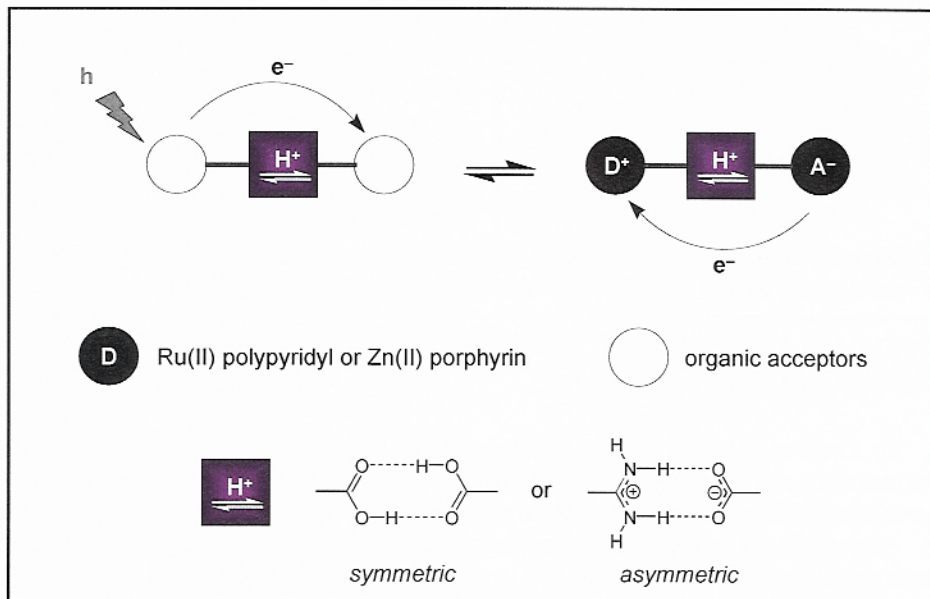


Figure 1. PCET pathways. The orange line describes the transfer of the electron followed by the proton (ET/PT). The green line describes PT followed by ET (PT/ET). All other possible PCET pathways are confined within the space of the green and orange paths. One especially important pathway is along the diagonal. Here the electron and proton transfer are concerted – this corresponds to hydrogen atom transfer (HAT).

Lester Wolfe Workshop in Laser Biomedicine

Optical Imaging and Cancer Progression

Tuesday, November 18, 2003 3:30-5:00 PM

**Massachusetts Institute of Technology, Room 34-401
77 Massachusetts Avenue, Cambridge**

Advances in cancer imaging are driven both by new developments in imaging technology and the design of new molecular contrast agents. Together they are enabling the bench to bedside translation of optical imaging of cancer progression and response to therapy.

State of the Art in Optical Imaging Technology

David Benaron, Spectros Corp., Portola Valley, CA

Optical Imaging Apoptosis

Lee Josephson, Massachusetts General Hospital, Boston, MA

Optical Imaging in the Operating Room

John V. Frangioni, Beth Israel Deaconess Hospital, Boston, MA

Refreshments served at 3:30 PM

Sponsored by the G. R. Harrison Spectroscopy Laboratory, MIT, MGH Wellman Laboratories, the Harvard-MIT Division of Health Sciences and Technology, and the Center For the Integration of Medicine and Innovative Technology (CIMIT)

PLEASE POST

Seminar on
**Modern Optics and
Spectroscopy**
Fall Semester 2003

- September 30** Michael McCarthy, Harvard-Smithsonian Center for Astrophysics
Exotic Carbon And Silicon Molecules in the Laboratory and in Space
- October 7** Sarah Bolton, Williams College
Ultrafast Measurements of Semiconductor Nanostructures
- October 14** Christopher Fecko, MIT
Hydrogen Bond Dynamics in the Ultrafast Infrared Spectroscopy of Water
- October 21** Warren Zipfel, Cornell University
In vivo Nonlinear Microscopy and the Promise of Multiphoton Endoscopy
- October 28** John Fourkas, Boston College
Seeing and Shaping the Microscopic World with Multiphoton Absorption
- November 4** David Pritchard, MIT
Precision Cyclotron Spectroscopy of Charged Molecules
- November 18** Xiaowei Zhuang, Harvard University
Visualizing Infection by Single Influenza Viruses and Folding of Single RNA Enzymes
- December 2** William Eaton, NIH
Protein Folding Dynamics
- December 9** Paul Champion, Northeastern University
Exploring Low Frequency Modes and Rebinding Dynamics in Heme Proteins Using Femtosecond Coherence Spectroscopy

TUESDAYS, 12:00 - 1:00 p.m., Grier Room (34-401)

Refreshments served following the seminar.

Sponsored by the George R. Harrison Spectroscopy Laboratory,
MIT School of Science, and the Rowland Institute for Science

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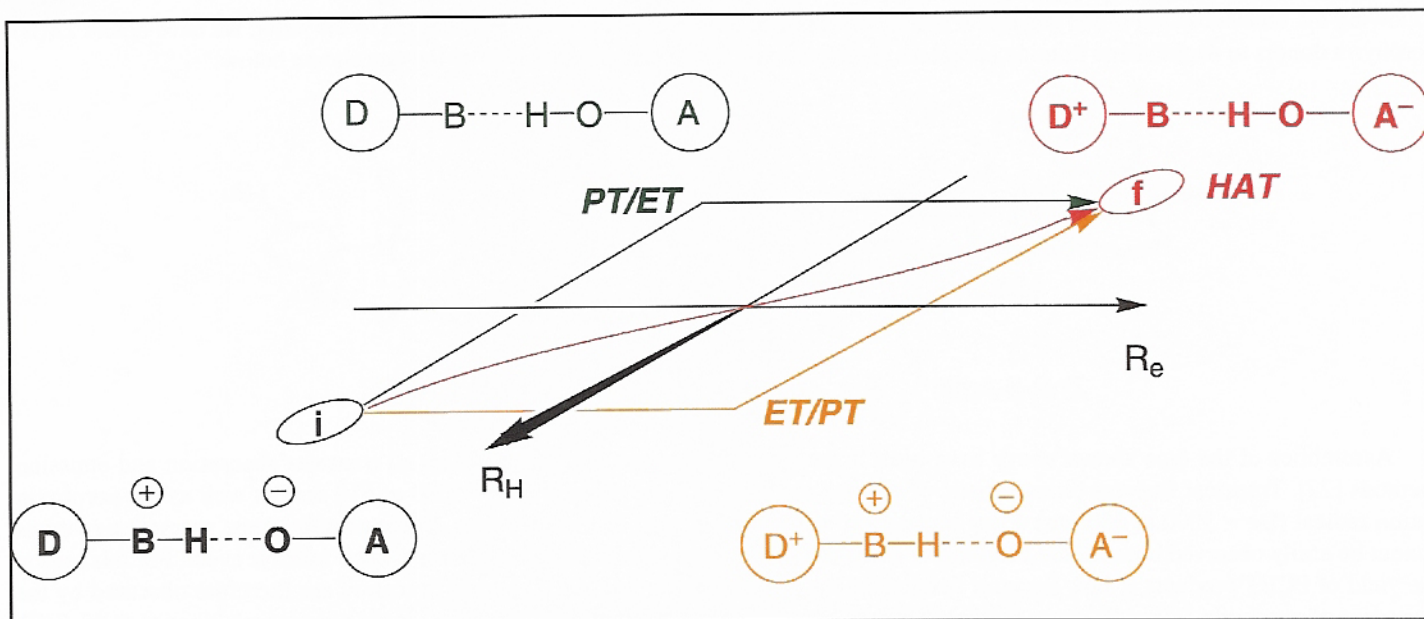


Figure 2. Schematic representation of hydrogen-bonded donor-acceptor assemblies used for mechanistic investigations of PCET.

O is the proton acceptor and A is the electron acceptor. Figure 2 illustrates the continuum of possible PCET reaction pathways. The initial state is {i} and the final PCET state is {f}. The two zigzag ET/PT pathways describe (i) a change of the proton coordinate to an appropriate configuration after which ET occurs (green path) or (ii) the transfer of an electron followed by the transfer of a proton (orange path). The pink diagonal pathway describes a concerted PCET reaction, which chemically corresponds to a hydrogen atom transfer [18]. Historically, the definition of hydrogen atom transfer is often reserved for the situation where the proton and electron are transferred between the same donor and acceptor pair. However, we note that the diagonal pathway in Figure 2 is completely general and does not distinguish between the sites of electron and proton transfer.

Accordingly, a concerted electron and proton transfer is designated hydrogen atom transfer even if the electron donor and acceptor differ from the proton donor and acceptor. The challenging feature to developing a PCET theory is the disparate timescales for electron and proton motion; a proton is a much less quantum mechanical object than an electron due to its mass. To date, the time scale (or mass) separation between the electron and the proton has been treated by a Born-Oppenheimer separation of the proton from the electron. Under these conditions, the PCET rate constant is given by [3, 17, 19, 20],

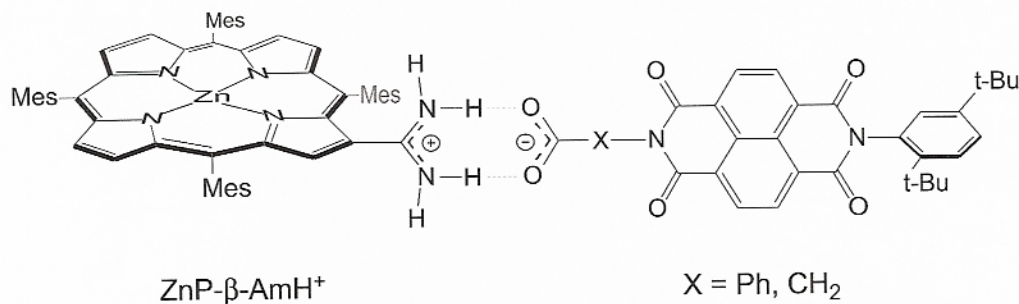
$$k_{PCET} = H_{AD}^2 \sqrt{\frac{4\pi^3}{h^2 \lambda_{PCET} k_B T}} \sum_{n'} \rho_{in'} \sum_n \left| \langle \chi_{fn} | \chi_{in'} \rangle \right|^2 \exp \left[\frac{-\left(\lambda_{PCET} + \Delta G_{PCET}^o + \Delta \epsilon_{n,n'} \right)^2}{4 \lambda_{PCET} k_B T} \right]$$

where $r_{in'}$ is a normalized Boltzmann factor accounting for the equilibrium distribution of the proton in the reactant well, with the electron in its initial state, i. In the above equation, the electronic coupling of the Marcus ET problem is weighted by Franck-Condon factors connecting the proton in its initial and final state, $\langle \chi_{fn} | \chi_{in'} \rangle^2$. The proton also contributes to both parts of the FC term. The $\Delta \epsilon_{n,n'}$ term accounts for the difference in vibrational energy levels for product and reactant states. The formalism assumes that each pair of reactant and product states has the same reorganization energy and that the coupling can be expressed as the product of a constant electronic coupling and a proton vibrational overlap. A formal derivation of a more general PCET rate expression has been presented [17]. From these treatments of PCET, we find that the driving force and reorganization energy depend on the charge distribution of the electron and the proton because the initial and final charge values are dependent on whether the process corresponds to ET, PT or PCET. Therefore, the two parameters that determine the rate of a charge transfer reaction, the activation energy and the electronic coupling, depend on the reaction pathway. The coupling of the charge shift resulting from electron *and* proton motion to the polarization of the surrounding environment thus embodies the essential distinguishing characteristic of a PCET reaction.

The desire to kinetically observe both the electron and proton transfer events has led us to develop new D—[H⁺]—A systems whose PCET products are amenable to detection by transient spectroscopic methods. Our attention turned to synthesizing Zn(II) porphyrin donors with an amidinium functionality directly fused to the *b* and *meso* positions of the porphyrin ring [13, 21]. In these systems, the porphyrin's B- and Q-bands can provide a spectroscopic handle for proton motion since these bands are sensitive to the protonation state of the amidine functionality when conjugated to the porphyrin macrocycle. The kinetics for ET may be monitored by

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following the time evolution of the porphyrin radical cation or of the reduced acceptor. With regard to the latter, we have bound Zn(II) porphyrin donors to naphthalene diimide acceptors functionalized with a carboxylate such as the one shown below:



Assemblies of the type shown above have been investigated by nanosecond and picosecond transient absorption and emission methods [22]. Transient features characteristic of the one-electron reduced diimide ($\lambda_{\text{max}} \sim 5000$ at 610 nm) as well as the porphyrin cation radical ($\lambda_{\text{max}} \sim 5000$ at 660 nm) occur in the long wavelength region of the spectrum. Unfortunately, these spectral signatures cannot be easily observed because the coupling of electron to the proton significantly retards the charge transfer event. For this reason the yield of PCET products is low. Spectral features of the reduced anion and Zn(II) porphyrin cation are therefore obscured by the dynamics of porphyrin S_1 and T_1 excited states. We have overcome this problem by performing single-wavelength kinetics at the S_1/T_1 isosbestic point ($\lambda_{\text{probe}} = 650$ nm). At this wavelength the dynamics of the porphyrin excited states are effectively nulled; absorption features due to PCET products may therefore be detected against a “flat” background. These data are shown in Figure 3. The solid circles show the kinetics for the porphyrin donor in the absence of carboxylate acceptor. Because the probe is at an isosbestic point, the DOD does not change in time, and a step function is obtained. Kinetics analysis of the trace yield forward and back PCET rates of $k_{\text{PCET}} = 9.3 \times 10^8 \text{ s}^{-1}$ and $1.4 \times 10^9 \text{ s}^{-1}$, respectively. The forward PCET rate is nearly two orders of magnitude slower than measured for covalently linked Zn(II) porphyrin-acceptor dyads of comparable driving forces [23, 24]. These results speak directly to the pronounced effect a proximal proton transfer network can have on an ET rate.

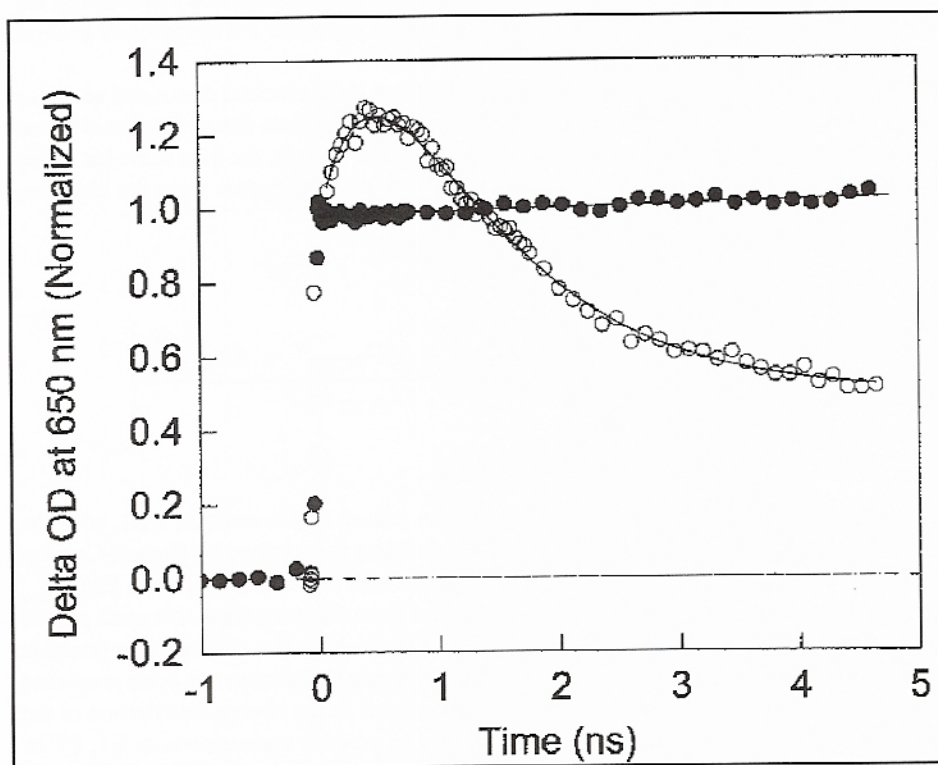


Figure 3. Transient kinetics of the assembly shown in the text for $X = \text{CH}_2$. The kinetics trace is for the porphyrin in absence (solid dots) and in the presence of the diimide carboxylate acceptor (open dots) probed at the S_1/T_1 isosbestic point of the porphyrin. Both spectra were collected using a 405-nm, 120-fs laser excitation pulse. See text for explanation of the different profiles.

The results of Figure 3 are noteworthy because they are the first to provide kinetics from directly detected intermediates of a PCET reaction in a salt-bridge assembly. However, the timing of the proton transfer has not been achieved because the porphyrin shows only modest spectral shifts with the protonation state of the amidine functionality. Instead, we are only afforded optical signatures pertinent to the electron transfer component of the reaction. Steric clashing between the exo protons of the amidinium interface with the protons on the macrocycle cause the amidinium to rotate out of the macrocyclic plane; geometry optimizations show that the amidinium is canted by 34° . This canting electronically decouples the amidinium functionality from the porphyrin chromophore. Current efforts are underway to synthesize new amidinium porphyrins in which the steric clashing between salt-bridge interface and porphyrin macrocycle is relieved while maintaining conjugation between the two moieties.

In closing, the importance of a proton network in controlling ET rates is becoming more apparent as the structural details of biological systems are revealed [25-26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37]. Our work establish that this emerging principle in biological charge transport can be modeled and studied directly in D—[H+]—A systems featuring proton transfer networks. We have recently extended PCET mechanistic investigations directly to biological systems. In collaboration with Professor JoAnne Stubbe of the Departments of Chemistry and Biology, we have begun studies of PCET and its role in the amino acid radical initiation and transport processes of ribonucleotide reductase the R2 C-terminus [39]. A schematic of the experiment is shown in Figure 5. Mutation of conserved tyrosines on the pathway to phenylalanine effectively deactivates radical initiation. The ability of a small peptide to replace the entire R2 subunit reproduces the radical initiation process of monomeric class II RNRs, in which the small molecule adenosylcobalamin initiates thiyl radical formation directly on the R1 equivalent. Thus, by controlling the PCET pathway, we have succeeded in converting class I RNR to its evolutionary class II predecessor. Taken together, our results underscore the importance of PCET in biological radical transport and begin to disentangle the complicated process of radical initiation of an essential enzyme involved in DNA replication and repair.

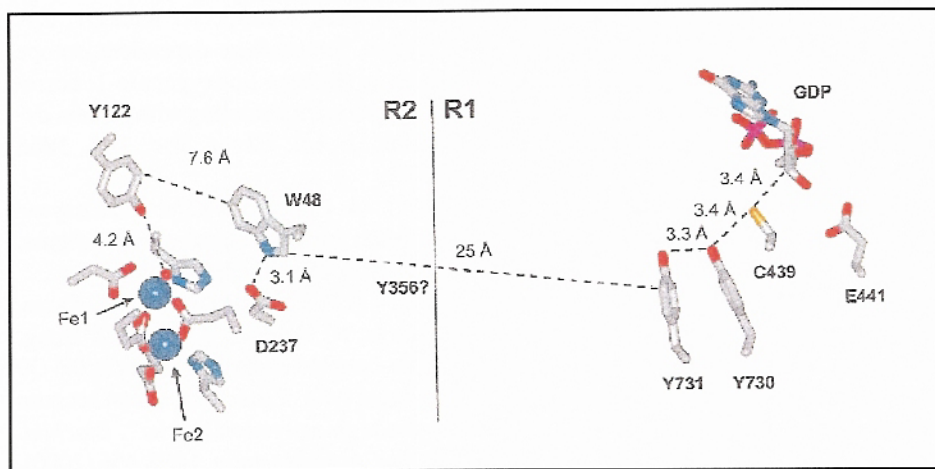
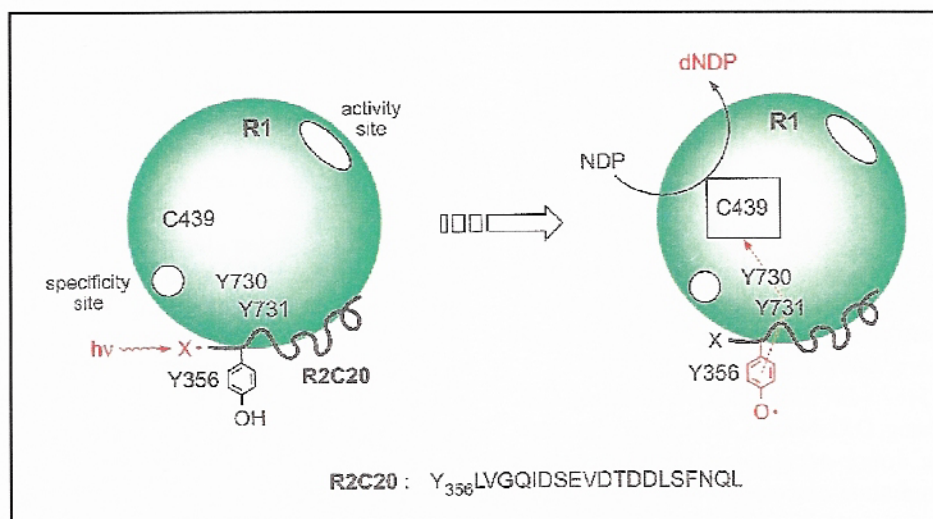


Figure 4. The PCET pathway and distances generated from the docking model of the R1 and R2 subunits of the class I RNR from *E. coli*. The last 35 to 40 amino acids of the C-terminal tail of R2, in which Y356 resides, are thermally labile and undetectable in available crystal structures. Thus, the distance between W48 on R2 and Y731 in R1 is based only on the docking model of a 1:1 complex of R1 and R2.

Figure 5. Strategy for the photochemical triggering of the Y731@Y730@C439 PCET pathway of Figure 4 for *E. coli* R1. NDP = nucleoside diphosphate substrate, dNDP = deoxynucleoside diphosphate product, X = Tryptophan. This strategy exploits the weak interaction between R1 and R2 (0.2 mM) and the ability of peptides to the C-terminus of R2 to completely inhibit nucleotide reduction in a competitive fashion.



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then used to extract diagnostic information.

"By analyzing the intensity variations in this back-scattered component from color to color, the nuclear size and density can be mapped," Feld said. Closely packed cells with larger-than-normal nuclei packed tightly with genetic material are markers of precancerous change.

"The images created with this new technique are different from ordinary microscopic images in that they provide hard and fast information about cellular features," he said. "We believe this is an important step that will lead to new optical tools for both [making] early cancer diagnoses and developing a better understanding of how changes in the genetic material inside the cell's nucleus make the tissue more vulnerable to cancer."

The NIH award, which is sponsored by the National Cancer Institute, builds on diagnostic technologies that have been developed at the spectroscopy laboratory over the past decade. Feld will head the project and Kamran Badizadegan, a pathologist and cell biologist at Massachusetts General Hospital (MGH), will be co-principal investigator.

MIT will pursue the research in collaboration with five institutions: Boston's Brigham and Women's Hospital, for clinical studies of cervical dysplasia; Boston Medical Center, for clinical studies of oral dysplasia; MGH, for diagnostic pathology and development of disease-specific spectroscopic markers; Harvard Medical School, for development of disease-specific spectroscopic markers; and Chicago's Northwestern University, for development of novel spectroscopic methodologies based on light-scattering spectroscopy. ❖

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