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Cover Story

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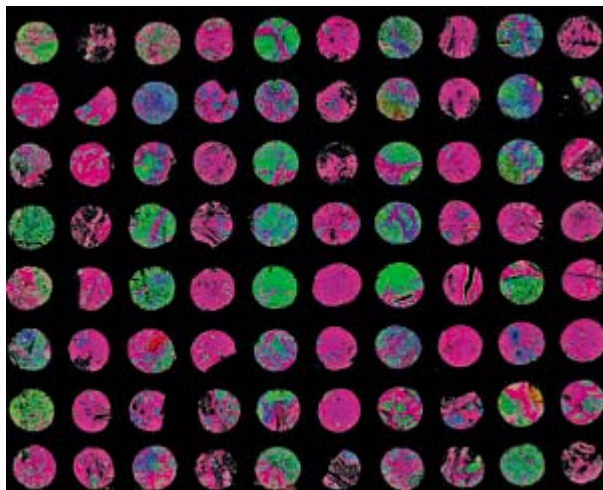
Moving From Bench To Bedside

Symposium emphasizes need to translate spectroscopic methods from the lab to the clinic

[Celia Henry Arnaud](#)

TO HAVE AN IMPACT on health care, analytical methods must move from the laboratory bench to the clinic. "Translational research"—a popular catchphrase in the medical community—focuses on this process of turning basic science and technology into practical applications for disease diagnosis and treatment. A symposium at Pittcon, held earlier this month in New Orleans, focused on the importance of translational research by using various kinds of vibrational spectroscopy as examples.

Translational research is a major focus at the National Institutes of Health and a key component of the NIH Roadmap for Medical Research, noted symposium organizer [Ira W. Levin](#), acting scientific director of intramural research at the National Institute of Diabetes & Digestive & Kidney Diseases at NIH.



Courtesy of Rohit Bhargava

Cancer Infrared chemical imaging can differentiate cancer and normal tissue in these microarrays of patients' breast tissue. Cancer tissue contains more epithelium (green) and lymphocytes (blue) than normal tissue does.

A primary use of spectroscopy in clinical settings is for the measurement of biomarkers, said [Stephen M. Hewitt](#), physician-scientist at the National Cancer Institute at NIH. He defined biomarkers as measurable parameters that relate to a specific patient outcome.

Hewitt divides biomarkers into three categories—diagnostic, prognostic, and predictive. Diagnostic biomarkers indicate the presence of disease. Prognostic biomarkers forecast outcomes on the basis of populations of patients. Predictive biomarkers reveal a particular patient's likely response to therapy. Some biomarkers, such as prostate-specific antigen, fall into multiple categories. The greatest need, Hewitt said, is for predictive biomarkers which can help physicians make decisions about treatment.

Pathology is a natural fit for biomarker detection by spectroscopy. When measurements of spectra are made simultaneously with collection of spatial information—a technique called spectroscopic, or chemical, imaging—the result is an image or "map" of the sample. Spectroscopic imaging can be engineered to generate pictures similar to those achieved by histological staining. [Rohit Bhargava](#), assistant professor of bioengineering at the University of Illinois, Urbana-Champaign, is developing practical protocols for spectroscopy-based pathology.

Bhargava acknowledged that pathologists are hard to beat with biomarker technology. "No marker has beaten pathologists" in identifying tumors in complex tissue, he said, but pathologists need more and better information, such as that offered by spectroscopy.

A first step in applying spectroscopy to pathology is devising a spectroscopic tissue classification scheme similar to what pathologists traditionally use, Bhargava said. Using computer algorithms that analyze spectroscopic images of tissue, he has developed classification schemes for infrared chemical imaging of prostate and breast cancers.

With these classification schemes, Bhargava identified epithelial cells in lymph nodes. Because epithelial cells are not usually found in lymph nodes, their presence is a biomarker for the spread of breast cancer. He was able to identify the epithelial cells even when only a few cells were present. Similarly, for prostate cancer, spectroscopic imaging misidentified only two samples out of 140, an error rate similar to that of pathologists.

Spectroscopy is finding use in other health-related areas as well. Three speakers described the use of spectroscopy to study skin.

In addition to his pathology work, Bhargava is using infrared spectroscopy to study an engineered model of melanoma skin cancer. He used the technique to show that the cancer cells induce transformations in seemingly healthy cells.

Another speaker, [Richard Mendelsohn](#), a professor of chemistry at Rutgers University, Newark, N.J., uses Raman and infrared microscopy to study drug permeation through skin and wound healing. He finds confocal Raman microscopy particularly useful for studying skin because it doesn't require the destruction of the sample.

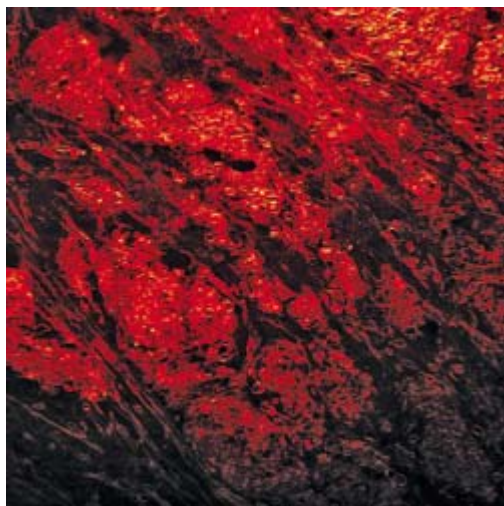
IN ONE EXAMPLE, Mendelsohn studied the delivery of a prodrug form of 5-fluorouracil, which can be used topically to treat basal cell carcinoma and psoriasis. Unlike 5-fluorouracil, the prodrug can easily cross the skin's outer barrier and permeate deeper into the skin, where it is metabolized to 5-fluorouracil. Mendelsohn used chemical imaging to observe the prodrug's delivery and metabolism.

Mendelsohn and his associates Guojin Zhang, Andrew H. Chan, and Carol R. Flach also use Raman imaging to study the early stages of wound healing. His collaborator, [Marjana Tomic-Canic](#) of the Hospital for Special Surgery in New York City, has developed a protocol that keeps tissue samples alive in a laboratory environment for seven days. During that time, the Mendelsohn and Tomic-Canic labs use Raman to watch temporal changes during healing of skin tissue obtained from patients. With this method, the researchers can detect the migration of different cell types to the wound and differentiate the many variants of keratin and collagen (the main protein structural components of skin) formed while the wound heals.

[Brian Saar](#), a graduate student in the lab of [X. Sunney Xie](#) at Harvard University, described the use of coherent anti-Stokes Raman scattering (CARS) to image the topical delivery of retinol, an antioxidant used in skin care products. The research was done in collaboration with Unilever Research & Development. CARS is a nonlinear optical technique in which two laser beams at different frequencies interact with a sample to produce a signal, which is enhanced when the frequency difference between the two beams equals a vibrational frequency of the sample.

The Xie group has also used CARS microscopy for brain imaging. The spatial resolution is such that it is possible to visualize the margins of brain tumors. Current research involves improving the understanding of the molecular signatures that provide contrast between healthy and cancerous tissue.

The ultimate goal for brain imaging with CARS is an endoscopic probe that can guide surgeons as they remove tumor tissue. The development of such a probe is hindered by the difficulty of delivering pulsed laser beams through an optical fiber, Saar said.



Courtesy of Brian Saar/Harvard University

Brains A CARS image of the lipid distribution in healthy brain tissue, highlighting the myelin sheaths on neurons.

Indeed, CARS remains much closer to the bench than the bedside, Saar admitted. "The challenge is developing an easier-to-use instrument that doesn't need an ultra-fast-laser specialist to operate it," he said.

Another area where spectroscopy could make an impact in health care is in the diagnosis of eye diseases. [Christopher M. Snively](#), a research assistant professor of materials science and engineering at the University of Delaware, described how he and his collaborators—[John F. Rabolt](#) of Delaware and D. Bruce Chase of [DuPont](#)—are developing focal plane array infrared spectroscopy for the diagnosis of cataracts, which form when proteins such as γ D-crystallin crystallize in the eye's lens.

Although their current emphasis is on cataracts, Snively maintains that the method will be more general. "We're basically just analyzing concentrations of different proteins within the eye," he said. "The appearance of certain proteins at certain points in a person's life can be indicative of a variety of eye diseases."

To be used for early diagnosis, the method must be able to detect proteins at lower concentrations than it currently can. The protein concentrations that Snively's group is currently looking at are equivalent to those in almost fully developed cataracts. "Ideally, you would want to detect cataracts five, 10, 20 years before they got to that point," he said. Diagnosing other eye diseases with this technique would require even lower detection limits.

The Delaware team collaborates with surgeons at Veterans General Hospital in Taipei, Taiwan. "We're in close communication with them to know what kinds of proteins to look for, what concentrations to look for, what's important, and what's not important," Snively said. "If we didn't have that, we would just be a bunch of spectroscopists looking at protein solutions. It might or might not have any relevance depending on if we happen to pick the right protein."

MUCH OF their development work has focused on shrinking the instrument to a size that is feasible to use in a doctor's or optometrist's office. In addition, they must develop methods that deal with background water vapor because the main protein bands in the spectrum overlap with the bands for water.

Many of these applications are still at the early stage of moving toward clinical settings, but Hewitt and others predict that these methods will gain widespread acceptance within the next five to 10 years. A critical area where

progress is needed is in developing automated systems that do not require close manual supervision and in which results can be interpreted by people not trained as spectroscopists. In fact, he noted, instruments and integrated data analysis methods already exist that are close to the needed turnkey operation. Hewitt adds, "These technologies are really getting there."

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