In 1977, Beckman Laser Institute (BLI) Co-founder Michael W. Berns had lab space in Steinhaus Hall and an electron microscope with no one to help him operate it. His electron microscopist had just married and relocated to Santa Barbara. This is not a position that can be easily replaced. The applicant must be well versed in a variety of techniques that include sectioning, embedding and staining which are used in histology, a branch of anatomy that deals with the minute structure of animal and plant tissues that can be seen with the microscope. An electron microscope is an electron-optical instrument in which a beam of electrons focused by means of an electron lens is used to produce an enlarged image of a minute object on a fluorescent screen or photographic plate. In addition to knowing the techniques and how to run the electron microscope, there is one more asset that distinguishes a good electron microscopist from a great one: a steady, precise hand.

Fortunately for Dr. Berns, Lih-Huei “Leacky” Liaw applied for the job. A native of Taiwan who earned a B.S. degree in Physics from the National Taiwan Normal University before coming to the U.S. in 1968 with her husband, Jiin, Leacky earned an M.S. degree in Physics at Northeastern University in Boston, MA. While Jiin worked on his Ph.D. degree, Leacky worked as a research staff member at the Medical School at Yale University. There, she had the opportunity to learn primary tissue culture and electron microscopy techniques. When Jiin finished school, they moved to Anaheim where Jiin got a job working for Rockwell, and Leacky applied for the electron microscopy job at UCI. With her experience at Yale, Dr. Berns assumed she would be a “gem” and immediately hired her. As Dr. Berns notes, “Leacky turned out to be more than a gem. She was (and still is) a whole treasure trove of gems!!”

Leacky was hired on July 1, 1977. In 1981, she and Dr. Berns published a manuscript entitled “Electron microscope autoradiography on serial sections of pre-selected single living cells” in the Journal of Ultrastructure Research. In this article, a method was described that permits electron microscope autoradiography of single cells that have been documented in the living stage. The pre-selected single cell was carefully marked and followed undergoing mitosis through embedding, serial thin sectioning, and staining. Serial sections were

(Farewell Leacky continued on p. 3)
"Leacky"

by Michael W. Berns, Ph.D.
Arnold and Mabel Beckman Professor
Co-Founder, Beckman Laser Institute

The dedication to Lih-Huei Liaw (Leacky) on the first page of this newsletter is more than fitting. But there is another aspect to Leacky that I personally would like to iterate, and that is her loyalty.

When I first hired Leacky back in 1977, I knew she had great potential. Sometimes when you interview someone, you just get a “gut” feeling that this is the right person for the job. Her technical skills, ability to teach others, and ability to help figure out problems and interpret data were traits that emerged the longer she worked for me. She became a mentor to my students and postdocs – and a colleague to me.

When I had the idea to build the Beckman Laser Institute, Leacky was there both in a supportive and creative role. I asked her to design the optimal electron microscope facility, and she came up with a plan that after 25 years is still an epitome of design and totally able to meet the needs of our scientists. The only regret I think she has is that digital technology made the large dark room obsolete, and it was no longer in vogue to develop negatives and experience the fun of putting a blank piece of paper into a developing solution and watching an image magically appear out of nothing.

Leacky’s loyalty has been unique. She has been by my side in the research lab (contributing as much in the creative realm as in the technical), and she has always been there when I have needed her for research, teaching my students and postdocs, and just being supportive of me (especially when difficult administrative and political issues were taking me away from the daily interactions with her and science). No matter how long I was absent from her lab or office, I knew I could always count on her for support at all levels.

So it was with sadness and joy that I learned from Leacky that she was retiring. I was sad because I knew we would be losing one of the most dedicated and committed original members of the BLI family. But there was joy because I knew she would be coming back out of retirement to work two a days a week for my lab, and thus, she could also continue to be a “resident” vessel of knowledge for the rest of the BLI. So I say “goodbye” with sadness and appreciation but “welcome back” with joy and anticipation.

Newsbriefs

PHOTONICS WEST PRESENTATIONS

SECOND ANNUAL ALLAN R. OSEROFF PHOTOMEDICINE LECTURE
The second annual Allan R. Oseroff Photomedicine Lecture was held on February 25, 2010, at the Beckman Laser Institute Library. Stephen M. Hahn, M.D., Chair and Henry K. Pancoast Professor of Radiation Oncology at the University of Pennsylvania School of Medicine, spoke on “The future of clinical photodynamic therapy—bringing science to patient care.”
learned from previous experience and relishing the challenge, developed laboratory techniques and designed protocols for individual research projects. In the routine histology procedure, she replaced the traditional toxic Xylene with an environmentally friendly chemical mixture, HistoClear, after testing on various animal tissues. Optical Coherence Tomography (OCT), two-photon microscopy and other emerging optical technologies are designed to image tissue without the need for exogenous contrast agents in living tissues. Leacky developed a tissue processing, fixation, and serial sectioning protocol to enable optimal matching and registration. For Scanning Electron Microscopy, a protocol using Hexamethyldisilazane (HMDS) replaced the traditional critical point dry method. In the early '90s, she developed the Shell-on Chorioallantoic Membrane (CAM) tumor model for the photodynamic therapy (PDT) research project. She is proud of these optimized protocols and newly developed techniques that have contributed to the research, grants, publications and education of students at the BLI. During her tenure here at the BLI, Leacky has been a co-author on 56 journal publications. Throughout Leacky’s 32 years at the BLI, she has always felt that BLI was her home and that everyone who worked here was part of her extended family. She embraced many newcomers with hospitality and advice, if needed. For many years, a Chinese New Year potluck banquet was celebrated under the direction of Leacky. Whenever you worked with Leacky, you never had to worry because you knew she would be patient, attentive to detail, always quick to smile, and more than capable of doing the job.

In September 2009, Leacky reluctantly decided to retire, effective March 31, 2010, and sent a touching e-mail to everyone at the BLI. In it, she expressed her mixed feelings of “joy, fear and sadness.” As conscientious as ever, she also assured everyone that the Histology Facility was going to continue to function as usual with well-trained personnel. In addition, she was compiling a histology facility handbook that would include “trouble-free step-by-step instructions” as well as illustrations, some of them hand-drawn. And then she thanked everyone “for allowing me to develop, without any restriction, my skills in helping with research projects, and giving me the opportunity to perform my responsibility as the head of the histopathology and electron microscope facility. And finally, and most importantly to me, thank you for letting me be a part of the BLI research team.”
A New Way to View Tissues

Scientists have devised many ways to image an object with a laser as the light source coupled with a method to interpret the image. In a clinical setting, the aim is to image various body tissues to aid in diagnosis. This means determining a way to deliver the laser light to the tissue and devising an accurate way to interpret the signals received from the tissue. Professors Zhongping Chen, Bruce Tromberg and Eric Potma, along with postdoctoral researchers Mihaela Balu and Gangjun Liu, have developed a new type of endoscope based on Coherence Anti-Stokes Raman Scattering (CARS).

Coherent anti-Stokes Raman scattering (CARS) imaging is a form of spectroscopy used primarily in chemistry, physics, and related fields. It is sensitive to the vibrational signatures of molecules as seen in Raman spectroscopy (typically, the vibrations of chemical bonds). However, in contrast to Raman spectroscopy, CARS employs multiple photons to address the molecular vibrations and produces a signal in which the emitted waves are coherent with one another. A tremendous advantage of CARS imaging is that it is label-free: the molecule of interest does not need to be labeled, e.g., with a stain, in order to be imaged.

An important step in optimizing this imaging technology for clinical studies is the development of a fiber-delivered probe which would enable patient-friendly CARS examination of superficial tissues. When the laser pulse (light) hits the tissue, a CARS signal is generated by the tissue and another separate CARS signal is generated from the fiber. To achieve a high contrast image of the tissue, the CARS signal from the fiber must be removed. In “Fiber delivered probe for efficient CARS imaging to tissues,” M. Balu, G. Liu, Z. Chen, B. J. Tromberg and E. O. Potma detailed how the fiber-generated anti-Stokes radiation was filtered out (Optics Express 18: 2380-2388, 2010). Different biological tissues were imaged ex vivo in order to assess the performance of the fiber-delivered probe for CARS imaging, an important advance towards label-free, in vivo probing of superficial tissues.

Building on this research, the Beckman Laser Institute team is now working on developing a suitable fiber-based probe for human studies. This could be used clinically for skin and eye imaging, neuro-surgical guidance, imaging and diagnosis of vascular diseases, and detecting cancer. This endoscope technology can also provide multimodal information based on second harmonic generation and two-photon excited fluorescence.

Further miniaturization will be required to optimize its use as a handheld probe suitable for clinical studies.

Second harmonic generation from collagen (blue) and CARS signal from adipocytes (red) in human skin.

CARS signal from the myelin sheath in mouse brain (cerebellum).

Congratulations to UROP Recipients

Each academic year, the Undergraduate Research Opportunities Program (UROP) awards fellowships to support noteworthy research. The following undergraduate students were named as UROP Fellows for 2009.

Brenton Alexander, Biomedical Engineering, who works with Drs. Albert Cerussi and Bruce Tromberg, received funding for “Measurement of colon tissue oxygen saturation during colon surgery and forced ischemia using near infrared spectroscopy.”

Shabnam Ghazizadeh, Biomedical Engineering, who works with Dr. Elliot Botvinick, received funding for “Laser softening of glutaraldehyde crosslinked bovine pericardium for an improved heart valve material.”

Deena Jamal, Biomedical Engineering, who works with Dr. Elliot Botvinick, received funding for “The role of the flycocalyx in mechanotransduction and its presence in vitro.”

Clement Kondru, Biomedical Engineering, who works in the lab of Dr. Anthony Durkin, received funding for “Modulated imaging of cutaneous melanoma.”

Amanda Lim, Biomedical Engineering, who works in the lab of Dr. Brian Wong, received funding for “Measuring the mechanical changes in rabbit septal and auricular cartilage following voltage application during electromechanical reshaping.”

Elaine Nguyen, Neurobiology, who works in the lab of Dr. Bernard Choi.

(UROP Fellows continued on p. 8)
Baggy Eyelids

If you are 30 years old, and after a good night’s sleep, you still have bags under your eyes, you might be interested in “Minimum invasive Holmium:YAG laser blepharoplasty.” Lower lid blepharoplasty is routinely performed to ameliorate the lower eyelid bulge which occurs as eyelid fat pads become more prominent with age. Much like a hernia is the result of a weakening in the abdominal wall, orbital fat is a consequence of loosening and relaxation of the skin, muscle, and, most notably, the orbital septum. While traditional blepharoplasty addresses prominent fat pads by surgical excision, it often results in a sunken or hollowed out appearance of the orbit, and this effect may not be seen until many years after the original surgery. More recent techniques have focused on shrinking and tightening rather than direct fat excision. After exposing the orbital septum via minimally invasive incisions, various patterns of electrocautery have been applied to the septum to produce a controlled tightening of this tissue.

With the advancement of technology in recent years, multiple lasers have been approved for use as general heating, coagulating, and cutting instruments in surgery. Not only have lasers been determined to be safe, multiple studies have demonstrated decreased surrounding thermal injury and decreased post-operative swelling. Professor and Director of the Division of Facial Plastic Surgery in the UCIMC Department of Otolaryngology-Head and Neck Surgery Brian Wong is exploring the use of the Holmium:YAG laser to more precisely create the desired remodeling required for orbital septal tightening in a minimally invasive fashion.

Dr. Wong is seeking volunteers for a clinical trial which will test a new method for reducing the sag that develops in some people’s lower eyelids once they reach around 30 years old. He is looking for volunteers who are “30 to 50 years-old, with good skin elasticity and not a lot of excess skin. We’re also looking for people who haven’t had eyelid treatment, and those who do not have eye disorders.” Further, candidates should have pronounced lower eyelid fat pads, be an appropriate candidate for elective, outpatient surgery, and be willing to participate in the study and adhere to a follow-up schedule as well as willing to sign the Informed Consent Form.

Participants will not be compensated for their involvement, but they also will not be charged for the surgery. Dr. Wong emphasized that he is not looking for older candidates who would benefit more from traditional eyelid surgery. If you are interested in participating in the study, you can contact Administrative Research Nurse Coordinator Montana Compton at mocomton@uci.edu.

Selected Recent Publications


Using Lasers to Improve Cancer Care

In 2003, UC Irvine Beckman Laser Institute (BLI) researchers received a $7 million grant from the National Cancer Institute (NCI) to standardize use of a laser imaging device they created for better breast cancer detection and treatment. Their effort is beginning to bear positive results.

In January, the researchers reported in the journal *Radiology* (Radiology 254: 277-284, 2010) that this laser breast scanner (LBS) can accurately distinguish between malignant and benign tumors, potentially providing an easy-to-use, non-invasive technique to see whether breast tumors need further aggressive treatment.

Their approach is based on a sophisticated new analysis method developed by UCI Biomedical Engineering Professor Enrico Gratton and M.D./Ph.D. student Shwayta Kukreti, that produces a spectral “fingerprint” or signature for each patient. Their technique was developed specifically for the hand-held laser breast scanner (LBS) developed by Beckman Laser Institute (BLI) Director and grant Principal Investigator, Professor Bruce Tromberg, and BLI Professor Albert Cerussi.

The scanner works by measuring metabolism in breast tumors and normal breast tissue. Unlike mammography, the LBS provides detailed functional information by measuring hemoglobin, fat and water content, as well as tumor oxygen consumption and tissue density. In the study, the researchers found that potentially dangerous malignant tumors have a different metabolic fingerprint compared to benign tumors.

“The LBS spectral signature method has the potential to help improve detection and diagnosis in women with dense breast tissue who don’t do well with mammography,” according to co-author and UCI surgical oncologist Dr. David Hsiang. “Unlike with other technologies, the laser breast scanner provides a metabolic fingerprint of tumors without the use of added contrast agents,” says Tromberg, who works with a multidisciplinary team of biomedical engineers and oncologists on this effort. “This can help make diagnosis more exact and treatment more focused.”

The *Radiology* study involved 60 subjects and the team’s next step is to continue the effort with a larger test group.

In a second area, the UCI laser breast scanner is being used to evaluate the effectiveness of chemotherapy treatments.

The scanner is proving beneficial for providing detailed information on changes in breast tumor metabolism during chemotherapy. This information, which can be accessed quickly at the bedside, can allow oncologists to target chemotherapy treatments more effectively and safely, tailoring them to how the patient responds.

“The use of chemotherapy for tumor reduction prior to surgery is an important approach for certain types of breast cancer,” says surgical oncologist Dr. John Butler, who works with medical oncologist Dr. Rita Mehta and the BLI team. “The metabolic fingerprint the laser breast scanner provides gives detailed clues on how the chemotherapy is working and allows doctors to adjust treatments as needed.”

Currently, the UCI researchers are also working with colleagues at the University of Pennsylvania, Dartmouth College, UC San Francisco and Massachusetts General Hospital in Boston to start a five-center clinical study, coordinated by the NCI and the American College of Radiology Imaging Networks (ACRIN), for monitoring and predicting the effectiveness of chemotherapy treatments in breast cancer patients. In addition, the Bay Area biotechnology company FirstScan has licensed the technology for commercial applications.

“This is an important opportunity to standardize our approach and determine, in a national multi-center trial, how this new technology can help improve the treatment and quality of life for breast cancer patients,” Tromberg says.

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A recent article in *Radiology* reports that the hand-held laser breast scanner (pictured above) can accurately distinguish between malignant and benign tumors.

**BLI Newsletter Staff**

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ARRIVALS

Anaïs Leproux, a French graduate student at the University of Amsterdam, The Netherlands, will be working with Dr. Bruce Tromberg on optical mammography in conjunction with the High Tech campus of Philips Research in Eindhoven, The Netherlands.

Magnus Lilledahl, a research scientist from the Norwegian Institute of Technology, Trondheim, Norway, will be working on Coherent Anti-Stokes Raman Scattering (CARS) multiphoton imaging with Drs. Bruce Tromberg, Eric Potma and Zhongping Chen.

Lisa Malenfant has been hired as an Associate Specialist and joins the software development team that is designing and coding the Virtual Tissue Simulator and the related Biophotonics Toolkits. She will be working with Drs. Jerry Spanier and Vasan Venugopalan.

Michele Martinelli, a graduate student with a B.S. in physics engineering from Politecnico di Milano, Italy, will be working with Drs. Vasan Venugopalan and David Cuccia in the field of biomedical optics.

DEPARTURES

Yeh-Chan Ahn, Ph.D., a Project Scientist working in the labs of Drs. Matthew Brenner and Zhongping Chen, has accepted a faculty position at Pukyong National University in Busan, South Korea, in the Department of Biomedical Engineering.

Jerome Chen, B.S., a student assistant who provided computer support, received a job offer in the Bay area.

Katherine Bhan, Ph.D., a postdoctoral researcher working with Drs. Jerry Spanier and Vasan Venugopalan, has an appointment at the Keck Institute of Applied Life Sciences in the Claremont Colleges consortium.

Willem Verykrusse, Ph.D., a postdoctoral researcher with Dr. J. Stuart Nelson, has accepted the position of Principal Scientist, Care and Health Applications, at Philips Research in Eindhoven, The Netherlands.

Jessie Weber, Ph.D., who worked in BLI Director Bruce Tromberg’s lab, defended her thesis, “The impact of spatial and spectral frequencies in structured light imaging of thick tissues,” on November 20, 2009, and has taken a postdoctoral research position at the G. R. Harrison Spectroscopy Laboratory at MIT. She will be working with Drs. Ramachandra Desari and Mike Feld on a number of biomedical optics projects including one involving the use of Raman spectroscopy within the context of malaria research.

Honors and Awards (cont’d from p. 1)

on brain and muscle tissue in the treatment of sub-lethal cyanide toxicity in a rabbit model.”

Petra Wilder-Smith, D.D.S., Ph.D.

Dental Director Petra Wilder-Smith has been awarded a grant from Colgate Palmolive for “Clinical research study to evaluate imaging capabilities of OCT in the oral cavity.”

Brian J. F. Wong, M.D.

Professor and Director of the Division of Facial Plastic Surgery in the UCIMC Department of Otolaryngology-Head and Neck Surgery Brian Wong was selected for the 4th straight year as a “Physician of Excellence” by the Orange County Medical Association in Otolaryngology/Head and Neck Surgery. Dr. Wong was also selected to be included in the Best Doctors in America 2009-2010 database. Doctors are selected after an exhaustive peer-review survey by thousands of doctors, and Dr. Wong earned the consensus support of his peers which is a remarkable honor.

Amanda Lim

Biomedical Engineering Premedical Undergraduate Student Amanda Lim was awarded the “2010 Best Oral Communication Prize for an Undergraduate” at the Head and Neck Optical Diagnostics Society Meeting held in San Francisco, CA. The title of her paper was “Methods for evaluating changes in cartilage stiffness following electromechanical reshaping.” Amanda is a student in Dr. Brian Wong’s lab.

Ed Wu

Ed Wu, a UCI 3rd year medical student in the M.D./M.B.A. program, was awarded a Student Research Grant from the American Society for Laser Medicine and Surgery. His project, under the supervision of Drs. Brian Wong and J. Stuart Nelson, is entitled “Laser auricular cartilage reshaping with carbon dioxide spray cooling.”
UROP Fellows (cont’d from p. 4)

received funding for “Utilizing wide-field imaging (WiFi) to monitor the hemo-dynamic and metabolic changes associated with focal cerebral ischemia.”

Andre Paredes, Biomedical Engineering, who works in the lab of Dr. Elliot Botvinick, received funding for “Measuring fibrinogen’s adhesive forces using optical tweezers.”

Natalie Popenko, Biological Sciences, who works with Dr. Brian Wong, received funds for “Determining the ideal lips: correlating adjusted lip dimensions and facial attractiveness scores.”

Timothy Quang, Biomedical Engineering, who works with Drs. Albert Cerussi and Bruce Tromberg, received funding for “Validation of calibration standards used in diffuse optical spectroscopy.”

Chasen Ranger, Mathematics, who works with Dr. Eric Potma, received funding for “Use of stage-scanning and variable beam configurations to reduce nonresonant background in coherent anti-Stokes Raman scattering microscopy.”

Arya Saidi, Biomedical Engineering, who works with Dr. Zhongping Chen, received funding for “Improving optical coherence tomography of human vocal cords and retina through the use of a swept source system as well as a unique light source, respectively.”

Scott Strayer, Biomedical Engineering, who works with Dr. Elliot Botvinick, received funding for “Design and construction of an active micro-rheometer.”

Erica Su, Biomedical Engineering, who works with Dr. Brian Wong, received funding for “Evaluation of femtosecond laser ablation of human cartilage and retina through the use of a swept source system as well as a unique light source, respectively.”

alternative to microfracture surgery.”

Victor Sun, Biomedical Engineering, who works with Dr. Wangcun Jia, received funding for “Safety and efficacy of topical rapamycin for inhibiting regeneration of photo-coagulated blood vessels.”

Travis Tucker, Biological Sciences/Spanish, who works in the lab of Dental Director Petra Wilder-Smith, received funding for two projects: “An alternative to surgical biopsy using varied lengths of microneedles and gold nanoparticles” and “Early cancer detection using microneedles as a means for dispersing gold nanoparticles.”

Diana Vu, Biological Sciences, working in the lab of Dental Director Petra Wilder-Smith, received funding to support her research project, “The investigation of a fluorescence/elastic scattering spectroscopy (F-ESS) for oral tissue characterization.”