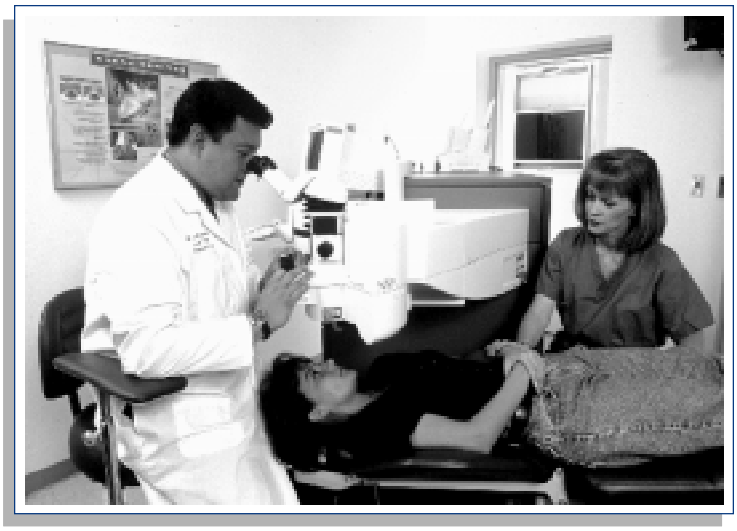
LASER
BECKMAN LASER INSTITUTE

IN THE NEWS

Fall 1999

NIH Praises Multi-Lab Grant Proposal

Researchers from three UC Irvine labs have combined their efforts on a five-year bioengineering project and are awaiting a final decision regarding funding from the National Institutes of Health (NIH). The grant proposal, submitted in response to the NIH's Bioengineering Research Projects (BRP) Program, could be worth more than $2.2 million. Funds would support the development of a new laser microscope platform, complete with micromachined (i.e., "microchip") capabilities, for single cell manipulation and analysis.



Dr. Lawrence Chao prepares a patient for vision correction. For more on the Institute's refractive surgery program, please see page 8.

The "integrated platform" project, tentatively slated to begin in January 2000, involves the collaboration of six investigators from three different academic programs on the campus of UC Irvine. Institute Director Michael Berns, Ph.D., will serve as principal investigator, along with Nancy Allbritton, M.D., Ph.D., G.P. Li, Ph.D., Christopher Sims, M.D., Vasan Venugopalan, Sc.D., and Mark Bachman, Ph.D., who will serve as co-investigators.

Initial reviews from NIH have been very enthusiastic. One member of the review group notes, "[This] application reflects a real partnership among the participants." Another panelist comments: "The experimental methods proposed to measure intracellular chemical composition, in real time, will open up a new methodology for the study of cellular biochemistry." Reviewers rated the overall project "of high significance" and have recommended the project for full funding. A final decision from NIH is expected soon.

"We're very excited at the idea of beginning a new, cross-campus collaboration," Dr. Berns reports. "And it's always nice to receive accolades from NIH. We're confident that the new microscope system will stretch the detection limits for a whole range of biochemical studies."

The new microscope will incorporate a "microfluidics chip" which will allow the integrated laser system to perform and reproduce various single-cell procedures. "We're going to delve further than ever before into the molecular machinery of cells," Dr. Berns says. ■

Government Core Support Has Made the Difference

by Michael Berns, Ph.D.
Arnold and Mabel Beckman Professor
President and Director

In past columns, I have thanked individual donors (such as the Beckmans and the Hesters) for their visionary gifts to the Institute. We have also profiled a number of charitable organizations, such as the Beckman, Whitaker, Packard, and Hoag Foundations, for their generous support.

As we approach the end of a very historical year, I would like to use this column to thank the federal agencies which have long provided BLI's core research support. These are: the Department of Defense, Office of Naval Research (ONR); the Department of Energy (DOE), Basic Energy Sciences Program; and the National Institutes of Health (NIH), Division of Research Resources.

Without these core research support grants, we simply could not sustain many of our key programs. Not only do these grants fund individual innovative research projects, they also provide money for major equipment acquisitions and support the salaries of high level technical support personnel. This type of funding is generally not available from other traditional investigator-initiated individual research grants.

With respect to ONR, we thank Dr. Michael Marron for his leadership and advice over the many years of this program. Working in concert with Dr. Marron and his external review teams, we have forged ahead in many new areas of laser biomedicine, including a particularly exciting development, the use of optical coherence tomography to study and eventually affect better treatments for traumatic wounds and burns.

Among our projects supported by DOE, the application of a variety of photodynamic approaches to the diagnosis and treatment of both malignant and non-malignant conditions in the area of women's health is of particular note. We thank Dr. Roland Hirsch for his guidance and stewardship of this very exciting and rewarding program which focuses on the development of new medical applications for lasers.

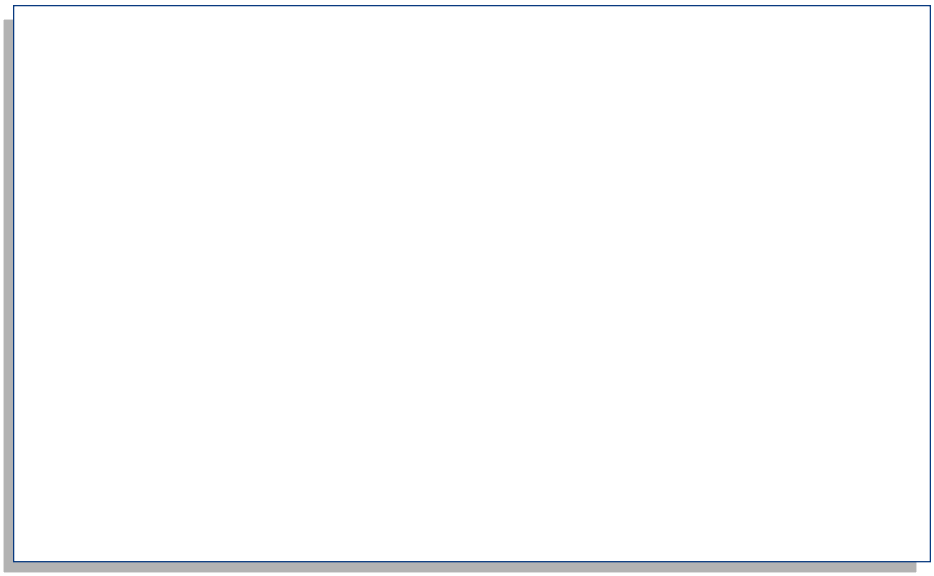
Last, but certainly not least, I want to mention the NIH Biotechnology Resource Program. In many ways, this program is the seed from which the rest of the Institute has blossomed. Funding was initiated in 1979, and the program continues to this day under the direction of Professor Bruce Tromberg. Initially designated LAMP (Laser Microbeam Program), and now LAMMP (after

(continued on p. 8)

Oral Cancer Research Lights Up

If you have smoked and are over 40, you could be among the 30,000 Americans who are diagnosed with oral cancer every year.

How to know? It's a tricky diagnosis to make. Dentists and doctors often can't tell whether a sore will heal or turn into cancer.



Dental Director Petra Wilder-Smith, Ph.D., D.D.S., uses a laser to check for oral cancer.

Dentists' Dilemma

"Most mouth lesions are benign, but may look malignant," explains Dental Director Petra Wilder-Smith, Ph.D., D.D.S. "A white sore might be harmless. On the other hand, an early malignant growth may be mistaken for a benign one. A clinician can't tell without a biopsy. But do you want to biopsy every mouth lesion? Of course not. That's the dilemma," she says.

Clinicians have no consistent, reliable way to predict whether a lesion will turn cancerous, Wilder-Smith adds.

No surprise, then, that 11 percent of dentists and 45 percent of physicians report that they don't have the expertise to look for oral cancer.

As a result, oral cancer kills 10,000 Americans every year, more than cervical or skin cancer. Only half of oral cancer patients survive more than five years, usually because the cancer is discovered at a late stage.

It is a disheartening record, and one that Wilder-Smith and UCLA professor Diana Messadi, D.D.S., D.M.Sc., aim to improve. Their instrument of change: photodynamic diagnosis (PDD), the pairing of a light-activated drug, ALA, and a hand-held laser they created to aid their search for oral cancer.

Lighting Up Cancer

In early studies, Wilder-Smith and her research team learned that pre-cancerous mouth lesions, mostly invisible to the human eye, become visible with the application of ALA, a chemical manufactured by DUSA, Inc., and laser light.

Researchers use ALA because it collects in cancer tissue where it changes into another compound, Photoporphyrin IX, which fluoresces under light.

A unique, fiber-optic instrument supplies the light. Wilder-Smith's team built it with the help of Allan Wong, M.D., Ph.D., of Physical Optics Corporation.

"First, we treat the patient's mouth with ALA," Wilder-Smith says. "Then, we shine the light and look for areas that fluoresce."

Wilder-Smith says they intend to enroll 50 patients over the next two years in clinical trials. The volunteers also will be examined and diagnosed with conventional means.

The researchers will compare photodynamic diagnosis to results from current techniques like physical examination and biopsy.

"If PDD predicts a pre-cancerous lesion," Wilder-Smith explains, "we will determine if biopsy supports that diagnosis."

Their goal is to gauge whether PDD can consistently identify pre-cancers and cancers.

And if they are successful?

"We would hope to put PDD in your dentist's office in the next five years," Wilder-Smith says. ■

Optical Spectroscopy Soon to Break Surface

The innovation of analytical instrumentation and techniques to provide real-time, non-invasive measurements of tissue optical properties *in vivo* represents one of the most exciting developments in the field of laser biomedicine.

By measuring the behavior of light waves as they pass through the body, scientists and clinicians can now collect a range of data which makes diagnoses more reliable and laser-based medical treatments more effective. Researchers at the Beckman Laser Institute are now poised to advance this promising technology one step further.

Extending Our Capabilities

Led by Vasan Venugopalan, Sc.D., assistant professor of chemical and biochemical engineering, researchers at BLI have launched a project which will extend the capabilities of existing "photon migration" spectroscopy technologies. Employing a new model to describe light propagation, Venugopalan and his team are developing an optical probe which can detect and measure physiological changes in epithelia (cells which cover and line most body cavities) and other superficial tissues.

The new probe promises to have extremely broad applications, particularly in the fields of oncology and women's health. For example, the probe could assist surgeons who need to quickly and accurately discriminate between healthy and cancerous tissues. This may reduce the need for biopsies and better aid surgeons so that recurrence rates for operable cancers can be curtailed.

"A number of optical techniques exist which provide *structural* images with excellent spatial resolution," Venugopalan says. "What the new probe will provide is complex *functional* information, including data on the biochemical composition of cells, tissues, and even whole organs."

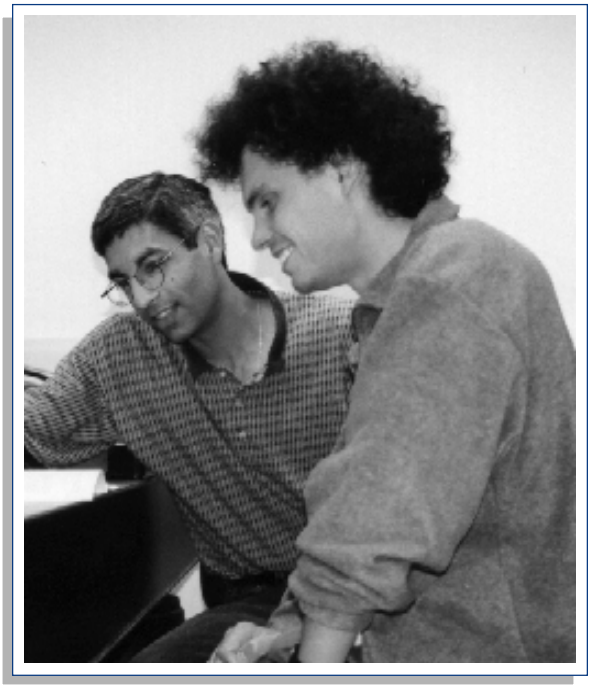
Optical spectroscopy has already been employed in traditional light microscopy to examine the biological structure of very thin tissue samples. More recently, optical spectroscopy has been effective on thicker tissues, however these samples typically involve very large tissue volumes.

The novelty of Venugopalan's probe is that it will allow scientists and clinicians to effectively monitor the superficial (i.e., shallow) layers of thick samples.

Piggyback Research

"I arrived at BLI as a postdoc three years ago," recalls Venugopalan. "Bruce Tromberg [associate professor of surgery and physiology / biophysics] and his group had already built a photon migration instrument, but there still remained untapped potential." This prompted Venugopalan to develop a new model for light propagation applicable for superficial tissues, which, in turn, paved the way for development of a "second generation" instrument. "Technological innovations like these almost never happen all at once," Venugopalan explains. "They reflect a creative progression."

Collaboration in a multi-disciplinary environment has been the key, according to Venugopalan. "Dr. Tromberg's work has given us an important head start. We've been able to piggyback on a well-developed research program and offer something which is, to our knowledge, completely new." ■



Vasan Venugopalan, Sc.D., and Frederic Belivacqua, Ph.D., have devised a "shallow tissue" model for a new optical probe.

PhotoSense to Market an Institute Technology

PhotoSense LLC, of Boulder, Colo., (www.photosense.com) and the Beckman Laser Institute recently agreed to jointly market frequency domain photon migration.

Photon migration uses laser light to identify the optical properties of human tissue. The photon migration device, a unique, hand-held instrument, beams harmless light into tissue, recording its optical properties. From this, scientists glean useful information, and can even determine whether tissue is healthy or diseased. The potential uses for photon migration range from cancer detection to blood gas analysis.

PhotoSense President Alan E. Baron, Ph.D., sees tremendous potential in the patented technology.

"We were impressed with its utility," Barons says. "Our company looks forward to combining the Institute's developments with our proprietary photonic systems in order to bring a commercially feasible system to market," he adds.

Although optical technologies similar to photon migration are currently available, the Institute's device compensates for the high levels of scattering and absorption that can distort other devices' tissue measurements.

Institute Associate Professor Bruce Tromberg, Ph.D., originally developed the photon migration instrument to detect malignant breast tissue. He and John Butler, M.D., director of the UCI Breast Center, have tested the device on patients since 1995. The researchers believe that photon migration may be useful in detecting cancer in dense breast tissue, and will complement current technology like mammography.

"We are particularly excited about our partnership with PhotoSense," says Director Michael Berns, Ph.D. "This joint project is the first for our Photonic Incubator," he notes. ■

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Board Welcomes Beckman Coulter Executive

Robert L. Stoy, Ph.D., is the newest addition to the Beckman Laser Institute Board of Directors. He is vice president and director of clinical systems development and systems engineering at Beckman Coulter in Brea, Calif.

Stoy's tenure at Beckman began in 1985 when he was hired as director of new product development. He had previously worked at several medical device firms.

A graduate of the Georgia Institute of Technology, Stoy started his career as an aerospace engineer and served as associate professor of mechanical and aerospace engineering at the University of Connecticut during the late 1960s and early 1970s. He was promoted to his current position of vice president-director in 1997.

At Beckman, Stoy has spearheaded the commercialization of new technologies. In the past two years, his development group has launched the IMMAGE protein analysis instrument system and the Synchron LX-20 chemistry instrument system, with annual sales topping the $100 million mark.

Stoy is a frequent speaker on the product development process and chaired the 1997 international conference of the Product Development Management Association held in Monterey, Calif.

The Institute Board welcomes Stoy's product development expertise, says Institute Director Michael Berns, Ph.D. "With the opening of the Photonic Incubator," he notes, "we hope to develop and market more Institute technologies." ■

New Board member Robert L. Stoy, Ph.D.

Kathy Spagnola: Nursing a Vision for the Future

Kathy Spagnola, R.N., cracks a broad smile when asked if she could have imagined herself living in Southern California when she finished nursing school in 1973. "Never in a million years," she laughs. And yet, here she is.

Born in Dayton, Ohio, Kathy arrived in Orange County in 1991 after a stint at the UCSD medical center. After eighteen years in the operating room, Kathy says she was ready for a change. "I was introduced to Joyce Zeiler [BLI's director of nursing] by a Candela representative, and, after crossing paths with each other on two separate occasions, I went to work at BLI in December 1992." Life in the clinic has evidently changed a lot since then. Kathy has assisted in nearly every procedure performed at BLIMC, but for the past year has specialized in vision correction.

"Working with the refractive surgery patients is very gratifying. The patients are so happy when they return for their follow-up visits. You can see it on their faces."

At home, Kathy spends her time with husband, Carmen, and their son, Jared, 14. "Jared's athletic endeavors fill up our spare time." Kathy's older son, Jim, lives in Ohio along with wife, Jennifer, and Kathy's two grandsons, Jordon, 2, and Jaime, 4. ■

Kathy Spagnola, R.N., outside the clinic.

PUBLICATIONS

Yona Tadir, M.D., published "Intrauterine Light Probe for Photodynamic Therapy" in *Obstetrics and Gynecology* and "Systemic Application of Photosensitizers in the Chick Chorioallantoic Membrane (CAM) Model: Photodynamic Response of CAM Vessels and ALA Uptake Kinetics by Transplantable Tumor" in the *Journal of Photochemistry and Photobiology B.*

Matt Brenner, M.D., published "Survival Following Bilateral Staple Lung Volume Reduction Surgery For Emphysema" in *Chest*.

Brian Wong, M.D., published "New Device for Laser-assisted Uvulopalatoplasty" in *ENT Journal*.

Boris Majaron, Ph.D., published "Thermo-mechanical Laser Ablation of Soft Biological Tissue: Modeling the Micro Explosions" in *Applied Physics*.

Sol Kimel, Ph.D., published the following: "Oxygen Depletion During *in vitro* Photodynamic Therapy: Structure-Activity Relationships of Sulfonated Aluminum Phthalocyanines" in the *Journal of Photochemistry and Photobiology B*; "Photodynamic Therapy of the Rat Endometrium by Systemic and Topical Administration of Tin Ethyl Etiopurpurin" in the *Journal of Gynecological Surgery*.

Xunbin Wei, Ph.D. candidate, published "Mapping the Sensitivity of T Cells with an Optical Trap: Polarity and Minimum Number of Receptors for Calcium Signaling" in *Proceedings of the National Academy of Sciences.*

PRESENTATIONS

J. Stuart Nelson, M.D., Ph.D., presented two talks at the symposium Controversies in Cutaneous Laser Surgery sponsored by the Department of Dermatology at Harvard Medical School. He also presented "Cryogen Spray Cooling During Pulsed Laser Treatment of Selected Dermatoses" as an invited speaker at the Food and Drug Administration's CDRH Science Seminar in Rockville, Md.

Zhongping Chen, Ph.D., presented "Phase Resolved Optical Coherence Tomography and Optical Doppler Tomography" at the Engineering Foundation Conference in Hawaii.

Johannes de Boer, Ph.D., presented "Determination of the Depth Resolved Stokes Parameters of Light Backscattered from Turbid Media Using Polarization Sensitive Optical Coherence Tomography" at CLEO / QELS in Baltimore.

Brian Wong, M.D., presented "Laser Thermal Shaping of Cartilage Implants" at the Engineering Foundation Conference.

Sol Kimel, Ph.D., presented the poster "Photodynamic Parameters in the Chick Chorioallantoic Membrane Bioassay for Topically and Systemically Administered Second-generation Photosensitizers and Uptake Kinetics of ALA by Transplantable Tumors" at the Engineering Foundation Conference.

Tatiana Krasieva, Ph.D., presented "Measurements of Optical Trap Stiffness Using Two-photon Fluorescence" at the Engineering Foundation Conference.

Shyam Srinivas, Ph.D. candidate, presented "Determination of Burn Depth by Polarization Sensitive Optical Coherence Tomography" at the annual meeting of the Association for the Advancement of Medical Instrumentation (AAMI) in Boston.

NOTABLES

Brian Wong, M.D., won a UCI Health Science Partners award.

Shyam Srinivas, Ph.D. candidate, earned top honors and $1,500 for a paper presented to the AAMI.

Uzma Naomani was awarded $500 by the University Research Opportunities Program for her project "Mechanisms of ALA Fluorescence in Malignant Tissues."

ARRIVALS

Peter McDonnell, M.D., Irving Leopold Professor and chair of ophthalmology

Roy Chuck, M.D., Ph.D., assistant professor of ophthalmology

Barbara Groff, R.N., clinical nurse II

Alexander Karn, senior writer

Melissa Killion, purchasing assistant

Melinda Szendefi, Ph.D., visiting postdoctoral researcher

("Director's Message," cont'd from p. 2)
adding a "Medical" component), this program forms one of BLI's core elements. Originally based around laser microscopy (the first such resource in the US), LAMMP still continues in that vein, but now also includes systems for disease diagnosis and treatment (such as frequency domain photon migration for the early detection of cancer).

In many ways, LAMMP embodies the identity of BLI. We have created a center where basic research, technology development, and the application of that technology to human disease occur under one roof, a place where clinicians conduct routine and experimental treatments alongside the researchers who work with them to achieve mutually rewarding goals. This has long been our mission, and we gratefully acknowledge the federal core support which makes our mission a reality. ■

Refractive Surgery Volume Doubles Over Six Months

Refractive surgery has taken off at BLIMC; in fact, the case-load for vision correction has increased by 100% in the past six months alone, as more and more UCI employees and associates avail themselves of the Institute's cutting-edge facilities and experienced medical staff.

In the area of research, a unique program to develop laser refractive surgery for corneal burns has received a favorable review by the Department of Defense, Office of Naval Research. Additionally, VISX, Inc. (Santa Clara, Calif.) now plans to fund a study at BLI to examine excimer laser interaction with new materials of interest to the company. Meanwhile, discussions continue with the FDA to designate BLI as a training site for agency research and regulatory personnel.

Institute Director Michael Berns comments: "The combination of research and patient treatment in the same facility keeps us at the forefront of medicine and bioengineering. This is one of the fundamental concepts that Dr. Beckman and I shared when we founded BLI." Dr. Berns adds that he expects to see continued progress in research and patient treatment, especially with the appointment of Peter McDonnell, M.D., as the new chair of ophthalmology, and the recruitment of new faculty. Dr. Berns and the rest of the BLI staff heartily welcome Dr. McDonnell on board.

For more information regarding refractive surgery and vision correction, call (949) 824-7980.

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