LASER
BECKMAN LASER INSTITUTE

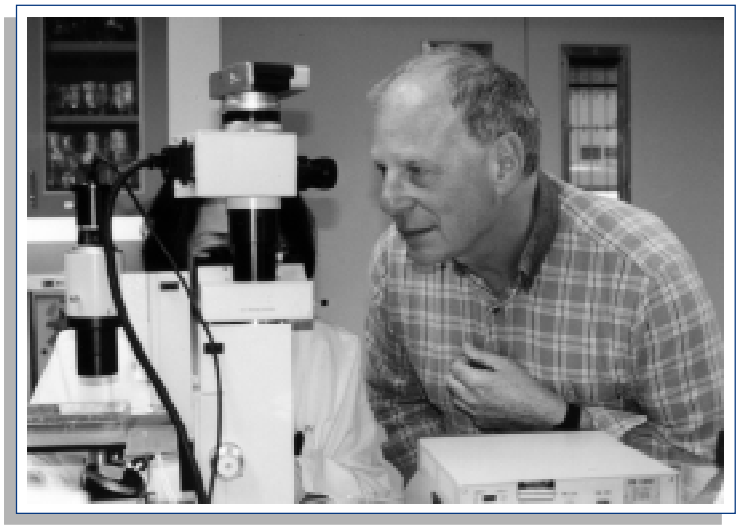
IN THE NEWS

Winter 1999

Institute Earns ONR Program Renewal

The Department of Defense, Office of Naval Research (DOD-ONR) will provide renewed funding to the Center for Free Electron Laser-Related Biomedical Research, one of three federally-designated "Centers of Excellence" housed at the Beckman Laser Institute.

The Free Electron Laser (FEL) Center, now in its fourteenth year of operation, received a two-year continuation grant from ONR. New funds, totaling $1.5 million, will be available beginning in August, 2000.



Henry Hirschberg, M.D., Ph.D., examines brain tumor cells after laser therapy. For more on brain PDT, please see page 3.

It is anticipated that the grant will support ongoing research in five project areas: orthopedic surgery, cartilage reshaping, optical coherence tomography (OCT), wound and burn imaging, and laser treatment for chemical burns to the eye. ONR funds these projects as part of its effort to support defense conversion technologies.

Among the reviewers' comments were special accolades for OCT and the burn management projects. Reviewers rated one subcomponent of the OCT project, polarization sensitive OCT, "the best non-invasive evidence known to us of thermal denaturation monitoring capability."

Institute Director Michael Berns, Ph.D., welcomes the continuation. "Federal core support makes comprehensive, interdisciplinary projects like the FEL Center possible. It's crucial that these funding opportunities be preserved." ■

Newsbriefs

NEW WHITAKER FUNDING

Johannes de Boer, Ph.D., Assistant Adjunct Professor of Surgery at the Beckman Laser Institute, has received new project funding from The Whitaker Foundation (Rosslyn, VA) to support burn depth assessment research using Polarization Sensitive Optical Coherence Tomography (please see "Research Update" on page four).

The three-year grant, funded through Whitaker's Biomedical Engineering Research Program, provides $209,000 for basic research, new instrumentation, and pre-clinical trials.

"We're very excited about Dr. de Boer's work," says Institute Director Michael Berns, Ph.D. "A grant like this one provides a real boost."

(newsbriefs continued on page 7)

At the Millennium: Taking the Past to the Future

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

In preparing this column, the last of the millennium or the first of a new era (assuming that some of you will read this before January 1, some after), I have debated whether to focus on the past (i.e., the list of accomplishments we have registered since opening our doors in 1986), or to focus on the future, that is, on our aspirations, ambitions, and hopes for the new millennium.

Mulling this over, I wonder if we can't employ our past productively? We should be able to learn from our past mistakes and, with the wisdom that time brings, avoid these same missteps farther down the road. At the same time, we should try to learn from our past successes, and using our store of knowledge, we should try to replicate and repeat the winning formulas we have used so often over the past fourteen years.

One Step Ahead of History

In many ways, I think that the Beckman Laser Institute appeared before its time. We were able to reach into the future and bring back what we saw.

The BLI founders had a vision of an interdisciplinary program that embodied basic and applied research under one roof, with patient care and technology transfer as key elements. We planned to unfurl our sails in the academic setting of a public university while keeping one foot in the private sector at the same time.

When Brian Demsey and I first proposed this vision to Arnold Beckman in 1982, and subsequently, when the three of us proposed it to Chancellor Dan Aldrich and Executive Vice Chancellor William Lillyman, we couldn't be certain whether our vision was viable or not.

Certainly, if one looks at our record of faculty peer-reviewed grants (over $30 million) and private fund-raising (another $30 million) or considers the patient volume we have seen in the BLI clinic (nearly 50,000 visits) or looks at the new technologies we have developed (sixty-seven intellectual property disclosures, thirteen patents, and four licensing agreements), it would be easy to conclude that we have achieved our vision.

Our past record of accomplishments has become, in a sense, a self-fulfilling prophecy. Like a small piece of DNA that modern biotechnology can now replicate, our fifteen year-old vision is becoming a model for other academic institutions around the country. By now, administrators at every major university recognize the importance of combined, interdisciplinary basic and applied research, and as a result, we see new strategies on the part of these institutions to

(continued on p. 7)

Intracavity PDT for Brain Cancer

The American Cancer Society estimates that 16,800 new cases of brain and other nervous system cancers will be diagnosed in the next twelve months. Even with the best available treatment, ninety-five percent of these patients will die within two years of diagnosis, a sobering statistic which makes this tumor-type one of the most lethal.

The poor prognosis for patients with malignant brain neoplasm has prompted a search for better treatment modalities. Henry Hirschberg, M.D., Ph.D., Professor of Neurosurgery at University Hospital, Rikshospital (Oslo, Norway) and a visiting researcher at the Beckman Laser Institute, may soon be able to offer some relief to patients with the most aggressive brain cancers.

Intracavity PDT

"These are the most malignant tumors in all of biology," explains Hirschberg. "Curing these patients hasn't been possible because the cancer migrates and regenerates so readily, but we may be on our way toward better management of the disease."

Hirschberg is working on a new treatment which combines close-contact radiation therapy with a laser-based treatment known as photodynamic therapy (PDT).

Working with Steen Madsen, Ph.D., a former BLI postdoctoral researcher and now on the faculty at the University of Nevada, Las Vegas, Chung-Ho Sun, Ph.D., and Bruce Tromberg, Ph.D., Director of BLI's Laser Microbeam and Medical Program (LAMMP), Hirschberg has developed a special, balloon-tipped applicator for combined brachy-photodynamic therapy. The new applicator is based on an instrument already in use in Oslo for intracavity brachytherapy.

"We're hoping that a combination of the two approaches will produce a synergistic effect which can't be achieved by one treatment modality alone," Hirschberg says.

Following resection, surgeons insert the applicator into the cavity left behind by the tumor. The balloon is then inflated to prevent the brain tissue from folding in on itself. Once the cavity is stabilized, doctors can deliver ionizing- and light-radiation directly to the tumor site where undetected "cancer nests" are thought to be embedded. For PDT, patients are first given a photosensitizing drug.

A laser fiber is then inserted directly into the balloon to activate the cancer-fighting drug. The combination of diffused light and photosensitive drugs begins a chemical reaction which kills cancer cells while sparing healthy tissue.

"Not only can we minimize the area of surgical resection, which gives patients improved postoperative function, we also provide ourselves an avenue for follow-up, post-operative treatments," Hirschberg says.

MRI scan showing implanted and inflated brachy-PDT applicator (dark circle at center).

Current Studies

At present, Dr. Hirschberg and his collaborators are conducting studies using *in vitro* "phantoms" to test which methods of delivery yield drug levels sufficient for photodynamic activation.

Patient studies could begin in Oslo as early as March, 2000, and U.S. trials, headed by Keith Black, M.D., Director of the Neurosurgical Institute at Cedars-Sinai and Chair of UCI's Department of Neurosurgery, could start within a year, pending approval from the Food and Drug Administration. Hirschberg remains cautiously optimistic.

"Until now, nothing has worked. Giving patients more time, whether that's something we measure in terms of months or years, would be highly significant." ■

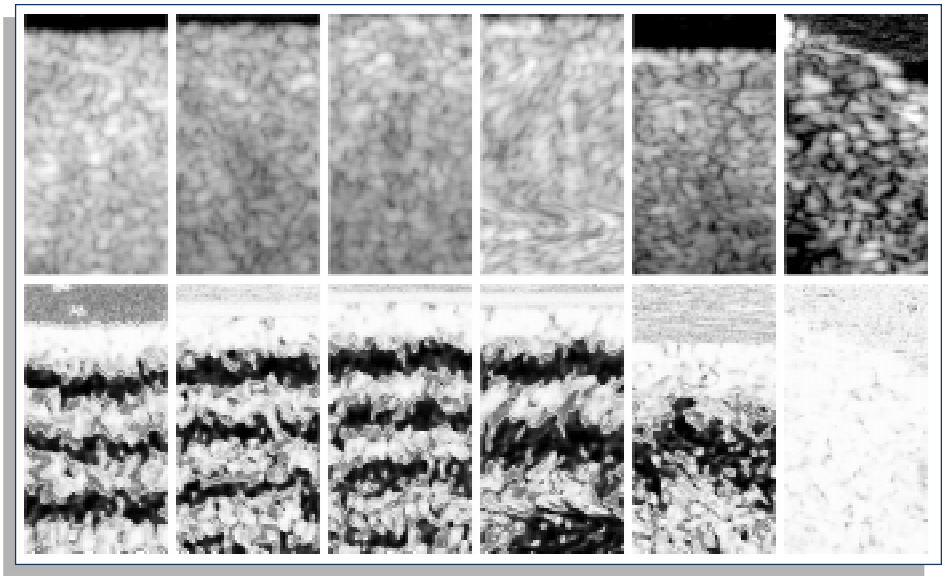
Polarization Sensitive Optical Coherence Tomography

As a postdoctoral researcher at the University of Amsterdam, Johannes de Boer, Ph.D., realized that light emitted from laser sources displayed unique properties which had untapped potential for biomedical diagnostics.

"Optical imaging depends on reflectivity," de Boer explains. "But we can retrieve more information than simple light quantity alone if we know what to look for."

De Boer, now an Assistant Adjunct Professor at the University of California, Irvine and a full-time researcher at the Beckman Laser Institute, has honed a technique which can detect and record the polarization state of light as it penetrates living tissues.

According to de Boer, Polarization Sensitive Optical Coherence Tomography (PS-OCT) fits a niche which existing techniques do not reach. "We get a nice combination of penetration and resolution, and light polarization provides information about tissue pathology which no other non-invasive technique can."



OCT (top row) and PS-OCT (bottom row) images of porcine tendon. As temperature and dynamic range increase (left to right), PS-OCT images show increased thermal damage (indicated by disruption of white and black strata).

A Physics Primer

PS-OCT works according to principles which may not be familiar to non-specialists.

Photons generated by laser sources can be polarized so that their electrical field is oriented either horizontally or vertically. Biological tissues, depending on their structure and composition, may alter the polarization of photons as they penetrate and backscatter. Birefringence is the term used to describe the material properties in tissues that induce changes in polarization and refractive quality as light enters and exits.

"We can chart and interpret changes in birefringence when tissue properties are altered as a result of disease or trauma," de Boer says. "This could give us a better window for medical intervention."

De Boer is currently working with J. Stuart Nelson, M.D., Ph.D., and Chris Saxer, Ph.D., to construct a fiber-based PS-OCT system which can be used in clinical and surgical settings.

Medical Applications

De Boer envisions two immediate medical applications for PS-OCT: burn-depth determination and early diagnosis for glaucoma.

The collagen molecule in healthy skin exhibits signature birefringence which burned and thermal-damaged samples do not exhibit. Deviations from normal birefringence patterns provide a thermal record of the burn. "We can actually see how much heat has passed through the skin and what the extent of the damage is."

PS-OCT also has the potential to catch glaucoma and other diseases affecting the optic nerve in their early stages. "Healthy nerve fibers are linear and highly birefringent," de Boer explains. "A reduction in birefringence might indicate a problem which could be treated before vision is compromised."

The Whitaker Foundation (Rosslyn, VA) has awarded de Boer a three-year, $209,000 grant to support instrument development and preclinical trials. If all goes well, PS-OCT should be ready for clinical trials at the end of the grant period. ■

Where the Wild Things Are: Laurie Newman, A.H.T.

Laurie Newman, A.H.T., doesn't describe herself as a people person, even though she thinks of herself as fun-loving.

"It sounds terrible," Laurie jokes, "and I don't want people to think I'm hard to get along with, but I prefer to work independently. Veterinary medicine was a natural step for me."

Dissatisfied with her career in banking, Laurie started training to become an animal health technician at Los Angeles Pierce College, earning her A.H.T. license in 1982.

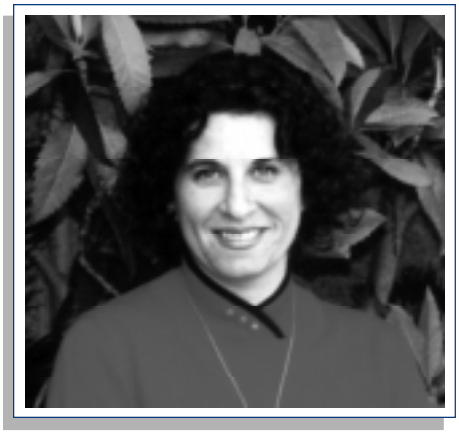
After stints in local veterinary clinics and emergency veterinary care facilities, Laurie arrived at the Beckman Laser Institute in 1995.

"Even though people sometimes have the wrong idea about what we do here, I prefer the research environment because we can practice our medicine without profit incentives and corporate bottom lines."

Laurie emphasizes that she works hard to instill a sense of compassion in the researchers and students who come through the Institute's veterinary suite. "The animals deserve the best treatment possible," she says.

"There is a purpose to the research we do, and part of that purpose is to ensure the animals' comfort and quality of life."

Laurie lives in Tustin with her fourteen year-old son, Devon, and her two cats, Kinky, a fifteen-pound Siamese, and T.C. She reports that her hobbies include "being way too busy to have any hobbies." ■



Laurie Newman, Veterinary Technician.

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Corporate Partnerships Cultivate New Technologies

The Beckman Laser Institute's "Photonic Incubator" is now officially open, and BLI has established a number of promising partnerships with high-tech firms in Southern California and beyond.

The Incubator was established to utilize photonic (light) technologies (lasers, optics, detectors, etc.) in the development of new biomedical systems for the detection, diagnosis, and treatment of disease. Funding for the Incubator came from a variety of sources, including a $1 million grant from the Economic Development Agency (Department of Commerce) and gifts from Institute donors, including the Beckman Family Trust and the Hester Family Foundation.

Positioned for the 21st Century

Walking the halls of the Incubator, Institute Director and Co-Founder Michael Berns likes what he sees. Not only has the Incubator provided much needed space for the Institute's rapidly expanding research program, it has also put BLI in position to compete in the 21st century marketplace.

"Every major university is looking to technology transfer as a source of revenue," Berns explains. "BLI stands out from the crowd with 14 years of experience with over 80 companies, a nice track-record on patents and disclosures, and, most importantly, dedicated space near the patients, biological material, and equipment which make innovation possible."

Federal funding, totaling $3 million annually, allows the Institute to provide leverage on funds contributed by corporate firms. Highly competitive, peer-reviewed NIH grant funding, stretching back 20 years, remains the most powerful endorsement of BLI's research programs.

Currently Incubating

Researchers at the Institute currently have three projects under development in the Incubator.

Bruce Tromberg, Ph.D., Director of the Laser Microbeam and Medical Program (LAMMP), heads a team working with Photosense L.L.C. (Boulder, CO) to develop and market Frequency Domain Photon Migration (FDPM) technology. One of BLI's patented technologies, FDPM uses light emitted by diode lasers to image and monitor human tissues.

Tromberg's group has already developed a portable FDPM instrument which they hope to miniaturize and market through Photosense.

Associate Professor J. Stuart Nelson, M.D., Ph.D., is working with the Candela Corporation (Wayland, MA) to further develop the dynamic cooling device™ (DCD) currently manufactured and marketed by Candela.

Under a licensing agreement negotiated with UC Irvine, BLI, and Candela, companies interested in using the DCD, which emits short bursts of cooled cryogen to the skin during laser-based dermatological procedures, can negotiate with Candela for sublicensing rights.

Bruce Tromberg, Ph.D., (standing) heads a group of BLI researchers working with Photosense L.L.C. to market Frequency Domain Photon Migration (FDPM) technology.

A group headed by Nancy Allbritton, M.D., Ph.D., is actively involved with several major companies interested in developing and marketing the laser micropipette system (LMS) developed jointly with BLI scientists. Olav Bergheim, general partner with Domain Associates (the nation's largest venture capital firm investing in health care start-up) states with respect to the LMS project, "We view BLI's scientists and management as clear leaders in their field."

"We built the Incubator to attract corporate interest and to ensure that new technologies reach the market through the path of least resistance," says Berns. "I hope that more companies will take this opportunity to get involved." ■

(cont'd from page 2)

Millennium Musings

commercialize the intellectual property of their faculty and students.

Competing in the Next Millennium

The new millennium promises great challenges. There will be more information to process, more competition for space and resources, not to mention increased competition for clinical patients, for the best students, and for the gold standard of excellence--the NIH dollar.

In addition, the university's faculty and students want to patent their ideas at the risk of pushing the ivory tower away from the free exchange of information toward a dichotomous struggle that pits realists against purists and greed against altruism.

Most medical schools and their affiliated clinical enterprises are currently under severe financial duress. Some will probably succumb to the belief that clinical revenue drives the academic process. Others (very likely those with large endowments and a ready supply of philanthropic alumni) will hold true to the belief that quality academic medicine is still rooted in basic and clinical research. And still others may be able to survive by adopting a hybrid scenario which combines research and clinical practice.

This is the BLI model, and it encompasses strong research support from the public and private sectors, as well as a clinical program with a balance between elective and non-elective procedures.

So where do I see BLI in the next millennium?

Since I believe that history repeats itself (and, yes, there is a lot we can learn from the past), I see BLI continuing to remain ahead of the curve.

I see new leaders carrying forward the original vision of the founders. I see a university (and other institutions as well) capitalizing on this pocket of excellence and replicating, as well as evolving, the founding vision to meet different programmatic and fiscal goals. I see academic medical enterprises embracing our interdisciplinary, hybrid approach to research, education, and clinical practice.

The paths to these ends will be twisted, uneven, and probably even hampered by an inherent myopic tendency on the part of some and by the inertia typically found in large institutional bureaucracies.

However, the desire of a core group of individuals to excel, combined with the need of the larger enterprise to survive, will lead to innovative and creative solutions--a scenario very similar to the vision first presented to Arnold Beckman in 1982. ■

We're On the Web...

The BLI homepage (www.bli.uci.edu) continues to grow and change. Pay us a visit in cyberspace to learn more about ongoing research, to read past issues of the BLI newsletter, to find out about clinical procedures performed in the Surgery Laser Clinic, or to contact researchers and clinicians. Also, look for a redesigned and revised Laser Microbeam and Medical Program (LAMMP) page in the coming months. Give us a *'click.'*

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Newsbriefs

CELLS ARRIVE FROM ZOO

The Beckman Laser Institute has established a collaboration with the Zoological Society of San Diego.

Through its world-famous Center for the Reproduction of Endangered Species (CRES), the Zoological Society is providing BLI researchers rat kangaroo (PTK) cells for continuing studies on cell genetics and cell biology.

The first shipment of cells, which arrived at the Institute in November, was established by CRES scientists from biopsies obtained at the Buffalo Zoo. The cells will be regularly cultured in the Institute's biochemistry facilities, providing an important, new cell system for cellular and genetic research.

"Our programs depend on a good supply of biological cultures," explains Institute Director Michael Berns. "In this case, we were able to solicit help from our colleagues at the San Diego Zoological Society, and we are hopeful that this will lead to even more extensive collaboration."

DIRECTOR TAPPED BY NIH

Institute Director Michael Berns has been invited by the National Institutes of Health (NIH) to serve as a member of the Center for Scientific Review Advisory Committee.

The review committee serves in an advisory role to the Center for Scientific Review (CSR) and reports to the Director of NIH. Its primary responsibility is to provide advice to the Center concerning matters of policy and practice as they relate to application and review procedures for NIH's biomedical and behavioral research programs. The committee will provide advice and counsel about the

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NEWSBRIEFS

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scope of review groups and their manner of operation. The appointment, which begins immediately, runs through June, 2003.

According to CSR Director Ellie Ehrenfeld, Ph.D., committee members are selected on the basis of "demonstrated competence and achievement in their discipline as evidenced by the quality of research accomplishments." Service on this senior NIH committee also requires "mature judgment and objectivity."

"I've been fortunate to receive NIH support since the beginning of my academic career in 1970," Dr. Berns notes. "Now it's time to give back in the form of time and energy to a system that has been good to me. I am honored to be selected to serve on this high-level panel."

BLI sent ten speedsters to this year's "Race for the Cure." The BLI squad included (L-R): Vincent Wallace, Rita Garcia, Michelle Duran, Melissa Killion, Vickie LaMorte, Frederic Belivacqua, and Albert Cerussi. Not pictured: Andrew Berger, Heather Lee, and Mariah Coleno.

STUDENT ON TO HARVARD

Xunbin Wei, Ph.D., successfully defended his doctoral dissertation, "Studying T-Lymphocytes at the Single Cell Level Using Optical Methods" and has accepted a fellowship in the laboratory of David E. Clapham, M.D., Ph.D., at the Howard Hughes Medical Institute (Children's Hospital, Harvard Medical School). ■

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