



BECKMAN LASER INSTITUTE

IN THE NEWS

Founder's Message	2
Fellow's Update	3
Veterinary Update	4

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Research May Make Invasive Oral Cancer Screens Obsolete

If oral cancer is detected and treated early, the survival rate is better than that for most other types of cancer. The inability to detect oral cancer early results in 10,000 U.S. deaths annually. Less than 50% of patients survive more than five years. Dr. Petra Wilder-Smith of the Beckman Laser Institute is spearheading an effort to revolutionize the way such oral cancers are detected and treated.



WILDER-SMITH

BLI's Dr. Petra Wilder-Smith

Developing Non-Surgical,

Fiber Optic Technique

for High Risk Patients

DISTINGUISHING TRAITS

Current diagnostic techniques require surgical biopsy and often cannot detect early cancerous change. Under laser light, precancerous and cancerous tissues fluoresce (glow) differently than healthy tissues. Pre-treatment with chemical agents (photosensitizers) such as ALA (5-Aminolevulinic acid) enhance this effect. Dr. Wilder-Smith's work has determined that very early precancerous changes invisible to the naked eye can be detected

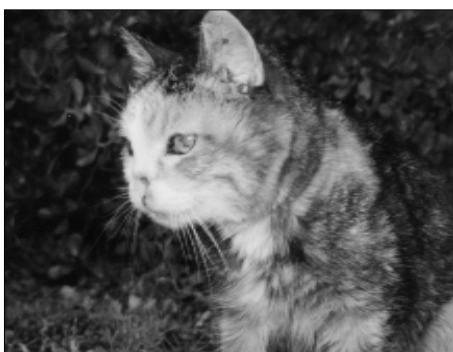
based on tissue fluorescence, and various stages of premalignancy and malignancy can be distinguished from each other.

A UNIQUE DATABASE

Also, most lesions in the mouth look the same, whether red or white. BLI (see *NON-INVASIVE* on p. 7)

The Long, Tall 'Tail' of Dagnar the Cat

Why are this Feline's Owners Still Purring about BLI Nine Years After Laser Surgery Saved Her Life?



Still Purring: At age 22, Dagnar may be the BLI's oldest living veterinary patient.

Answers, and although he has neither seen nor spoken to the caller in nearly a decade, he remembers her vividly.

The caller is Sherie Miller, owner of an aging calico cat named Dagnar. Miller, who lives in North Hollywood, CA, has called to thank Dr. Peavy for giving her an extra nine years with her precious pet — nine important and joy-filled years that once seemed impossible to fathom.

NINE LIVES INDEED

In 1993, at the age of 13, Dagnar was brought to the Beckman Laser Institute for treatment of a malignancy on her nose — a procedure Miller recalls as a "last-ditch effort" to save the cat's life. After a year and a half of effort to treat the cancer, Miller and her husband, Ron, decided the BLI's veterinary program would likely be their last and best chance to save the life

(see *DAGMAR* on p. 7)

Looking Back, Looking Forward

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

As many of you know, I've stepped down as the "Director" of the Beckman Laser Institute academic program at UC Irvine. Over the past several years, we've turned a patch of dirt into a world-famous program. This could not have been accomplished without the faculty, students (past and present), staff, supporters (at UCI as well as in the community) who make BLI what it is. You all deserve the credit.

PASSING THE BATON

It's really time for me to get back to what I really enjoy: research, teaching and moving our technology into the real world via BLI's Economic Development

Administration (EDA) Photonics Incubator. Now it's time for someone else to take over administration of the BLI academic program. There's a lot of talent around; I am confident that the university will find a successor who can carry on with the vision Arnold Beckman and I had 16 years ago.



"Over the past several years we've turned a patch of dirt into a world-famous program."

— Dr. Michael W. Berns

IN GOOD HANDS

I realize that many of you who are part of the UCI laser program - as well as those close to the program - may have some

anxieties and uncertainties over the future. Let me assure you that we have an excellent and strong faculty as well as a superb administrative staff. Also, don't forget that I will still be active as a faculty member and as the CEO of the BLI non-profit corporation. I truly anticipate a strong future for the program. We have a level of excitement and commitment to excellence that should sustain us well into the 21st century.

A Tribute to Two Friends

I met Fred Grazer when the BLI was no more than a dream in my mind. My wife, Robbie, and I had met Fred and his wife, Betty, through mutual acquaintances and immediately hit it off. Fred was one of those rare individuals who had a passion for his profession but also made the time to encourage and support others in their diverse endeavors. Fred approached plastic surgery like an artist approaches a canvas and a sculptor approaches his/her clay. He viewed the human body as a thing of beauty, and he devoted his life to realizing that image. He was so good at it that people came from all over the world for his talents.

Personally, Fred took on the BLI as if we were one of his patients. He became a core element of our Children's Treatment

Fund (CIF) by serving on the committee that reviewed applications from families of children who could not afford the lengthy and often expensive laser procedures developed by BLI physicians to remove disfiguring birthmarks. But what I remember most about Fred is his just popping by my office on many occasions over the years just to chat. I miss that and I miss Fred. In fact, the entire BLI misses this inspirational member of the community.

Like Fred Grazer, Bruce Achauer also devoted his life to helping people. Bruce was the first plastic surgeon to use the BLI lasers, and in fact, Bruce was a pioneer in the development and use of lasers in the field of plastic surgery. Bruce spent many hours and days at the BLI, particularly in

the early years when we were just trying to establish our reputation. In many ways Bruce was instrumental in putting the Beckman Laser Institute name "on the map" of lasers in plastic surgery and dermatology. Dr. Achauer not only treated many patients at the BLI and developed new laser techniques, but he also taught residents and physicians in specialized laser courses. It is fair to say that Bruce Achauer was one of the few physicians who shaped this field in the clinic, in the classroom, and in the research world.

It has, indeed, been a sad year. It seems a bit trite to say that the accomplishments of these two giants in Plastic Surgery will live on. But that is the truth. The Beckman Laser Institute is partly what it is today because of them.

Jolly Good Fellows: BLI Trio Impresses

Since the inception of the Beckman Fellows Program at the Beckman Laser Institute (BLI), great strides have been made. Funding from this program came from the Arnold and Mabel Beckman Foundation in the amount of \$1.1 million.

ANTHONY DURKIN

Dr. Anthony Durkin was awarded the first Beckman Fellowship and began work at BLI in January 2001.

His research focuses on quantitative spectroscopy and imaging of in-vivo tissue. Since arriving at BLI, he has become involved in numerous projects with Bruce Tromberg, Albert Cerussi and Frederic Bevilacqua as well as members of the UCI Medical Center General Clinical Research Center.

The first of these investigations combines Magnetic Resonance Imaging (MRI) and near-infrared spectroscopy (NIRS). A first generation combined MRI/NIRS instrument has been built and preclinical studies have been performed. Preliminary results indicate that this combination of technologies yields information that may be invaluable for drug development investigations. It provides a means for monitoring tumor response to therapeutic drugs over long periods of time.

A second project involves NIRS and MRI to examine the progression and severity of delayed onset muscle soreness (DOMS) in children and young adults. In a related investigation, Durkin has designed a protocol for clinical testing of NIRS to probe bone density. These studies will pave the way for the development of new clinical tools for the evaluation and treatment of muscle and joint inflammation, muscular injuries and bone health.

Durkin also maintains an interest in medical lasers and is collaborating with Glenn Healey, Electrical Engineering, and Stuart Nelson, BLI on the development of hyperspectral imaging to quantify tissue response to cutaneous laser therapy.

Durkin participated in writing a section of the Laser Microbeam and Medical Program (LAMMP) grant renewal that proposes investigations of tissue outside of the NIR spectral window.

At the invitation of Dr. Petra Wilder-Smith, he has begun to co-formulate a proposal focused on the development of optical technologies to better understand the progression of oral cancer. He hopes to pursue a similar path for skin cancer.

Durkin recently became the co-editor of a biomedical optics feature issue of *Applied Optics* and was named Biomedical Optics Division Chair-Elect for the Optical Society of America.

ELLIOT BOTVINICK

During his nine month tenure as the second Beckman Fellow, Dr. Elliot Botvinick has set up a new lab linking BLI and the UCSD campus and designed and built a fully automated imaging/laser system. Dr. Botvinick's work focuses on using and improving existing laser techniques and developing new techniques to study biological systems.

Dr. Botvinick and BLI's Zifu Wang designed RoboLase, a Robotic Laser Microscope facility, that incorporates a design that can move specimens in the focal plane, acquire data, radiate a specimen, and make decisions at a faster rate far exceeding that of the best trained technician. The RoboLase incorporates these ideas and includes a user interface allowing complete

operation via a standard Internet connection. The goal of RoboLase was to build a valuable tool for biological studies as well as a worldwide resource for new research and collaborations between the BLI and remote laboratories.

The RoboLase project has come to fruition and is ready for biological experiments that guided its development. Botvinick, in collaboration with Dr. Jagesh Shah, is working on the molecular control of mitosis - understanding the informatics of mitosis regulation.

The UCSD RoboLase system is the new grounds for the collaboration between the San Diego Zoological Society's Center for Reproduction of Endangered Species (CRES) and the BLI. CRES Director, Dr. Alan Dixson, and his postdoctoral fellow, Dr. Matthew Anderson, are looking for cellular mechanisms of sperm competition in certain species of primates. Using the RoboLase facility, researchers are mapping sperm performance data to investigate sperm competition.

Two additional projects Dr. Botvinick is undertaking include measuring membrane flow and understanding the physics of cutting microtubules with laser scissors.

BERNARD CHOI

Dr. Bernard Choi is the third Beckman Fellow. His current research involves work with Dr. Stuart Nelson on optimizing the treatment of port wine stains (PWS). Over the past decade, an infrared tomography (IRT) system has been developed at BLI to noninvasively image PWS skin structure. Dr. Choi and other researchers believe that knowledge of PWS anatomy will provide the clinician with key information (*see JOLLY GOOD FELLOWS on p. 8*)

Alligator Gender and Global Warming?

One might ask, "What on earth is the connection between alligator sex and global warming? How could just a few degrees in temperature change of the environment affect the sex of an alligator?" Well, a lot – and not only for alligators, but also for many endangered turtles and lizards.

A MATTER OF DEGREES

By mechanisms unknown, apparently just a few degrees difference in the environmental temperature can cause an alligator embryo to develop into a male or female. The physiological and anatomical explanation for this has puzzled biologists for decades. Now a team of BLI scientists working in collaboration with scientists from the Center for Reproduction of Endangered Species (CRES) at the San Diego Zoological Society, are applying sophisticated laser and optical technologies to try to solve this puzzling question. Once an understanding is achieved, it may be possible to apply this knowledge to stabilize sex ratios and provide a conservation intervention in the event of unusual environmental fluctuations in temperature that may drive the sex ratio into such an imbalance that the species/populations can not survive.

TEAMING UP

The BLI team consists of staff scientist Marie Wilson, specialist Leaky Liaw, associate specialist Dr. Bernard Choi, associate professor Dr. Zhongping Chen, and professor Dr. Michael Berns. The CRES team is Dr. Valentine Lance, Head of Reproductive Endocrinology, and technician, Willow Gabriel.

DANGEROUS TERRITORY

What makes this project challenging is not only the logistics of getting the alligator eggs (retrieving them from nests protected by rather aggressive females) but also getting the eggs to the lab from the Rockefeller Preserve in remote Western Louisiana.

TIME IS OF THE ESSENCE

In addition, the eggs are only available for a 3- 4 week period each year – so there is only one crack at the experiment per year. The time leading up to the experiment is spent making phantom and model measurements on chicken eggs and a variety of tissues discarded from the slaughterhouse. Add to this the ever-present Murphy's Law – after collecting the eggs, working through the maze of explaining to the airline personnel that these are alligator eggs, and no, they can't be x-rayed, and no, they are not tiny little bombs, and no, they can't go in a non-pressurized cold cargo hold – we get them back to the lab and find out that they were a bad batch of eggs in the first place. So back Val Lance goes to Louisiana for a second batch of eggs.

TEMPERATURE SPECIFIC

The key experiment is to see if, in fact, there is a special area in the brain that controls the sex development and if this area is sensitive to temperature. For if the embryo is between 91 and 93 degrees Fahrenheit during a certain developmental time period, all the embryos develop into males and if the embryos are below 85 degrees Fahrenheit all the embryos develop into females.

So our experiment is to expose the brain of embryos to the laser to create different temperature levels in the tissue, and then follow the embryo until the sex can be determined. A variation of this experiment will be to expose the embryonic gonadal tissue to the same set of laser parameters in order to determine if the temperature sensitive region is in the developing reproductive tissue itself.

TECHNICALLY CHALLENGING

Technically, this is a very challenging experiment. The whole experiment is done by focusing the laser through the membrane that covers the embryo after having gently removed about a square centimeter of the hard shell over the region of interest. As you read this, approximately two dozen alligator embryos are growing in the BLI research incubators. There is hope to design and conduct a more definitive set of studies next summer based on this year's results.

LONG-TERM OPTIMISM

Hopefully, the answers we get can be applied to developing strategies to protect many of the threatened and endangered animals on this planet. We thank the David and Lucile Packard Foundation for providing support that can be used in the future for this study.

Getting to Know Guillermo Aguilar

In this issue of LASER, we are proud to introduce you to Adjunct Assistant Professor Guillermo Aguilar.

1. What is your official title at BLI, and what are the duties of your current position?

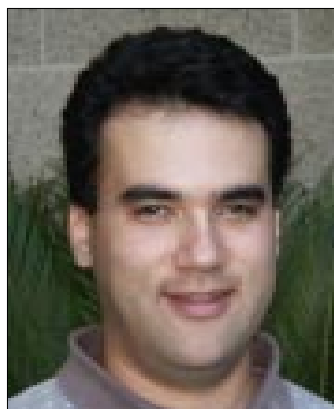
GA: I'm an Adjunct Assistant Professor in the Biomedical Engineering (BME) Department. My duties include conducting biomedical-oriented research, teaching engineering BME courses and supervising engineering students.

My main research is focused on cryogen spray atomization, evaporation, and deposition; cryogen skin cooling; and response of human tissue to combined cryogen spray cooling and photo-thermal heating. These studies are carried out in collaboration with Dr. J. Stuart Nelson. Other research projects in collaboration with other faculty and researchers include thermo-mechanical behavior of cartilage during laser irradiation (with Drs. Brian Wong and Sergio Diaz), photo-acoustic measurement of epidermal melanin (Drs. John Viator and Bernard Choi), cryo-freezing and cryo-injury of human tissue (Drs. Bernard Choi, Lars Svaasand, and GuoXiang Wang).

Regarding teaching, I teach an upper level undergraduate course at the BME Department (ChE 180, transport phenomena in living systems). I also supervise and co-advise engineering students (two grad students, four undergrad, and five summer interns).

2. We understand you've recently been awarded a new grant. Can you provide details of the award and what kind of research you'll be performing as a result?

GA: I was awarded a NIH-K01 grant for five years. This is a "Mentored Research Scientist Development Award," designed to provide support for "an intensive, supervised career development experience in one of the biomedical, behavioral, or clinical sciences leading to research independence." For the most part, the research comprises fundamental and clinical studies on port wine stain (PWS) laser therapy. The aim is to improve the therapeutic outcome of PWS patients, particularly infants and young children, by enhancing epidermal protection and



"I was awarded a NIH-K01 grant for five years. This is a 'Mentored Research Scientist Development Award.'"

including higher energy deposition within the targeted blood vessels with sufficient thermal confinement.

3. How long have you worked at BLI?

GA: I've worked at BLI for over three years.

4. Describe your life outside of BLI.

GA: I'm married. My wife's name is Erika Coll. We have a lovely (and according to some, cute) five-year old boy. His name is Andres (Andy). My main hobby and passion used to be playing baseball. It is no longer a hobby, but it still remains my passion. Even more so now that Andy started to play T-ball and I get to be his team's coach. Occasionally, I still play other sports (tennis, basketball, soccer, volleyball), but the most important one of them is softball. I am proudly a member of the Beckman Lasers softball team.

I also like to travel. With not much time for this, we usually take the opportunities to visit our families in Mexico City. While we're there, we like to drive around the

countryside and enjoy some of the local Mexican food and folklore.

'Panda-monium' Grips BLI

There are only about one thousand pandas left alive in the world so every birth is a major "happening." It's especially difficult to breed pandas in captivity although last year at the San Diego Zoo, Qu Mei was born following artificial insemination.

UNRAVELING THE MYSTERY

Very little is known about panda reproduction, and what studies have been done on their hormone cycle have been inconclusive with respect to detecting pregnancy. Any technique that can help determine if the panda is pregnant would be very useful, especially in terms of preparing for the birth and/or scheduling another breeding session (you don't want to breed the Panda if she is already pregnant).

MAKING A DETERMINATION

After hearing a lecture by Dr. Barbara Durrant, Head of Reproductive Physiology

at the San Diego Zoo's Center for Reproduction of Endangered Species (CRES), BLI Co-Founder Dr. Michael Bems suggested the possibility of using BLI's unique non-invasive optical diagnostics tools to determine if the panda, Bai Yun was indeed pregnant. Bems' reasoning was that the non-invasive optical diagnostic system developed by BLI's Bruce Tromberg and his team might be able to detect subtle changes in the breast tissue of Bai Yun if she were pregnant.

In the past, the only sign that a panda was pregnant was a swelling of the mammary tissue a couple of days prior to birth. The rationale was that the sensitive optical measurements should be able to detect changes in the blood, water, and fat in the breast significantly sooner than the visual observation of breast changes.

NEW MEASUREMENT METHOD

Under the direction of researcher Albert

Cerussi the BLI team brought the newly developed "portable" system down to the zoo in order to measure several different points on Bai Yun.

Unfortunately, that would be the day that she was "cranky" and would not lie down on her back like the "sweet little panda that she usually is." So back up the freeway the BLI team went, with the next attempt scheduled for a few days later, only to be foiled this time by a tanker spill that closed down the freeway for the day.

But on Monday, August 5, approximately 2-3 weeks before the panda would give birth (if she was pregnant), all the stars were aligned, the optical system worked beautifully, and Bai Yun behaved like a dream. She lay on her back munching apples and carrots for almost 20 minutes while the BLI team made the first such optical measurements ever made on a panda. The data is being analyzed as this story goes to press, and hopefully more measurements will be made such that changes can be detected that are predictive of pregnancy in the rare panda and maybe in other threatened and endangered species as well.

In the future, this research will likely be supported, in part, by funds provided from the David and Lucile Packard Foundation. David Packard served on the BLI Board of Directors until his death in 1996, and conservation of wildlife was one of his major interests. This study is dedicated to his memory.



A panda enjoying life at the San Diego Zoo

(cont'd from p. 1)

DAGMAR: TWENTY-TWO-YEAR-OLD CAT HAS BLI TO THANK

of a cat they'd rescued from a San Fernando Valley animal shelter on the night before it was scheduled to be euthanized.

Dr. Peavy conducted a delicate procedure in which Dagnar's nose — which had severe skin cancer — was removed entirely. The vacancy left by the amputation was closed by a "purse string" stitch.

A TRUE LIFE-SAVER

"Without treatment, we absolutely would have had to put her down," Miller recalls. "We couldn't just let her suffer. I believe the BLI treatment saved her life, and it also stopped the cancer [from spreading]."

"We thought this was our only option. We either had to put her down or get the [laser] surgery."

Nine years later, Dagnar has outlived the two dogs and two other cats the Millers owned in 1993. Now 22 years old, she's cancer-free and living out the term of her natural life.

A SUPERB CANDIDATE

To the Millers' amazement, the treatment Dagnar received at the BLI was not only effective — it was free. The Millers were beneficiaries of a program that makes state of the art and developing technologies available for veterinary patient treatment where other forms of conventional therapy are not available for patient care. Dr. Peavy combined CO₂ laser surgery and photodynamic therapy to heat the malignancy that had taken over Dagnar's nose.

NOT JUST FOR PETS

In addition to dogs, cats and horses the Institute's Veterinary Outreach Program has provided care to reptiles of the San Diego Zoo, a tiger at the Wildlife Way Station and a sea lion at the Long Beach Aquarium. "Every day is a new adventure," says Dr. Peavy. "When I get a phone call or receive an e-mail, it may be about an administrative problem that needs attention or it may be the L.A. Zoo wanting me

to come up and take a look at a camel.

Southern California has been very fortunate to have the resources of the Institute available for veterinary patient treatment, and the support of Dr. Bems, the Institute's Board of Directors, the Beckman family, and our many individual donors who allow this program to provide very unique and specialized care."

We absolutely would have had to put her down. I believe the BLI treatment saved her life."

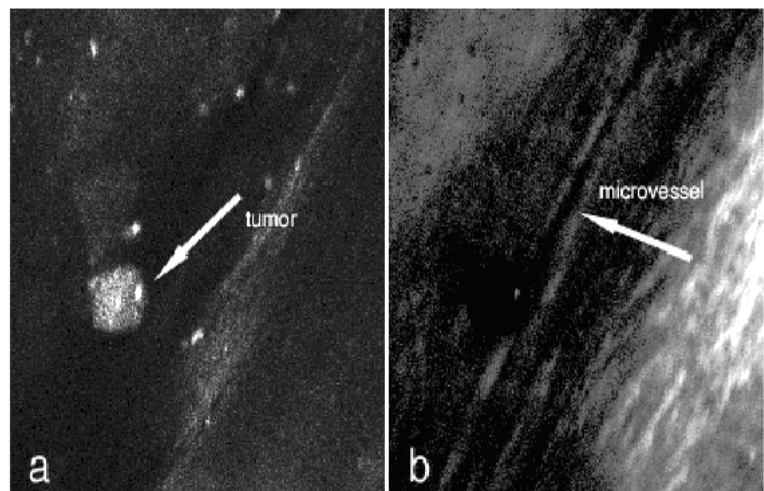
— Sherie Miller, Dagnar's Owner

(cont'd from p. 1)

NON-INVASIVE TECHNIQUES TO DETECT ORAL CANCERS

researchers are compiling a database of fluorescence characteristics of all oral lesions so that in the long term clinicians will be able to scan across suspected areas and provide an instant diagnosis.

The research being conducted by Dr. Wilder-Smith and her team will optimize the early detection of cancer, providing accurate, clinically relevant results. With the capability for direct diagnosis of suspect lesions, fewer surgical biopsies will be necessary and early detection is facilitated. Screening of high-risk populations and monitoring of suspect lesions becomes possible. This clinical modality should enhance early diagnosis and treatment.



Diagnostic images of early oral cancer: Two photon-induced fluorescence of tumor located within healthy oral tissue (a). Second harmonic imaging reveals microvasculature of early oral cancer (b).

NEWSBRIEFS

A CELEBRATION OF 25 YEARS

Four members of the Beckman Laser Institute staff commemorated 25 years of service with a celebration on May 8, 2002. Dr. Michael W. Berns, Leacky Liaw, Elaine Kato and Marie Wilson were honored with tokens of the BLI's appreciation for their years of dedication.

(cont'd from page 3)

JOLLY GOOD FELLOWS

to select optimal laser and cooling parameters for treating a given patient. Choi and Dr. Boris Majaron have developed a numerical model to serve as a test of Choi's existing reconstruction algorithm. Dr. John Viator and he are working on experimental verification of IRT with a tissue-simulating gel model.

Finally, Dr. Choi is exploring the use of in-vivo models to validate his IRT images. His other main project involves the use of optical clearing agents (CA) to re-



Joyous Occasion: (From left to right) Leacky Liaw, Dr. Michael Berns, Elaine Kato, and Marie Wilson celebrate 25 years at the Beckman Laser Institute.

duce the amount of light scattering in tissue, specifically skin. Skin is highly scattering, and thus it is oftentimes difficult to deliver sufficient light to surface targets for optimal imaging and therapy. He works with other researchers to investigate the use of different CA to reduce skin scattering via topical application. To investigate the

underlying mechanisms of CA action on skin, Dr. Choi and Dr. Alvin Yeh are using multiphoton microscopy to determine the effects of CA on collagenous tissues in vitro and in vivo. Dr. Choi hopes to progress towards the development of optimized treatment plans for FWS therapy on an individual patient basis.



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