IGERT Grant Creates New Ph.D. Program in Biophotonics

Professor of Chemical Engineering & Materials Science Vasan Venugopalan has received a 5-year, $3 million grant from the National Science Foundation (NSF) to create a doctoral level program entitled “Biophotonics Across Energy, Space and Time (BEST)” under the Integrative Graduate Education & Research Traineeship (IGERT) program.

The BEST IGERT program will develop a spectrum of new courses, hands-on training experiences, workshops and forums in order to immerse Biophotonics students within an interdisciplinary education and research environment at the earliest stages of their graduate student experience. The program will enroll as many as six new trainees each year who will be drawn from over ten academic departments spanning the Schools of Biological Sciences, Engineering, Medicine, and Physical Sciences. BEST IGERT trainees will develop doctoral research topics with significant input from two faculty advisors with different disciplinary backgrounds. The program has over twenty participating faculty members including many affiliated with the Beckman Laser Institute (BLI): Vasan Venugopalan, Bruce Tromberg, Michael Berns, Elliot Botvinick, Zhongping Chen, Bernard Choi, Anthony Durkin, Enrico Gratton and Eric Potma.

According to Prof. Venugopalan, “While UCI is highly regarded as a global leader in biophotonics research, there has been no systematic effort to formulate an integrated, multi-disciplinary

2012 BEST IGERT Class (left to right): Julie Hsu (Chemistry), Kyle Nadeau (Biomedical Engineering), Justin Luo (Biomedical Engineering), Joanna Laird (Molecular Biology & Biochemistry), Joseph Jing (Biomedical Engineering), Vasan Venugopalan (BEST IGERT PI). (BEST IGERT continued on p. 5)

Newsbriefs

PWS Article Highlighted
An article published online August 21, 2012, in Lasers in Surgery and Medicine entitled “Spatial frequency domain imaging of port wine stain biochemical composition in response to laser therapy: a pilot study” by A. Mazhar, S. A. Sharif, D. J. Cuccia, J. S. Nelson, K. M. Kelly and A. J. Durkin was highlighted on the website, Doctors Lounge, at http://www.doctorslounge.com/index.php/news/pb/31883. Amaan Mazhar, Ph.D., formerly a Beckman Laser Institute (BLI) postdoctoral fellow and now Director of Research of Modulated Imaging, Inc., located in the BLI Photonic Incubator, and colleagues conducted a pilot study to investigate the use of a new light emitting diode spatial frequency domain imaging (SFDI) device to record biochemical compositional changes in port wine stain (PWS) lesions in four subjects who underwent five laser treatment sessions. The SFDI-derived wide-field optical properties and tissue chromophore concentrations were assessed in PWS lesions before and after treatment and were compared with those of normal skin. The researchers found that in all PWS lesions before treatment, elevated oxy-hemoglobin and tissue oxygen saturation were observed. In all PWS lesions, laser treatment correlated with a more than 100% increase in deoxyhemoglobin, a more than 10% decrease in tissue oxygen saturation, and a more than 15% decrease in scattering. For the one patient who underwent two consecutive laser treatments, there was a 45% decrease in scattering.

(Newsbriefs continued on p. 6)
Messages from Arnold O. Beckman

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

This is the time of year I reflect on the past and think about the future. It is when I reconnect with Arnold O. Beckman and re-set my compass to make sure I have not drifted too far off course.

On September 29, 1992, Arnold O. Beckman, at the age of 92, sat down for an informal luncheon at the Beckman Laser Institute as part of the UCI CEO Roundtable, a group of Orange County business leaders and UCI administrators and faculty. I always enjoyed listening to his humor: the story about a writer who asked him for a million dollars so he could write without any pressure, and the story about the kid who asked his father about “this thing called ethics” – a story too long to repeat here, but it is funny. And then there were the serious things in response to questions from the audience. “How do you decide which projects to fund?” His answer was direct and to the point. He said that he knew almost nothing about the detailed projects that were submitted. “That is why I set up a panel consisting of the directors of the five Beckman Institutes.” He went on to explain that this group represented people he trusted, and they should be the ones evaluating the proposals sent to his foundation. When asked about high risk, innovative proposals, he came down strongly in favor of funding that type of research. He pointed out that those kinds of projects would inevitably be denied by the National Institutes of Health (NIH) and the National Science Foundation (NSF), a failure of the peer review system. They were going to fund the “safe” projects rather than the high risk ones. He also expressed the view that scientists needed to communicate better with the public—explain their research in layman terms which could be understood by the average person. And he felt that universities needed to constantly get articles in the newspapers about the research accomplishments of their faculty.

It was always an uplifting experience for me to watch and listen to one of the great men of the 20th century, and I feel honored to have had a close personal relationship with Dr. Beckman. As we move further into the current century with constant internet access and media stimulation, it might be helpful to take a break from digital overload and reflect on the ideas and principles of the great men and women who have influenced our lives, before they become distant memories.

The Laser Breast Scanner Goes To Japan

“From benchtop to bedside” is an oft-used phrase to describe one of the goals of the Beckman Laser Institute (BLI). The recent journey of BLI’s miniature laser breast scanner (m-LBS) to Japan is an illustration of this aim. The development of the m-LBS, led by Dr. Albert Cerussi, has involved dozens of researchers over the past 10 years. The technology began as a large, refrigerator-size platform designed to improve breast cancer detection and treatment 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 previous studies, it was found that potentially dangerous malignant tumors have a different metabolic fingerprint compared to benign tumors.

The latest m-LBS includes a board-based device that replaces many of the standard LBS components. The board-based hardware has several important features including replacing approximately $80,000 of technology with a $3,000 board that provides equivalent performance while also being small and portable. Currently, the refrigerator-size platform has been reduced to the size of a 13”D x 17” W x 3.5” H console. It is this instrument that was sent to Japan.

Dr. Anais Leproux, a postdoctoral fellow at BLI working on breast imaging, was in charge of delivering the LBS to Saitama Medical University International Medical Center located approximately 50 miles northwest of Tokyo in July 2012. The final paper

(LBS Japan continued on p. 6)
**Miniature Fiberoptic Probe**

With funding from the Air Force Office of Scientific Research (AFOSR), Military Medical Photonics Program Director Dr. George Peavy and Dental Director Dr. Petra Wilder-Smith are working in collaboration with Dr. Eric Potma, Associate Professor of Chemistry, to build a prototype benchtop fiber optic probe based on non-linear optical microscopy (NLOM). The goal of this work is to develop a clinical NLOM probe to provide direct, rapid *in vivo* information and imaging at a cellular and molecular level of tissue effects from injuries due to inhalation of toxic agents.

The impetus for building a fiberoptic *in vivo* imaging probe was provided by previous studies using Dr. Wilder-Smith’s hamster model for upper airway injury. In those investigations, also funded by the AFOSR, the effects of half mustard gas (HMG) exposure were identified and characterized. One important finding is that damage from HMG exposure extended beyond the superficial epithelial layers, where most of the tissue injury was previously thought to occur, down to the muscle fiber layer. This information, in turn, has led to further work to develop better treatment approaches. The hamster model work was initially performed using a clinical optical coherence tomography (OCT) probe and a standard non-linear optical microscope.

Chemical Engineering and Materials Science graduate student Richa Mittal, working with Drs. Potma and Wilder-Smith, is now refining the design and improving the performance of the prototype NLOM fiber probe. The multimodality probe integrates signals from two-photon excited fluorescence (TPEF) (showing elastin fibers), second-harmonic generation (SHG) (showing collagen I fibers), and stimulated Raman scattering (SRS) imaging, which reveals protein, water and lipid content. Ultimately, this system will provide three-dimensional high-resolution structural images of tissue without using external stains. The combination of these imaging modalities integrated into a flexible hand-held probe will provide a powerful tool for *in vivo* clinical and research applications.

A practical example of how such a probe would work would be on a wounded soldier who inhaled a chemical agent. A miniature fiberoptic probe could be easily inserted in the nasal or throat passageway, and the images provided would parallel images from conventional bronchoscopy and even closely resemble a stained slide viewed with a microscope.

While the initial specific interest in the development of a miniature NLOM probe is the study, diagnosis and treatment of airway injury related to inhalation of smoke and chemical warfare agents, the device has unique capabilities that could easily be extended into several other areas of medicine.

---

**Collaboration with Lutronic**

With the initiation of a collaboration with Lutronic Corporation, which Beckman Laser Institute (BLI) Director Bruce Tromberg describes as “an exciting and an impressive commitment to stimulating creative new ideas,” Dr. Won-Serk Kim has arrived at the BLI for a one year stay. Dr. Kim, from South Korea, is an Associate Professor in the Department of Dermatology, Sungkyunkwan University School of Medicine, and also the Chairman of the Dermatology Department of Kangbuk Samsung Hospital, an affiliate of the Samsung Company. Lutronic is South Korea’s #1 laser company and has developed many new innovative lasers used in cosmetic dermatology as well as dentistry and ophthalmology. A great strength of the Lutronic Corporation is its investment in fundamental research. The company has received significant research support from the Korean government and works with various other companies, universities, and clinicians.

As part of this investment in fundamental research, Lutronic sought a collaboration with BLI because of BLI’s extensive background and experience in technology, especially in imaging, diagnosis, and physiological monitoring. Dr. Kim hopes to combine these technologies with practical treatments using the laser which will then generate more precise and cost-effective procedures for patients.

Initially, Dr. Kim will familiarize himself with the various research projects at the BLI in order to formulate ideas and plans for what he wants to accomplish when he returns to Korea. So far, he has discussed stem cell...(Lutronic continued on p. 7)
BLI Study on Breast Cancer Published in Cancer Research


Neoadjuvant chemotherapy (chemotherapy before surgery) has been recommended as a standard treatment for locally advanced breast cancer and is currently accepted for patients having operable breast cancer. In the neoadjuvant setting, knowing how chemotherapy will affect the tumor before surgery is important because it is correlated with a favorable prognosis including longer disease-free survival and overall survival. Having a reliable predictor of response may also help physicians find the best drug combination for a given individual or spare patients a lengthy (4-6 month) course of treatment. There is currently an effort to explore various biomarkers associated with sensitivity to chemotherapy to aid in treatment planning. One promising biomarker is oxygen saturation (the fraction of oxygenated hemoglobin in the tumor). To date, there are no clinically accepted prognostic imaging indicators available before treatment that can be used to determine how an individual patient will respond to neoadjuvant chemotherapy. Because tissue oxygen saturation provides insight into tumor metabolism, it may be a useful biomarker to predict patient outcome.

In the BLI study reported in Cancer Research, the technology Diffuse Optical Spectroscopic Imaging (DOSI) was used to noninvasively measure tumor oxygen saturation in 41 breast cancer patients. DOSI uses near-infrared light to measure tissue concentrations of oxygenated and deoxygenated hemoglobin, water, and lipid. These measurements are directly related to tumor perfusion and metabolism. Previous studies by the BLI group and others have shown that DOSI and similar techniques are able to localize and characterize functional properties of breast tumors at baseline and during neoadjuvant treatment.

Patients underwent surgery following chemotherapy, and clinical response was determined by a pathologist who examined the surgical biopsy site. If the pathologist felt the patient had no residual cancer, she was designated as a “complete responder.” This is the first study where the relationship between baseline (i.e., pre-therapy) tumor oxygenation determined by DOSI and final post-surgical biopsy has been investigated. The authors concluded that DOSI measurements alone are a very good predictor of patient clinical response with a sensitivity and specificity of about 70%. The combination of DOSI imaging and the tissue-specific biomarker, estrogen receptor (ER) status, provided an even more powerful prediction, improving sensitivity and specificity to about 90%.

Ultimately, this information could be used to identify subjects who are likely to be non-responsive to chemotherapy before surgery. These individuals could immediately undergo surgical resection without having to endure the significant side effects of chemotherapy with no change in overall outcome.

Honors and Awards

Matthew Brenner, M.D.

Dr. Matthew Brenner has been awarded two grants by the National Institutes of Health/ U.S. Army Medical Research Institute of Chemical Defense (NIH/USAMRICD). The first is entitled “Collaborative studies for acceleration of advanced CN antidote agents for mass casualty exposure treatments: DMTS.” The second grant is a subcontract with UC San Diego and is entitled “Translational studies of new effective cyanide antidotes for mass casualty settings: testing of intramuscular injection by autoinjector versus intraosseous injection versus inhalational delivery.”

Thomas O’Sullivan, Ph.D.

Thomas O’Sullivan received a three-year Department of Defense Breast Cancer Research Program Postdoctoral Fellowship for “Development of a quantitative tissue optical index of breast density for hormone therapy response.” The grant will fund a clinical study to examine whether diffuse optical spectroscopic imaging (DOSI) is sensitive to changes in breast density caused by the drug, tamoxifen, which is commonly given as treatment to patients with hormone-receptor positive breast cancer.

Adam Gardner, Ph.D.

Adam Gardner defended his thesis, “Modeling and computation of radiative transfer on the mesoscale,” on August 21, 2012. He worked with Dr. Vasan Venugopalan. Adam will continue as a (Honors and Awards continued on p. 8)
Dental Hygiene: Older Adults May Learn Something from a Younger Generation

Tooth decay (dental caries) commonly develops in the pits and fissures of premolar and molar teeth. The National Institutes of Health (NIH) recently recognized that adults aged 65-74 years, a growing population, are as likely to have untreated caries as adolescents and have listed preventing caries in adults aged 65-74 years as a Healthy People 2020 objective. Although effective strategies to prevent and arrest early dental caries have been developed, those efforts have focused on children and adolescents, and their effectiveness in adults is unknown. Funded by a University of California, Irvine, School of Medicine faculty research grant, a pilot study was conducted by Beckman Laser Institute (BLI) Assistant Researcher Jennifer Holtzman and Dental Director Petra Wilder-Smith to gather baseline data in order to build a database of early caries prevalence in the growing population of 65-74 year olds.

One hundred fifty active adults aged 65-74 years were recruited from the Laguna Woods community, formerly known as Leisure World, Laguna Hills, CA. Its 18,000 residents range in age from 55 to over 100, with an average age of 78. Oral exams were conducted, and pits and fissures in various stages of early caries were identified, photographed, and imaged with an Optical Coherence Tomography (OCT) imaging system.

The findings of Drs. Wilder-Smith and Holtzman substantiated their hypothesis that active adults of 65-74 years had teeth that would benefit from a caries preventive intervention program, and few (4% of the sample) showed evidence of receiving such care. Although a high percentage of the sample

(Best IGERT continued from p. 1)

Biophotonics program for graduate students. This program will expose graduate students to the biophotonics field from different disciplinary perspectives. My hope is that the graduate trainees will emerge from the program with a comprehensive view of the challenges and opportunities in biophotonics and the facility to effectively communicate and collaborate with other biophotonics researchers from different educational backgrounds.”

The educational program will educate the IGERT trainees in the interaction mechanisms of light with biomolecules, cells, and tissues and their effects on fundamental biological and physiological processes across spatial and temporal scales. These interaction mechanisms have been leveraged in the development of a host of biophotonics technologies including: laser microbeams; nonlinear optical microscopies; optical coherence tomography; functionalized nanoparticles; photodynamic and photothermal therapies; and bioluminescence, fluorescence, and diffuse optical tomographies. Application of these technologies, individually and in concert, has had a profound impact in basic and applied biological research and both medical diagnosis and treatment. The research framework of the BEST program has been organized into five general areas: (a) Microscopy and Microbeams, (b) Wide-Field Functional Imaging, (c) Diffuse Optical Spectroscopy and Imaging, (d) Multiscale Molecular Probes, and (e) Biophotonics Modeling and Computation.

The first BEST IGERT graduate course “Molecular and Cellular Biophotonics” will be offered in Winter 2013. The course is being formulated by Profs. Venugopalan, Elliot Botvinick (Biomedical Engineering), Steven Gross (Developmental & Cell Biology), Susanne Rafelski (Developmental & Cell Biology), Michelle Digman (BME, Developmental & Cell Biology), Eric Potma (Chemistry), and James Jester (Ophthalmology). “We are having great fun putting this course together,” Prof. Venugopalan adds. “The course provides an opportunity to present important biophotonics mechanisms and technologies from many disciplinary perspectives within the context of specific research themes in Molecular and Cellular Biology. We will also be challenging students to work together to determine how to choose specific biophotonics approaches to examine various biological processes.”

In the end, the BEST IGERT is intended to provide trainees with not merely an awareness of other disciplines but also a powerful set of multi-disciplinary skills. Trainees with a disciplinary foothold in engineering or the physical sciences will emerge from this program with a broad knowledge of biological and physiological issues from molecular to organismic levels. Moreover, they will acquire the ability to identify new problems and opportunities together with the skills necessary to communicate and collaborate effectively with their life science colleagues. Trainees with life science backgrounds will acquire an understanding of the basic mechanisms underlying biophotonics tools, their connections to the fundamental biological and physiological processes, and a solid grasp of instrumentation, quantitative analysis, and modeling. These life science trainees will be better equipped to engage in the development, usage, and analysis of biophotonic processes and tools and will be able to communicate and collaborate effectively with their engineering/physical science colleagues.

As a result, all BEST IGERT trainees, independent of discipline, will acquire enhanced capabilities to solve important biological and biomedical problems, and prepare them for leadership positions in academia, government, and industry. •
Newsbriefs (cont’d from p. 1)
decrease in dermal blood volume. The authors concluded, “SFDI is a rapid non-contact wide-field optical technique that shows potential as an imaging device that can be used to quantify biochemical compositional changes in PWS after laser therapy.” Modulated Imaging, Inc. developed the spatial frequency domain imaging device used in the study.

Visit from NIH Program Manager
The Beckman Laser Institute (BLI) hosted Dr. Richard Conroy, the new program manager of the Laser Microbeam and Medical Program (LAMMP), National Institutes of Health (NIH)/National Institute of Biomedical Imaging and Bioengineering (NIBIB) on the afternoon of August 14, 2012. Dr. Conroy toured the Institute which included visits to the medical clinic operating rooms and various labs.

Collaboration with Vixar Awarded a Grant
Drs. Albert Cerussi and Thomas O’Sullivan in collaboration with the laser company, Vixar, Inc., have been awarded a National Institutes of Health (NIH) Small Business Innovation Research (SBIR) Phase 1 contract to demonstrate the feasibility of a wavelength-tunable vertical-cavity surface-emitting laser (VCSEL). The swept near-infrared source would improve the performance and commercialization potential of a handheld DOSI (diffuse optical spectroscopic imaging) instrument by allowing 3-D subsurface imaging, improving the signal-to-noise ratio of the image by delivering a much higher photon intensity to the detector, and enabling miniaturization of such a device to be compatible with routine clinical use.

Named to Editorial Board
Professor Brian Wong, M.D., Ph.D., has been named to the Editorial Board of JAMA Facial Plastic Surgery. This is a publication of the American Medical Association.

LBS Japan (cont’d from p. 2)
work for taking the instrument out of the U.S. was accomplished only a few days before departure. The instrument was somewhat disassembled so it would fit in a case that could be a carry-on. The case weighed 35 pounds, and Anais bought a trolley so she could carry the case. In the plane, as Anais explains, “It took all of my muscle to lift the case up to the overhead bin. I did not want to ask the flight attendants for help as the case was certainly over the allowed weight for carry-ons, and I did not want the instrument to be checked in.”

At the hospital, she met with Drs. Shigeto Ueda and Hideki Takeuchi. Dr. Ueda previously spent 2 years (2009-2011) at the BLI working on optical imaging of breast cancer, and Dr. Takeuchi is continuing Dr. Ueda’s research at the BLI for another 2 years (2011-2013). The three of them worked at getting the instrument installed. Dr. Takeuchi took care of the logistics, Anais put the instrument back together and taught Dr. Ueda how to do it himself and troubleshoot components. Before the trip, the m-LBS underwent several weeks of testing and evaluation at the BLI.

Anais trained her Japanese colleagues on the operation of the m-LBS, ate a lot of tasty sushi, and gave a lecture on diffuse optical spectroscopic imaging (DOSI) - the underlying technology behind the m-LBS. The Japanese m-LBS is now part of an international collaboration designed to evaluate how DOSI technology can be used in the clinical management of breast cancer patients (see Clinical Update on page 4). Saitama University brings unique capabilities to this program because of their state-of-the-art breast oncology trials and their ability to combine m-LBS scans with multi-modality MRI and PET imaging for each patient. In addition, this is an important opportunity to determine whether there are breast cancer features that may be different in Japanese vs. North American women.

Check out http://saitama-med-bre.sakura.ne.jp/english_hp/ for more information about Saitama Medical University International Medical Center..

Assemblywoman Tours BLI
California Assemblywoman Kristin Olsen (R-Modesto) visited the Beckman Laser Institute (BLI) on November 27, 2012, for a tour. As Vice Chair of the Assembly Higher Education Committee, she was especially interested in meeting the BLI postdoctoral research fellows, graduate and undergraduate students. She was impressed with the cross-discipline and collaborative nature of all the programs as well as learning about the research leading to practical applications and new business development.

BLI Newsletter Staff
Editor: Bruce Tromberg
Writers: Elaine Kato, Erin Miller, Deborah Birnie
Layout & Design: Brian Hill
People had restored teeth, the findings suggested that approximately 80% of those adults had 4 or more premolars and/or molars that would be candidates for caries prevention, and few were accessing such preventive care. The majority of adults in this age group was clearly at risk of developing caries since they had a history of caries (considered the most valid and reliable predictor of future caries) and were likely to be at increased caries risk as they aged. Aging is frequently accompanied with deficits in self-care skills, neuromuscular changes that reduce the ability of saliva, lips, tongue and cheeks to clear the mouth of food, and reduction in the protection of saliva with the use of medications that reduce salivary flow.

The Laguna Woods sample (62.5% female, 37.5% male) had slightly higher rates of dental restorations and lower untreated caries than the national sample. Only one of the subjects had no current source of dental care, and this subject had rampant, untreated caries. Four percent of the sample reported recent filling of a "small cavity" that the dentist was watching, a surgical intervention that could likely have been avoided with a dental sealant.

The pilot study provided important baseline data indicating that adults of 65-74 years of age have teeth that are both vulnerable to dental caries and may benefit from the same caries preventive strategies found to be effective in children and adolescents.

Nima Khatibzadeh, Ph.D., has joined Dr. Michael W. Berns’ lab as a post-doctoral fellow. Dr. Khatibzadeh received his Ph.D. in Mechanical Engineering at UC Riverside and will be studying the response of nerve axons to optical damage as well as optically growing axons in the direction of the shear force.

Robert Wilson, Ph.D., is the George Hewitt Postdoctoral Fellow and will be working in the lab of Dr. Bruce Tromberg. Dr. Wilson is from the University of Michigan at Ann Arbor and will be working on spatial frequency domain and hyperspectral imaging.


Honors and Awards (cont’d from p. 4)

postdoctoral researcher at BLI in Dr. Venugopalan’s lab. His focus will be to translate the radiation transport algorithms developed for his thesis for application in functional tissue imaging, specifically problems where the diffusion approximation is invalid. Using these methods, the aim is to better characterize tissue noninvasively with visible wavelengths. In addition, he will also be carrying out modeling efforts on a project that aims to use spatial frequency domain imaging (SFDI) to characterize fibrous tissues, including brain and muscle.

Veronica Gomez-Godinez, Ph.D.
Veronica Gomez-Godinez defended her thesis, “DNA damage responses of mitotic cells following laser microirradiation,” on September 10, 2012. Veronica worked in the lab of Dr. Michael W. Berns, and her future plans are to continue doing research related to cancer and aging within a pharmaceutical or biotechnology company.

Hosain Haghany, Ph.D.
Hosain Haghany defended his thesis, “A portable broadband, multi-channel instrument for frequency-domain diffuse optical spectroscopy and imaging,” on September 20, 2012. He continues to work in collaboration at the Beckman Laser Institute while also looking to continue his research in a related industry.