FINAL REPORT

DOE/ER/61971--T1

DOE Center of Excellence in Medical Laser Applications

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DE-FG03-95ER61971
University of Texas M. D. Anderson Cancer Center (UTMDA)

DE-FG05-91ER617226, Sep 15 1991 - Sep 14, 1994, UTMDA
DE-FG03-95ER61971, Dec 1, 1994 - Nov. 30, 1997, UTMDA
DE-FG03-97ER62346, Dec 1, 1997 - Jan. 31, 1998, OMLC
DE-FG03-97ER62346, Feb 1, 1998 - Jan 31, 1999, OMLC

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Summary

An engineering network of collaborating medical laser laboratories are developing laser and optical technologies for medical diagnosis and therapy and are translating the engineering into medical centers in Portland OR, Houston TX, and Galveston TX. The Center includes the the University of Texas M. D. Anderson Cancer Center, the University of Texas-Austin, Texas A&M University, Rice University, the University Texas Medical Branch-Galveston, Oregon Medical Laser Center (Providence St. Vincent Medical Center, Oregon Health Sciences University, and Oregon Graduate Institute, Portland, OR), and the University of Oregon. DIAGNOSTICS include reflectance, fluorescence, Raman IR, laser photoacoustics, optical coherence tomography, and several new video techniques for spectroscopy and imaging. THERAPIES include photocoagulation therapy, laser welding, pulsed laser ablation, and light-activated chemotherapy of cancer (photodynamic therapy, or PDT). Medical applications reaching the clinic include optical monitoring of hyperbilirubinemia in newborns, fluorescence detection of cervical dysplasia, laser thrombolysis of blood clots in heart attack and brain stroke, photothermal coagulation of benign prostate hyperplasia, and PDT for both veterinary and human cancer. New technologies include laser optoacoustic imaging of breast tumors and hemorrhage in head trauma and brain stroke, quality control monitoring of dosimetry during PDT for esophageal and lung cancer, polarization video reflectometry of skin cancer, laser welding of artificial tissue replacements, and feedback control of laser welding. Find us at http://ece.ogi.edu/omlc/doe/index.html.

DISCLAIMER

CENTER MEMBERS

The University of Texas M. D. Anderson Cancer Ctr.	UTMDA
The University of Texas-Austin	UTA
Texas A&M University	TAMU
Rice University,	RICE
The University of Texas Medical Branch-Galveston.	UTMB
Oregon Medical Laser Center	OMLC
• Providence St. Vincent Medical Center	PStV
• Oregon Health Sciences University	OHSU
• Oregon Graduate Institute, Portland, OR	OGI
University of Oregon	UO

STATEMENT OF WORK

The scope of work for our DOE Center of Excellence is outlined:

A. DIAGNOSTICS

1. Fluorescence spectroscopy and imaging
2. Reflectance spectroscopy and imaging
3. Raman spectroscopy
4. Other spectroscopy and imaging

B. THERAPIES

1. Photocoagulation therapy
2. Laser welding
3. Cardiology
4. Pulsed lasers
5. Photodynamic therapy (PDT)

Progress in all these areas was achieved and is retrievable in the published work of the following investigators:

UTMDA	Steven L. Jacques
	Sharon Thomsen MD
UTA	A. J. Welch
	Rebecca Richards-Kortum
UTMB	Massoud Motamedi
TAMU	Sohi Rastegar
RICE	Frank Tittel
OMLC, UO	Steven L. Jacques
UO	Michael Raymer

PUBLICATIONS

Our Center has published the following articles directly and indirectly supported by our DOE funding to date in our 6-year period of funding:

Peer-reviewed journals	156
Conference papers	155
Book chapters	27
Conference abstracts	79

STUDENTS

Collectively our Center has graduated during our 6-year period of DOE funding:

18 Ph.D. students
17 M.S. students

OTHER SUPPORT

The Center members have collectively raised over $13.9 million in the past six years. That means we have secured nearly **eight dollars for every seed dollar** from the DOE. The support has been utilized to promote the overall mission of DOE Center of Excellence in the areas of:

1. Basic science and engineering including pre-clinical animal studies
2. Clinical Studies
3. Product Development
4. Education and Training

PATENTS

1. Jacques, S.L., I.S. Saidi, D.G. Oelberg: Method and apparatus for optical measurement of bilirubin in tissue. Assigned to University of Texas. (Awarded 1995.) Licensed to SpectRx, Inc., Atlanta, GA.

2. L. Wang, S.L. Jacques: Ultrasound modulated light transport for imaging biological tissues. Assigned to University of Texas. (Awarded 1995.)

3. S. Thomsen, S.L. Jacques, B-M. Kim: Minimally traumatic interstitial fiber optic probe for optical detection of lethal thermal injury in vivo. (Awarded 1997.) Licensed to Rare Earth Medical, Inc., MA.

4. A. Oraevsky, S.L. Jacques, R. Esenaliev: Optoacoustic imaging with pulsed laser. (Awarded 1998).

CLINICAL IMPACT

Our center has several projects which have or are in progress of translating into the clinic. The following briefly describes these projects.

• Optical monitoring of hyperbilirubinemia in newborns

Bilirubin is a breakdown product of hemoglobin and the trauma of childbirth will often yield a serum load of bilirubin in a newborn. Hyperbilirubinemia is a condition experienced by many neonates whose livers are not yet fully functional in oxidizing bilirubin for secretion into the bile. Consequently, serum levels of bilirubin rise after birth and exceed the holding capacity of albumin for bilirubin. At this point, bilirubin begins to leak from the vasculature into surrounding tissues. In the skin, this condition causes a yellow appearance to the skin called "jaundice". In the brain, the leakage of bilirubin can lead to bilirubin precipitation in brain tissues which causes permanent brain damage, a condition called "kernicterus". With the current trend of hospitals to send mothers home at 1-2 days post partum, there has been an alarming rise in the occurence of kernicterus.

Steven Jacques (UTMDA, OMLC) has developed white-light optical-fiber reflectance spectroscopy for monitoring cutaneous levels of bilirubin as an indicator for hyperbilirubinemia. Improving on previous attempts, the project was based on first principles of light transport in skin and a data base of neonatal skin optical properties as a function of gestational age which was generated from measurements on autopsy skin samples from 26 neonatal still births. The method quantifies the skin melanin, blood content, and dermal scattering before specifying the bilirubin level. Hence, the system is robust against the range of natural skin variation. The system allows non-invasive rapid assessment of cutaneous bilirubin, avoiding the pain of a heel stick to draw blood and the delay and expense of sending a blood sample to the laboratory for analysis.

The clinical project included clinical trials on about 60 neonates at the Neonatal Intensive Care Unit (NICU) at Herman Hospital, Univ. of Texas Health Sciences Center at Houston. The concept was granted a US patent which was licences to SpectRx Inc. (Atlanta) who has proceeded with further clinical testing at several centers on 465 neonates so far and more centers are being included in the trials. Prof. Jacques remains involved in the analysis of clinical data.

SpectRx has now produced a hand-held flash-light with a spectrometer-on-a-chip and a microprocessor which can be used by parents at home. This home-based optical monitoring would be assigned by the hospital to parents for monitoring their newborn's hyperbilirubinemia during the critical first few days after returning from the hospital when bilirubin levels can rise and threaten the newborn. The device should improve parental compliance regarding home testing for hyperbilirubinemia since today parents must use the heel stick method which is painful to the newborn and stressful to the parents.

• Optical detection of cervical dysplasia

Rebecca Richards-Kortum (UTA) has pioneered the use of optical detection of cervical dysplasia. With the help of Michelle Follen Mitchell (UTMDA-Gynecology)

regarding the clinical activities, the help of Sharon Thomsen (UTMDA) regarding pathology, the help of AJ Welch (UTA) regarding tissue optics, and equipment from our previous DOE funding, Prof. Richards-Kortum has developed the use of Laser-Induced Fluorescence (LIF) and Raman Spectroscopy for detection of pre-malignant tissues in the cervix. She has established that LIF detection of cervical dysplasia is a cost-effective method with sufficient sensitivity and specificity to earn a role in assessment and management of cervical disease. She has developed a Raman spectroscopic probe as well for detection of cervical precancers.

Prof. Richards-Kortum now has a Whitaker Foundation award for this project. The project has patents pending and has received industrial support from Patient Technologies Inc. and later from LifeSpex Inc. to support clinical trials.

- **Laser Optoacoustic Imaging System (LOIS)**

Alexander Oraevsky (RICE) and Steven Jacques (UTMDA, OMLC) have been developing a novel approach toward deep imaging of tissues based on acoustic signals generated in absorbing structures such as tumor vasculature in response to pulsed lasers. The method combines the spectral richness of optical spectroscopy with the spatial resolution achieved with sound waves (see proposal).

Alexander Oraevsky has implemented the system in a form suitable for imaging breast cancer when then first begin to become highly vascularized. Working with a team of clinical collaborators at UT MD Anderson Cancer Center (see proposal), a clinical study of 50-100 breast cancer patients scheduled for simple, modified radical, or radical surgical mastectomy will be imaged with X-ray, ultrasound, and LOIS.

The project has a patent pending and is being licensed by a consortium of partners including Spectra Science Inc. (Minnesota) which specializes in minimally invasive medical technologies, a pharmaceutical company producing contrast agents for medical imaging, and a company specializing in piezoelectric transducers (Laser Sonic Tecnologies Inc., Houston).

- **Photodynamic therapy (PDT)**

Steven Jacques (UTMDA, OMLC) has been investigating PDT for treatment of cancer in cell culture and animal models under our previous DOE funding. He was the first to propose the use of prolonged light exposure in combination with ALA/PPIX (δ-aminolevulenic acid-induced protoporphyrin IX). Since PPIX is made in the mitochondria, continuous light activiates the PPIX the moment it is synthesized before it can diffuse from the mitochondria. This strategy appears to improve the efficacy of PPIX by directly targeting mitochondria, an especially sensitive cellular site. He is also preparing to participate in studies with PDT Inc. ($SnET_2$ photosensitizer) and Pharmacyclics Inc. (Texaphyrin photosensitizer).

Upon moving to the OMLC, Prof. Jacques began organizing a **PDT Cancer Treatment Center** at PStV Medical Center. The program is a mixture of standard FDA-approved insurance-reimbursed protocols for obstructing esophageal cancer and for lung cancer (by end of 1997) using the photosensitizer Photofrin™, and pilot IRB-approved clincal studies on new applications. The new applications being developed are treatment of prostate cancer (with Dr. Brian Shaffer) and Barrett's esophagus, a

premalignant condition (with Drs. George Koval and Rodger Sleven). The first esophageal patient is scheduled for treatment on Sept. 17. Prostate studies should begin this Winter. The website for the **PDT Cancer Treatment Center** can be reached via **http://ece.ogi.edu/omlc/pdt**.

- **Veterinary applications of PDT and fluorescence**

Sohi Rastegar and Theresa Fossum DVM, PhD (TAMU) are bringing optical technologies for diagnosis and treatment to the veterinary clinic. A Veterinary Medical Laser Laboratory has been established at TAMU College of Veterinary Medicine with Dr. Fossum. Photodynamic therapy is being investigated and applied in veterinary health care (see proposal on PDT for oral cancer). In addition to helping veterinary health care, the program provides a venue for performing spontaneous animal studies which is an important intermediate step between experimental animal studies and clinical studies. Pharmacokinetic and safety studies have been performed for use of the photosensitizer ALA-induced PPIX in the oral cavity of normal dogs. Two veterinary oncologists have joined the TAMU team and will assist in performing PPIX fluorescence studies in dogs with suspicion of oral cancer who are scheduled for biopsy.

- **Real-time optical feedback during photocoagulative therapy**

Beop-Min Kim (TAMU and now at LLNL), under the co-supervision of Profs. Rastegar, Motamedi, and Jacques, worked with Drs. Levy and Dr. Sharon Thomsen MD (UTMDA) on development and application of a catheter for in-vivo measurement of optical properties in intraluminal geometry, for the prostate. He also developed a non-linear finite-element model for analysis of thermally induced changes in optical properties and perfusion in the prostate. The project led to a patent application on a real-time optical monitor, an interstitial optical fiber placed with a needle into the liver during transcutaneous liver photocoagulation or the prostate during transurethral photocoagulation of benign prostate hyperplasia.

This patent was licensed by Rare Earth Medical Inc. (Massachusetts) and the project received NIH SBIR funding. Dr Thomsen is pursing the project, applying the concept to monitoring of liver during photocoagulation of liver tumor nodules.

- **Prostate disease: benign prostate hyperplasia (BPH)**

Massoud Motamedi (UTMB) has pioneered the use of laser photocoagulation for treatment of Benign Prostate Hyperplasia (BPH).

The human studies were conducted under approved human protocols. The DOE grant supported the basic development and design efforts using animal and phantom tissue models which catalyze this technology transfer. Their clinical studies suggest that laser treatment of BPH causes less patient trauma, fewer complications such as bleeding, requires shorter hospital stay, and can be performed much faster than current techniques with possibly local anesthesia Today they have treated over 50 patients with BPH using the approach developed in our preclinical animal studies. The results are highly encouraging and have been reported at both national and international meetings.

Learning from their experience using low power Nd:YAG laser, they developed a protocol using diode laser for treatment of BPH. To date 11 patients have been treated using diode laser with a side firing laser catheter. Among this group, four patients were

treated under local anesthesia. This shows the great potential for this procedure to become an office-based procedure in the near future.

They also have been testing the efficacy and safety of laser procedure for patients who fail to meet the criteria for TURP (gold standard) and who would otherwise require open prostatectomy The preliminary findings suggest that laser treatment of BPH appears to offer an effective and safe alternative to open prostatectomy, and associated with reduced morbidity, hospital stay, convalescence and cost. Six patients have been treated who have very large prostates, fail to meet the criteria for TURP, and would otherwise require open prostatectomy. The findings suggest that laser treatment of large prostate that would otherwise require surgery is effective and a safe alternative to open prostatectomy, and associated with reduced morbidity, hospital stay, convalescence and cost.

Motamedi and colleauges were able to further increase their collaboration with industry to facilitate the transfer of this technology to clinical arena. The support from the DOE enabled collection of additional preliminary results needed to secure further external funding needed to develop the proposed system. Since the DOE grant was awarded, they have received additional funding of over one million dollars from federal agencies and industry to support clinical and technology development research for laser therapy of bengin prostate hyperplasia.

- **Laser thrombolysis: acute myocardial infarction and stroke**

Kenton Gregory and Scott Prahl (OMLC) have been working no the use of pulsed lasers to remove blood clots during myocardial infarction and stroke.

They have conducted a pilot clinical trial at Providence St. Vincent Medical Center (PStV) in which clots during myocardial infarction were removed with a pulsed dye laser.

An interesting story: At a wedding in Portland, the minister collapsed due to a heart attack. One of the OMLC staff was at the wedding and arranged for the minister to be rushed to PStV for laser thrombolysis. Within hours the patient's episode was over and he was out of the hospital by the next day.