Award Number: DAMD17-98-1-8186

TITLE: Measurements of Breast Tissue Optical Properties

PRINCIPAL INVESTIGATOR: Albert Cerussi, Ph.D.

CONTRACTING ORGANIZATION: University of California
Irvine, California 92697-1875

REPORT DATE: October 1999

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Measurements of Breast Tissue Optical Properties

Albert Cerussi, Ph.D.

University of California
Beckman Laser Institute and Medical Clinic
1002 Health Sciences Road, East
Irvine, California 92697-1875

e-mail: acerussi@bli.uci.edu

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

Near-infrared light offers unique possibilities for extracting physiological information from within biological tissues without injections, surgery, dangerous radiation, or great expense. Near-infrared light probes a centimeter deep or more, allowing non-invasive measurements below the skin surface. By separating tissue absorption from tissue scattering, near-infrared optical tissue spectroscopy quantifies the concentration and the oxygenation state of hemoglobin. Thus, one can characterize breast lesions and physiology in non-invasive fashion. Such information may provide new criteria for judging lesions as benign or malignant, and minimize the ambiguities and false-negatives encountered in conventional breast examinations.

Optically monitoring physiological changes in breast tissue also provides a new way to look at disease progression and prevention. Using our custom-built instrument, we have observed in vivo changes in hemodynamics and structure that are characteristic of tumors. In addition, we have observed in vivo changes in breast tissue physiology resulting from hormone replacement therapy, menopausal status, and estrous cycle. Because our technique is safe, non invasive, and comparable in cost to ultrasound, patients can be studied as often as necessary without risk. Currently, we are preparing to perform extensive clinical measurements on women with breast tumors and on volunteers receiving hormone replacement therapy with estrogen/progesterone, tamoxifen, and raloxifene.
FOREWORD

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Albert Cerny  18 October 99
PI - Signature  Date
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INTRODUCTION

Near-infrared light offers unique possibilities for revealing physiological information from within biological tissues without injections, surgery, dangerous radiation, or great expense. Although it has been known for some time that non-ionizing near-infrared light penetrates a few centimeters into biological tissues, only recently have scientists been able to take advantage of this penetration by taking into account tissue scattering. Near-infrared light provides a way to quantify the concentration and the oxygenation state of hemoglobin and also the scattering properties of the tissue and thus provide criteria to characterize breast lesions in vivo without surgery. This optical information will provide clinicians with entirely new criteria for deciding if lesions are benign or malignant, which may help reduce some of the ambiguities and false-negatives currently encountered in conventional breast examinations.

Optically monitoring physiological changes in breast tissue also provides a new way to look at both disease progression and prevention. Using near-infrared light from an instrument we have developed, we have observed changes in hemodynamics and structure that are characteristic of tumors. In addition, we have also observed changes in breast tissue physiology resulting from hormone replacement therapy, menopausal status, and estrous cycle stage. Because our technique is safe, non-invasive and comparable in cost to ultrasound, patients can be studied as often as necessary without risk. Currently, we are in the process of performing clinical measurements on women with breast tumors and on normal volunteers receiving hormone replacement therapy with selective estrogen receptor modulator drugs (such as tamoxifen).
DATES OF ACTIVATION

Although this grant was activated in October of 1998, I did not start work officially until mid-February of 1999. Dr. Joshua Fishkin, who is no longer working at the Beckman Laser Institute and Medical Clinic (BLIMC), wrote the original proposal, “Measurement of Breast Tissue Optical Properties”. I assumed his role in this proposal, starting in mid-February of 1999.

ITEMS IN THE ORIGINAL SPECIFIC AIMS

For convenience, I will list below summaries of the specific aims of the original proposal, “Measurement of Breast Optical Properties”:

(1) Optimize the instrumentation and theory currently used to extract the absolute optical absorption and reduced scattering parameters.

(2) Perform clinical measurements of breast tissue optical properties in order to determine exact absorption and scattering factors in different tissue regions.

(3) Compare optical property measurements to gross pathology, histopathology, ultrasound, and mammography results in order to determine absorption and scattering factors characteristic of tumor and normal tissue.

In the following section, I will relate to you all of the research-related experiences I am gaining as a Post-Doctoral Fellow in Dr. Bruce Tromberg’s laboratory. Within each training area I will demonstrate how I am pushing forward in each of these three specific aim items (listed as Items in the section below).

PROGRESS IN TRAINING AND SPECIFIC AIMS

Summary
My work at the BLIMC to date has been teaching me to translate new ideas into reality within the medical research field. Since my arrival in mid-February 1999, I have been exposed to several different problems of interest related to the early detection and assessment of breast cancer. My training has encompassed several different levels, as I outline below.

Protocol Design, Construction, and Implementation
The first aspect of my training has been to design, write, and manage protocols involving human patients. The most prolific of my protocol experiences has been the design, construction, and
implementation of a new human subjects research protocol. This new protocol is quite ambitious in scope, and it involves the coordination of researchers, clinicians, and administrators on many different levels.

The subject of this trial is the introduction of optical methods as a means to assess anti-estrogenic compounds that are known to prevent breast cancer in women known to be at high risk for the disease. The National Surgical Adjuvant Breast and Bowel Project (NSABP) have begun a new trial across the nation, the “Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer.” The Chao Family Comprehensive Cancer Center at UCI is enrolled as a STAR center. Dr. Joshua Fishkin did not mention this new STAR optical trial in the original Statement of Work. However, I am convinced that this novel study conforms very neatly to the scope of the original Statement of Work, and presents a unique opportunity where optical methods could provide a significant impact upon the laborious fight against breast cancer.

My colleagues and I propose in this new protocol to measure the functional changes in breast tissue resulting from tamoxifen and raloxifene using our non-invasive optical technique, as described in the original proposal. Our approach is unique because it provides functional hemodynamic information without ionizing radiation or drawing a single drop of blood, in a cost-effective and rapid manner. In this measurement, we plan to determine the absolute concentrations of deoxygenated hemoglobin, oxygenated hemoglobin, water, and lipids, as well as calculate the hemoglobin saturation (SaO₂) and the blood volume fraction for different regions on the breast. Further, we will measure the tissue scattering, which allows us to infer cellular structure information, such as the cellular volume fraction. The goal is to generate a low-resolution functional map of the breast in order to indicate the effects of hormone replacement therapy drugs. Ultimately this information may be used to predict efficacy, minimize side effects, and enhance our understanding of breast physiology.

Designing and writing this protocol has been a tremendous experience for me. Learning how to describe my vision for research to the medical and administrative community will be quite a valuable skill that I will use frequently in my future and present work. As of this writing, the protocol I have written UCI# 99-2183, entitled “Non-Invasive Functional Mapping of Breast Tissue Physiology Using Quantitative Near-Infrared Spectroscopy: Effects of Selective Estrogen Receptor Modulators (A Pilot Study Subset o the STAR NASBP Protocol P-2),” has passed the UCI Internal Review Board Committee Review, and is pending for its final Administrative Review.

This study goes beyond the scope of the original Statement of Work, but is closely related to Item #3. The ability to correlate non-invasive optical measurements with actual breast physiology is of paramount importance in correctly diagnosing cancer because our technique is inherently sensitive to physiological changes in the tissue. In addition, the novel work described by this new protocol may provide key information for the important goal of promoting cancer prevention by helping reveal the effectiveness and mechanisms of cancer prevention medications.
Clinician Interaction
Designing and implementing human patient research necessitates the need for interaction with clinicians. For example, I have been very fortunate to be able to work with Dr. Randall Holcombe and Donna Jackson at the Chao Family Comprehensive Cancer Center at UCI. Both have provided a lot of clinical insight into the STAR optical protocol, as well as insight into how one performs clinical research in general. Clinicians, of course, have a different perspective on medical-based research than physicists and chemists, and know which problems will have great impact upon the medical community. The interaction I am experiencing with medical practitioners is vital to my development as a breast cancer researcher, since I will always have to rely upon clinicians in order to execute any clinical measurements. The Beckman Laser Institute and Medical Clinic at UCI is one of the few places in the world were I could so easily obtain this essential interaction and feedback.

This type of interaction is important for Item #2. Since the eventual instrumentation will be in the hands of clinicians, it is important for them to have used the equipment and generate feedback so that researchers will know what will be important for future research.

Instrumentation
Another area of learning for me has been in the repair, design, and construction of near-IR clinical instrumentation. Upon my arrival, our original Frequency-Domain Photon Migration (FDPM) instrument was in the process of an upgrade. I spent considerable time in repairing and improving the instrument, which is now functional once again. In addition, I am working on the construction of a second FDPM instrument that will be dedicated for clinical measurements. Our eventual goal is to have multiple instruments in order to facilitate performing clinical measurements.

As a result of this hands-on experience, I have been able to assess the shortcomings of our current instrumentation, and have sought out ways to improve it. I am building some of these changes into the second instrument. I hope at some point to construct another instrument with even more improvements.

The ability to translate measurement ideas into a working instrument is also a challenging area of clinical research. The experience of working with hands-on cutting-edge instrumentation will also benefit my career as a breast cancer researcher. When the need arises to develop or exploit some clinical concept, I will have experience in designing and developing the tools clinicians need to perform actual measurements.

These points are closely associated with Item #1. Our revisions to the instrumentation will help improve the quality of our future measurements. Dr. Bruce Tromberg and I have discussed several exciting alternatives in our measurement conditions that could improve our current measurements (although I have not yet developed these ideas). In addition, having a second functional instrument will help us assess more patients, and thus make Item #2 an easier goal.
Working with Students
As a Post-Doctoral Fellow in Dr. Bruce Tromberg’s laboratory, I have had the chance to interact with his graduate and undergraduate students. This interaction has proven to be a valuable asset to my training since student interaction is the backbone of academic research. Not only have I been able to help the students work on their own projects, but also I have been able to branch out in my work in breast cancer as a result.

For example, I have been working very closely with Ryan Lanning. He is working on providing measurements of the excised tumors of breast cancer patients. This information will allow us to try and correlate our optical measurements with the histopathology of the tumors in an effort to differentiate tumors in vivo by their specific optical signatures. In addition, Ryan and I will be performing measurements on human tumors in mice (which is covered on a different protocol which is pending approval) in order to better understand this key link between the microscopic tumor characteristics (i.e., vessel counts, collagen disruption) and the macroscopic optical properties that we measure in vivo.

I have also worked closely with another of Dr. Bruce Tromberg’s students, Natasha Shah. Building upon work she has started some time ago, we are looking at how normal physiological variations in breast tissue affect our optical measurements. This information is critical for breast cancer research since normal physiological variations in the breast might conceal cancerous or pre-cancerous lesions in the tissue. In order to enhance the sensitivity of the optical method, we must understand how our measurements are sensitive to these daily physiological variations in breast tissue. Such work is rather scarce in our field, and we are ready to begin some extensive measurements on volunteers in order to assess normal variations in breast tissue that affect optical measurements.

My interaction with Bruce’s students is also preparing me for the time when I may have students of my own. Although this in and of itself does not satisfy a particular specific aim, the results of these interactions will be of tremendous value in attacking Item #3. Both of the projects listed above will help define the sensitivity of optical methods in breast tissue, which is the spirit behind Item #3. In addition, as a result of looking at both normal and cancerous tissue we have begun to see patterns in the tissue that are consistent with how we believe cancerous growths will perturb optical signals in breast tissue. Learning how to exploit these patterns will help us employ new measurement strategies, which is the meaning behind Item #1.

Attendance at Conferences
I was also fortunate to attend the 1999 California Breast Cancer Research Symposium in Los Angeles, California this September. This distinctive meeting combines a strong research program along with social and psychological aspects of the disease. My attendance at this conference was very fruitful since it broadened my horizons in three areas. First, the conference exposed me to different problems of interest in breast cancer research. Some of these problems have led to discussions involving future research collaborations, particularly in the area of how breast physiology relates to the onset and the progression of breast cancer. Second, the conference brought me up to date on new developments in breast cancer research. I heard several exciting talks presented by key researchers, including Dr. Richard Love (University of
Wisconsin-Madison) on the effects of chemopreventative therapy, Dr. Ana Soto, (Tufts University) on the effects of environmental estrogens, Dr. Laura Esserman (University of California at San Francisco) on improving screening mammography, Dr. G. Shyamala (Lawrence Berkley National Laboratory) on the role of steroid hormones in normal breast development and cancer, and Dr. Susan Love (University of California at Los Angeles) on the overall status of breast cancer research. Finally, the conference demonstrated the reality of the disease on a personal level. It is one thing to look for cancer cells in the lab; it is an entirely different experience to see breast cancer survivors and realize that these are the people that you are trying to help. In addition to all of the knowledge I gained at the meeting, my work in Dr. Bruce Tromberg's lab received prominent recognition with the Cornelius L. Hopper Scientific Achievement Award for the “Most Innovative” poster.

**TARGETS FOR NEXT YEAR**

Clearly it is disappointing in that I cannot report mass amounts of clinical measurements at this time. I was able to measure only one (normal) patient during my initial seven-month stay here at the Beckman Laser Institute. The original measurement protocol, UCI 95-563, entitled “Measurement of Breast Tissue Optical Properties,” had to be extended, and is currently awaiting approval. I fully expect the protocol to be activated sometime within the next two months maximum. Between upgrading the instrument and extending our protocol, I had very little time when our protocol was active with a working instrument in order to perform clinical measurements. However, I am now on the verge of performing extensive clinical measurements, and I plan on presenting a variety of clinical results at the US Army meeting next June.

In addition, I am also hoping that a series of related measurements will help provide valuable insight into optical breast cancer detection and assessment. Studying the effect of hormone replacement therapy in breast tissue may provide key information that will aid in distinguishing benign from cancerous tissue. In addition, measurements on human tumors in mice may also provide the link needed to characterize tumors by their optical properties.
APPENDIX TO SUMMARY

Research-Related Accomplishments
- initiation of a new protocol to measure the effect of breast cancer prevention drugs on the physiology of breast tissue as a predictor of drug efficacy.
- installation of a 915 nm diode for quantifying fat content in the tissue
- original instrumentation back on line
- second generation instrument completion pending

Reportable Outcomes
- Cornelius L. Hopper Scientific Achievement Award for “Most Innovative” poster, issued at the 1999 California Breast Cancer Research Symposium on 18 September 1999.