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13. ABSTRACT (Maximum 200 words) This grant provided support to expand the scientific program and infrastructure at the University of Washington's Center for Industrial and Medical Ultrasound (CIMU). The many disparate facilities and technical capabilities available to CIMU staff and students were integrated and enhanced to provide a world-class, advanced research center for bioengineering development and graduate education in high-intensity, focused ultrasound (HIFU). This included leveraging of overall research in understanding of acoustic hemostasis and improvement of research tools. Significant progress was made in developing a highly automated transducer characterization capability. Features include acoustic field mapping by scanned hydrophones, acoustic power efficiency measurement, electric and acoustic impedance measurement, medical ultrasound imaging and RF data collection, optical methods of acoustic field mapping (Schlieren apparatus), and for each system a convenient software interface and user manual. Specialized fixtures and instruments were developed to measure HIFU dose response <i>in vitro</i> , an essential component of developing reliable and realistic computer models for HIFU simulation and treatment planning. Single-element HIFU transducers were refined with liquid, gel, and solid coupling media and other improvements to be more powerful, convenient, and robust. These technological enhancements have enabled the development of HIFU arrays and image-guided ultrasound systems for greater flexibility and control in clinical treatment protocol. Lastly, significant bioacoustic model development was undertaken for use in practical engineering design as well as for fundamental research of the mechanisms of ultrasound therapy.				
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**FINAL TECHNICAL REPORT FOR ONR GRANT N00014-99-1-0982  
"MEDICAL ULTRASOUND TECHNOLOGY RESEARCH AND DEVELOPMENT AT  
THE UNIVERSITY OF WASHINGTON CENTER FOR INDUSTRIAL AND  
MEDICAL ULTRASOUND"**

**Lawrence A. Crum, Principal Investigator**

**I. Background**

This grant supported a research effort to understand more fully the basic science issues that comprise High Intensity Focused Ultrasound (HIFU) technology, and to build the basis for more expansive development of this general technology. Specific areas of interest included the use of HIFU in the treatment of hemorrhagic trauma and related pathological conditions, especially in organs that are difficult to treat using conventional medical and surgical techniques. Direct applications include combat casualty care, as well as many civilian uses in non-invasive or minimally invasive trauma management, bloodless surgery, and ultrasound-mediated drug therapy. Research efforts also explored imaging and simulation techniques associated with treatment, targeting and monitoring the effectiveness of HIFU therapy. A significant portion of the grant was directed toward renovation of laboratory spaces to enable the research efforts described above. The period of performance of the grant was from 1 July 1999 to 30 June 2003.

**II. Accomplishments**

**A. Executive Summary**

This grant provided support to expand the scientific program and infrastructure at the University of Washington (UW) Center for Industrial and Medical Ultrasound (CIMU). The broad objectives falling within this scope included:

- To understand more fully the physical and biological mechanisms that give rise to acoustic hemostasis and HIFU surgical lesion production.
- To develop techniques for the utilization of gas-filled ultrasound contrast agents in the detection and localization of bleeding.
- To develop and validate theoretical models of acoustic hemostasis and HIFU surgical lesion production.
- To develop techniques for the real-time monitoring of HIFU-induced lesions in tissue.
- To develop additional laboratory transducer designs that produce acoustic hemostasis and HIFU lesions, and to extend these laboratory designs toward engineering prototypes.
- To understand more fully and to optimize the physical and biological mechanisms that give rise to ultrasound-mediated drug delivery.

During the performance period the many disparate facilities and technical capabilities available to CIMU staff and students were integrated and enhanced to provide a world-class, advanced research center for HIFU bioengineering development and graduate education. Program funds were used to leverage overall research efforts in understanding of acoustic hemostasis and improve research tools. Significant progress was made in developing a highly automated transducer characterization capability, including providing dedicated instrumentation and facilities for this purpose. Features include acoustic field mapping by scanned hydrophones, acoustic power efficiency measurement, electric and acoustic impedance measurement, acoustic and material parameter measurement, medical ultrasound imaging and RF data collection, optical methods of acoustic field mapping (Schlieren apparatus), and for each system a convenient software interface and user manual. Specialized fixtures and instruments were developed to measure HIFU dose response *in vitro*, an essential component of developing reliable and realistic computer models for HIFU simulation and treatment planning. Single element HIFU transducers were refined with liquid, gel, and solid coupling media and other improvements to be more powerful, convenient, and robust. These technological enhancements have enabled the development of HIFU arrays and image-guided ultrasound systems for greater flexibility and control in clinical HIFU treatment protocol. Lastly, significant bioacoustic model development was undertaken for use in practical engineering design as well as for fundamental research of the mechanisms of ultrasound therapy.

## **B. R&D Facilities Improvements**

A significant portion of this grant was directed toward renovation of laboratories to support research efforts at the newly created Center for Industrial and Medical Ultrasound. Space was acquired in the University of Washington Old Fisheries Center (OFC), conveniently located near the UW's Medical Center and Health Sciences buildings, but facilities improvements were urgently needed. Working in careful coordination with facilities crews from both the Applied Physics Laboratory and Main Campus, the best possible use was made of renovation funds provided under this grant.

One of the major benefits of the laboratory renovation has been to create good quality laboratory facilities that are proximal to the clinical facilities i.e. the UW Medical School and Medical Center. This location allows clinicians to be able to interact with the laboratories and still be closely available to their clinical duties. This becomes increasingly important as diagnostic and therapeutic ultrasound projects involve more clinical input. It is also more convenient for the subjects/patients. The proximity of the location to the Dept. of Radiology is particularly important for projects such as vascular ultrasound where input is needed on imaging and image guided therapy. The ultrasound patient studies laboratory (OFC room 119) provides specially-needed facilities for obtaining 3D images, eg. a non-magnetic environment for image registration.

Other highlights of the renovation efforts are described and illustrated in the following paragraphs.

### *OFC Room 102N: Joint Imaging Laboratory*

This laboratory was the most significantly in need of repair, as it contained unidentified chemicals, discarded nonfunctional equipment, and peeling lead-based wall and fixture paint. Lead-based paint abatement was completed, new paint applied, and the rusted countertops were sanded and buffed; before and after photographs are shown in Figure 1. This lab now serves as the joint imaging lab, used by multiple investigators working on new ultrasound imaging and detection algorithms, and systems integration for image-guided therapy.

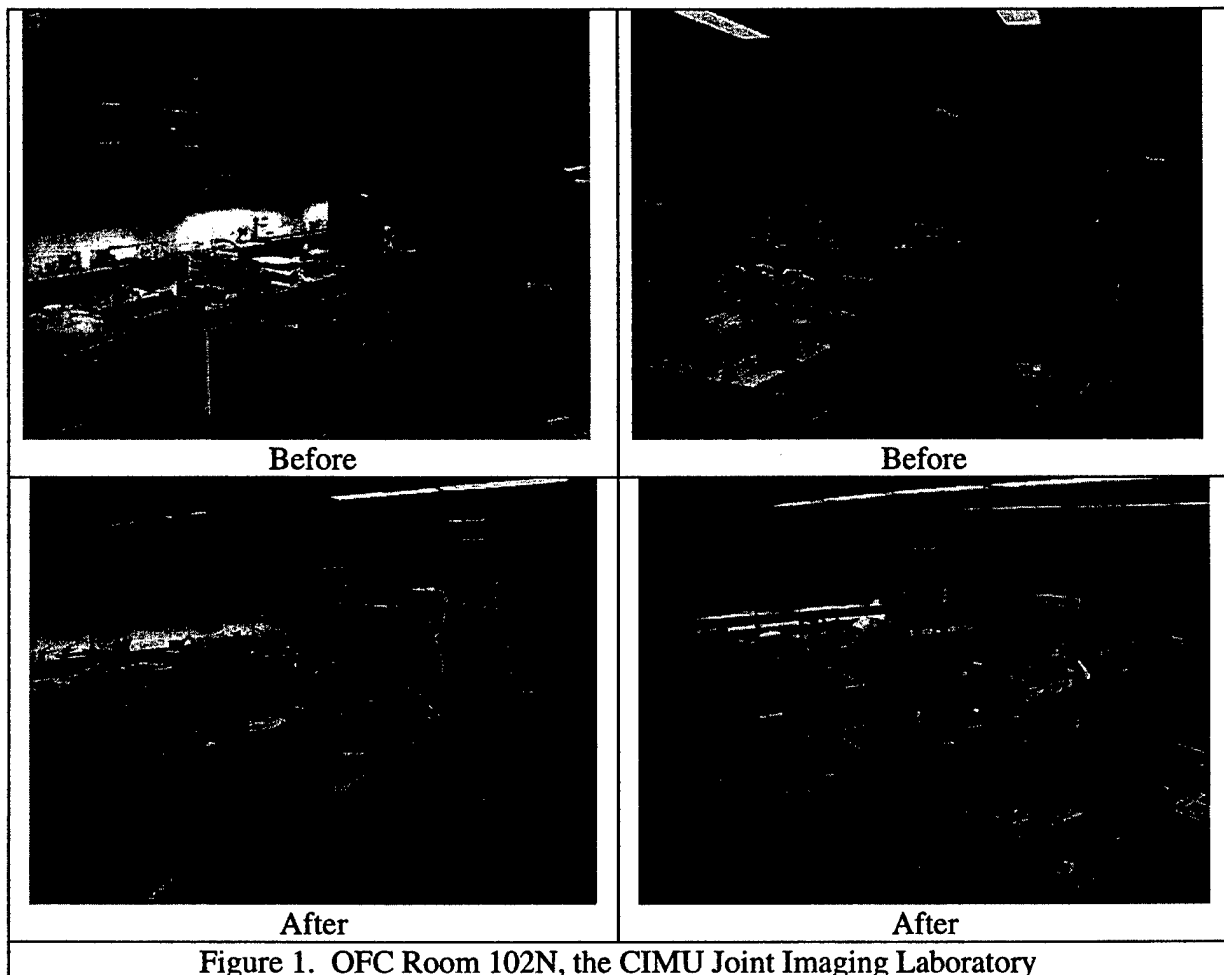
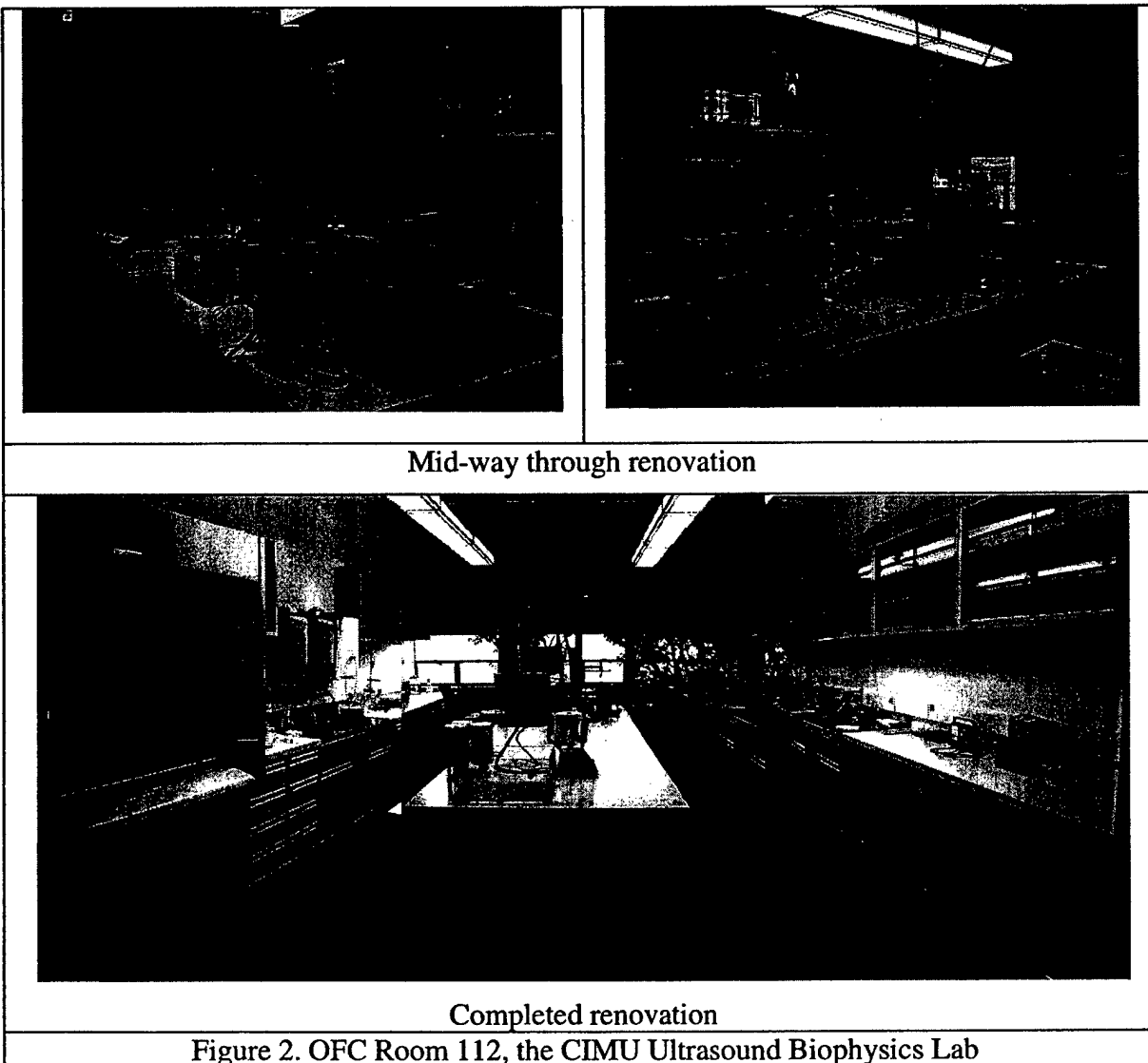


Figure 1. OFC Room 102N, the CIMU Joint Imaging Laboratory

### *OFC Room 112: Ultrasound Biophysics Laboratory*

This laboratory was completely remodeled to serve as an ultrasound bioeffects laboratory for both *in vitro* and *in vivo* experimentation. It had been a radiation biophysics lab with extremely limited peripheral bench surfaces, no work surface in the center of the room, worn-out wooden cabinetry, and very low quality water supply. The original walls contained asbestos, which required significant abatement efforts. The laboratory now features modern steel cabinetry, spacious bench areas, including a sizable central island affording unrestricted access to large and complex experimental setups (or animals) from all sides, and providing a great deal of flexibility with respect to equipment configuration. All surfaces are clad in

impermeable materials and can be chemically disinfected to remove either potentially biohazardous contaminants or to prepare surfaces for animal research. Abundant 120 V (and one 220 V) power drops were installed overhead to permit the use of a large number electronic instruments without encumbering the work surfaces with power cords. The lab now has two spatially separate sink areas (one dedicated to conventional use, and the other dedicated to disposal of biohazardous fluids and initial decontamination of equipment exposed to biohazardous fluids). A high quality water purifier has been installed. Basic utilities (gas, compressed air) are available in a large fume hood used for various chemical procedures. The lab is equipped with instrumentation for transducer characterization/exposimetry, apparatus for sonication of *in vitro* and *in vivo* biological specimens, a dual-beam spectrophotometer, a small drying oven, and is amenable to general chemistry operations (preparation of gel phantoms, *etc.*). See Figure 2 for photographs during and following the renovation.



#### *OFC Room 114: Tissue Culture/Media Preparation Lab*

This laboratory is composed of a larger outer room, and two small inner rooms. The outer room and one of the two inner rooms have been renovated; the second inner room was left unaltered since its primary purpose is to store voluminous tissue culture supplies and other consumables. Photographs are shown in Figure 3. The second small inner room, which required lead-liner removal, was transformed into a dedicated tissue culture facility. Installed features include wall-mounted cabinetry for sterile supply storage, a small sink and base cabinet and a drawer unit with disinfectable work surface. The room houses a laminar flow hood for aseptic transfers, a CO<sub>2</sub> incubator, a Coulter Z1 particle counter, a clinical centrifuge, vacuum pump, and water bath. The renovated outer room contains a central island work bench, a sink and base cabinet, and several wall-mounted cabinets for glassware storage. The principal purpose of this room is for media preparation, but it was also designed to accommodate *in vivo* studies of small animals. Installed equipment includes an old but serviceable fume hood (existing), an ice machine, and a small autoclave for sterilization of tissue culture supplies and the degassing of water for use in ultrasound tanks. Appliances or mobile equipment/supply items include a refrigerator (media and/or biological specimen storage), balances, pH meters, chemical storage cabinet and salts, *etc.*

#### *OFC Room 125: CIMU In Vitro/Ex Vivo Studies Laboratory*

This room was also completely renovated, having had only exposed concrete walls and floors and primary use as a storage area – see Figure 4. This room is located in the western wing of the building, near the CIMU ultrasound patient studies and systems development laboratories. Room 125 now is used by all CIMU staff and students to conduct bench top, *in vitro* experiments, involving tissue characterization, tissue-mimicking phantom production, and transducer fabrication. It also houses a wall-mounted water distiller that is heavily used by CIMU staff and students working in this far wing of the building. A small refrigerator provides chemical storage.

#### *OFC Room 102M: CIMU Ultrasonic Characterization Laboratory*

This room required minor renovations, including installation of plumbing and a small sink, new paint, new power and communications conduit, and custom curtains for the optical studies area. A photograph of the workspaces is provided in Figure 5. The laboratory is used by all staff and students to conduct transducer radiation force, field mapping and schlieren optical measurements. *In vitro* and *ex vivo* HIFU dose response and lesion monitoring studies are also conducted in this laboratory.

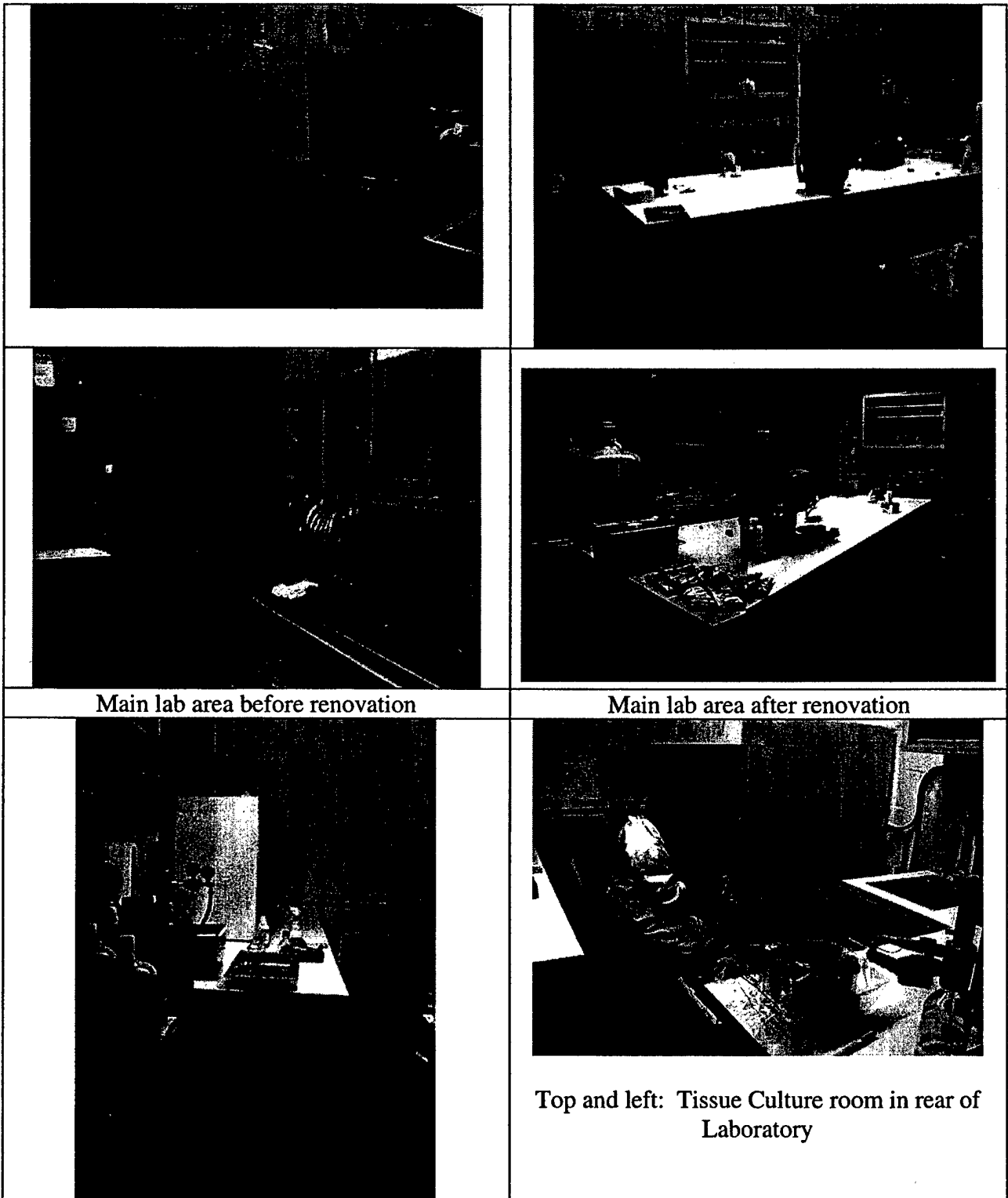
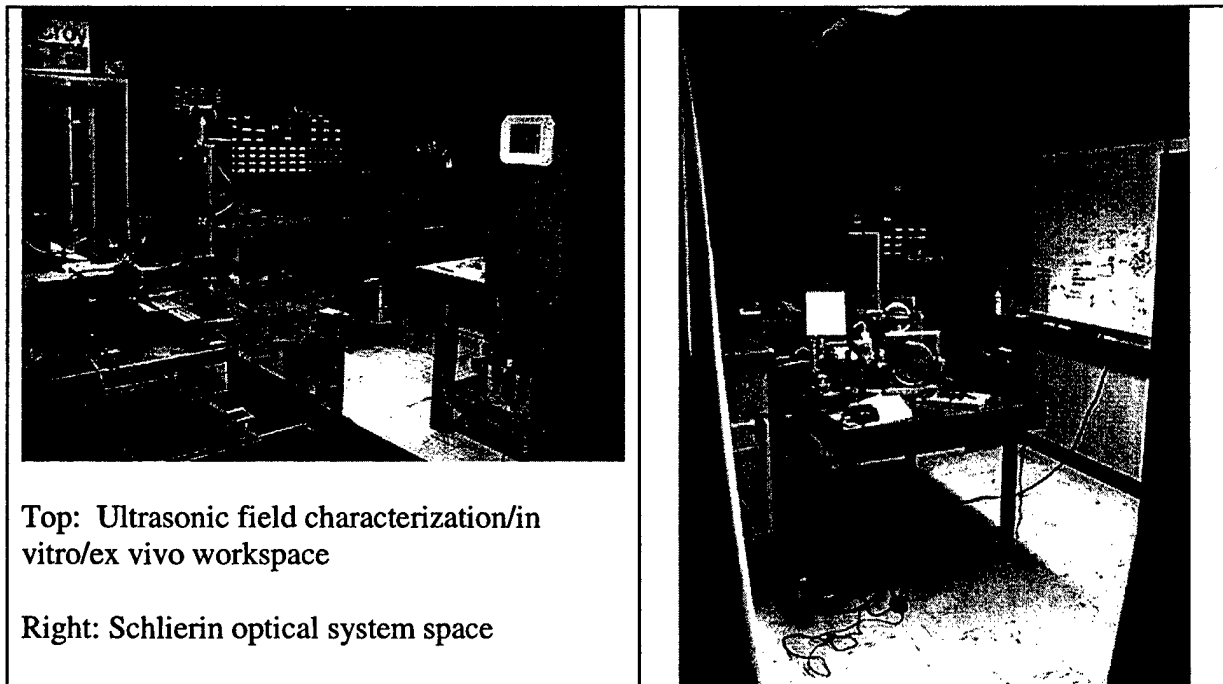


Figure 3. OFC Room 114: CIMU Tissue Culture/Media Preparation Lab



Figure 4. OFC Room 125CIMU Bioeffects Laboratory



Top: Ultrasonic field characterization/in vitro/ex vivo workspace

Right: Schlieren optical system space

Figure 5. OFC Room 102M: CIMU Ultrasonic Characterization Laboratory

### C. Research Efforts

As indicated above, this grant enabled the integration of many disparate facilities and technical capabilities to provide advanced acoustic research spaces for HIFU bioengineering development and graduate education. A summary the research highlights from this project is outlined below. This list of graduate student theses supported by this grant is provided in

section II.D. A complete bibliography of research papers and presentations funded by or relevant to this grant is provided in section II.F.

### *C.1 Modeling Efforts*

A 2-D full-wave, fully nonlinear acoustic model was developed as part of a Ph.D. student's dissertation (see Curra under the list of student theses in Section II.F). This type of model is considered the "gold standard," and can be used to benchmark other, particularly approximate models, and to perform the most complete theoretical investigations into the physical and biological mechanisms of HIFU therapy. Full-wave models are highly complex, and thus require both significant computing resources as well as computing time. To reduce computational intensity, efforts also were directed toward the development of an approximate field model, in particular an implementation of a nonlinear parabolic wave equation (the KZK equation). These models have been used to perform simulation studies to support HIFU transducer design and protocol development.

### *C.2 Transducer Design Studies*

During the course of this grant significant progress was made toward developing a highly automated transducer characterization capability with dedicated instrumentation and facilities for this purpose. New capabilities include acoustic field mapping by scanned hydrophones, acoustic power efficiency measurement, electric and acoustic impedance measurement, acoustic and material parameter measurement, medical ultrasound imaging and RF data collection, optical methods of acoustic field mapping (Schlieren apparatus), and for each system a convenient software interface and user manual. Specialized fixtures and instruments were also developed to measure HIFU dose response *in vitro*, which forms an essential component of in the verification and development of reliable and realistic computer models for HIFU simulation and treatment planning. Single element HIFU transducers were refined with liquid, gel, and solid coupling media and other improvements to be more powerful, convenient, and robust. These various technological enhancements have enabled further development of HIFU arrays and image-guided ultrasound systems for greater flexibility and control in clinical HIFU treatment protocol.

### *C.3 HIFU Monitoring Efforts*

Efforts in developing HIFU monitoring techniques were focused on two efforts. The first component focused on using B-mode diagnostic imaging to monitor lesion evolution. This type of monitoring is possible because lesions formed by HIFU are hyperechoic for several seconds after treatment; CIMU studies using overpressure indicate mild cavitation is responsible for the echogenicity in the focal region. At low intensity levels the HIFU focus can be observed using interleaved B-mode imaging for a brief time (1 second or less) without causing permanent damage (i.e. no lesions were found in acute studies at such exposures). This feature enabled targeting with low HIFU exposures before applying HIFU at full treatment levels. Then, by interleaving HIFU therapy with diagnostic ultrasound interrogation, the focal region can be imaged and monitored during therapy application. This effort represents a major thrust of CIMU Image Guided Therapy (IGT) development.

The second monitoring component focused on developing new signal processing algorithms using the raw Radio Frequency (RF) ultrasound backscatter data from a diagnostic ultrasound machine, in this case the HDI-1000 developed by ATL, Inc., in Bothell, WA. Significant treatment information, including tissue motion and tissue temperature, can be obtained from the RF ultrasound data. This research effort was initiated during the latter part of the performance period and is being completed under other grants.

#### *C.4 HIFU Bioeffects Studies*

In order to understand more fully how tissue properties change with HIFU treatment, studies were conducted in which the bulk properties of ultrasound attenuation and sound speed were measured before and after HIFU treatment. These demonstrated that ultrasound attenuation increases after HIFU treatment, whereas the speed sound remains statistically the same. These results are useful in developing treatment protocols and optimizing parameters for image-guided HIFU systems.

Instrumentation was developed to study quantitative *in vitro* dose response and to use in careful comparison with numerical simulations of HIFU therapy. *In vitro* dose response studies were initiated during the latter part of this grant and have continued under other funding vehicles. Of particular interest is investigating the threshold below which results a purely thermal effect and above which results in thermal and mechanical effects, in particular acoustic and/or vaporous cavitation.

HIFU-induced biological mechanisms leading to hemostasis in solid organs and in vascular wounds were investigated, and this effort has continued via funding from other projects. Research was directed specifically at understanding how the tissue emulsion produced during surgical treatment in intraoperative studies is formed and why it aids hemostasis.

#### *C.5 Contrast Agent Studies*

These studies occurred during the early part of the grant and focused on contrast agent microbubble behavior in an ultrasound field. Bubble destruction thresholds, inertial cavitation thresholds, and bubble dissolution rates were studied for a variety of contrast agents. This effort has evolved into a major area of study which is now funded by the National Institutes of Health.

### **D. Degrees and Fellowships Conferred**

The following individuals earned degrees through funding provided in whole or in part by this project

- Francesco Curra, Ph.D., 2001, dissertation title "Medical Ultrasound Algorithm for Noninvasive High Intensity Ultrasound Applications."

- Jonathan Yuen, M.S., 2001, thesis title "Characterization of lesion formation in a tissue- mimicking phantom for focused ultrasound surgery."
- Sandra Poliachik, Ph.D., 2002, dissertation title "An Investigation of the Mechanisms of High Intensity Focused Ultrasound Induced Platelet Activity."
- Tyrone Porter, Ph.D., 2003, dissertation title, "An investigation of the synergy between ultrasound and membrane-disruptive polymers and its effect on cell membranes."

The following individual's Post-Doctoral Fellowship was funded in part by this project:

- Dr. Cyril Lafon.

The following student is continuing research efforts that were initiated under this project:

- Ajay Anand, Ph.D. candidate, dissertation title "A Model-Based Noninvasive Temperature Estimation Technique for HIFU Therapy Monitoring Using Backscattered Ultrasound."

#### **E. Intellectual Property**

One invention disclosure was filed at the University of Washington: 2031-3433 Medusa Version 1.0. The form DD 882, Report of Inventions and Disclosures, will be forward separately from the UW Office of Technology Licensing.

#### **F. Publications**

##### Refereed Journal Articles

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Vaezy S, Martin RW, and Crum LA. Acoustic Surgery. *Physics World* 2001; 14(8): 35-39.

Vaezy S, Martin RW, and Crum LA. High intensity focused ultrasound: a method of hemostasis. *Echocardiography* 2001; 18(4): 309-15.

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Curra FP and Crum LA, "Therapeutic ultrasound: Surgery and drug delivery," *Acoustic Science and Technology*, 24, 6 (2003).

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#### Books or Book Chapters

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Poliachik, S. "An Investigation of the Mechanisms of High Intensity Focused Ultrasound Induced Platelet Activity," Ph.D. Dissertation, University of Washington, 2002.

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Yuen, J, "Characterization of lesion formation in a tissue- mimicking phantom for focused ultrasound surgery," M.S. Thesis, University of Washington, December, 2001.

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