AD_____

Award Number: DAMD17-02-2-0006

TITLE: Center for Integration of Medicine and Innovative Technology (CIMIT)

PRINCIPAL INVESTIGATOR: John A. Parrish, M.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, Massachusetts 02114

REPORT DATE: October 2002

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2002	Annual (1 Oct 01 - 30 Sep 02)

4. TITLE AND SUBTITLE
Center for Integration of Medicine and Innovative Technology (CIMIT)

5. FUNDING NUMBERS
DAMD17-02-2-0006

6. AUTHOR(S):
John A. Parrish, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Massachusetts General Hospital
Boston, Massachusetts 02114

EMail: jparrish@cbrc.mgh.harvard.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Original contains color plates: All DTIC reproductions will be in black and white.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

The Center for Integration of Medicine and Innovative Technology (CIMIT), is a consortium of nonprofit Massachusetts-based institutions led by Massachusetts General Hospital and includes Brigham and Women's Hospital, Massachusetts Institute of Technology and Draper Laboratory. The primary aim of the Center is to develop technologies that will advance the capability of modern medicine to diagnose and treat patients using minimally invasive and less costly approaches. CIMIT will coordinate and implement research programs in cardiovascular disease, cancer, stroke, trauma and critical care, that are supported by basic science and engineering development in biomaterials, endoscopic tools, energy delivery, intelligent decision systems, medical imaging, micro-sensors, outcomes, robotics and simulation. A unique military/civilian partnership fostered by CIMIT will allow DOD technologies to be evaluated by CIMIT investigators and facilitate the transfer to the military of successful minimally invasive approaches developed at CIMIT. An educational program, which includes coursework, seminars, and on-site training opportunities, will serve the shared needs of academic and military physicians and scientists. The overall goal of CIMIT is to create a national program that combines clinical and technological excellence in order to generate, develop, and reduce-to-practice innovative and high-impact concepts in minimally invasive therapy.

14. SUBJECT TERMS:
medicine, technology, integration, minimally invasive, diagnosis

15. NUMBER OF PAGES
144

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

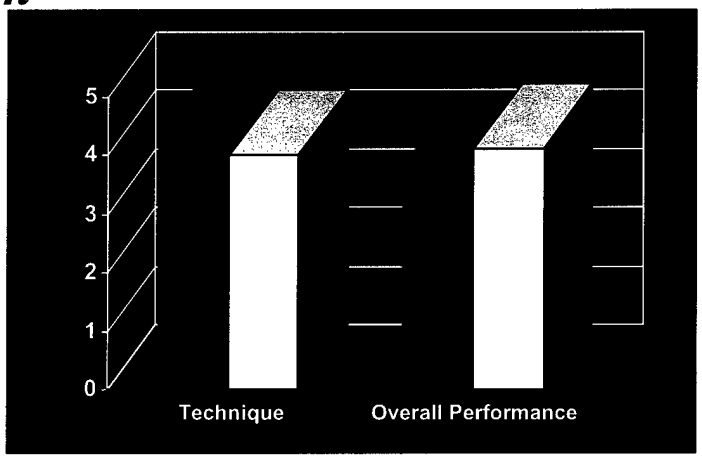
CIMIT *Innovative Technology for Medicine*

VIRGIL™

Chest Trauma Training System

from Development

to Validation



Top: CIMIT team, led by Dr. Steve Dawson (second from right), developed VIRGIL™.
Bottom: Results of first validation trials using VIRGIL™.

Annual Progress Report

October 1, 2001 – September 30, 2002

DAMD17-02-2-0006

DAMD17-02-2-0006

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

X	Where copyrighted material is quoted, permission has been obtained to use such material.
X	Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.
X	Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.
X	In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).
X	For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45 CFR 46.
X	In conducting research utilizing recombinant DNA, the investigator(s) adhered to NIH Guidelines for Research Involving Recombinant DNA Molecules.
X	In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

James E Myatt 10/29/02

SIGNATURE DATE

CENTER FOR INTEGRATION OF MEDICINE AND INNOVATIVE TECHNOLOGY
Annual Progress Report - October 1, 2001 – September 30, 2002

TABLE OF CONTENTS

CENTER FOR INTEGRATION OF MEDICINE AND INNOVATIVE TECHNOLOGY
Annual Progress Report - October 1, 2001 – September 30, 2002

1.0 INTRODUCTION

The Center for Integration of Medicine and Innovative Technology (CIMIT) has completed the first year of DoD support under Cooperative Agreement Number DAMD17-02-2-0006. CIMIT is a non-profit consortium of world-leading academic and research institutions founded by Partners HealthCare System, Massachusetts General Hospital, Brigham and Women's Hospital, Massachusetts Institute of Technology, and Charles Stark Draper Laboratory. The overall goal of the program has evolved beyond minimally invasive therapy to include other aspects of acute care using high technology approaches.

CIMIT's mission is to improve patient care by bringing together scientists, engineers, and clinicians to catalyze development of innovative technology, emphasizing minimally invasive diagnosis and therapy.

1.1 Key Accomplishments by Program - Project – Principal Investigator

Endovascular Devices Program

Cardiomyocyte Repopulation – Craig Thompson, MD, MGH
The key results over the past year are as follows:

- Development of a reproducible, myocardial infarction heart failure model.
- Reliable cell labeling system for histologic evaluation of cell grafts.
- Refinement of transvenous, direct myocardial cell delivery.
- Refinement of endo- and epicardial mapping techniques to evaluate cell graft arrythmia and electromechanical properties in a large animal human surrogate (porcine) model.
- Preliminary data suggest electrical normalization of epicardial potentials compared to endocardial potentials. We hypothesize that cell grafts have a proclivity for maturation with proximity to the epicardial surface its robust vascular network.
- *See Section 1.4: Highlight Project on page 17.*

Radio Frequency Ablation with Needle-Tipped Catheter – William Stevenson, MD, BWH
A retractable needle electrode can be imbedded into ventricular myocardium guided by fluoroscopic imaging and used to apply RF ablation current deep to the endocardium. The resulting RF lesions are deep and can be transmural, but are narrow, such that precise positioning of the ablation needle would be required and would be likely to interrupt only small or narrow reentry circuits. Infusing normal saline through the electrode prior to and during RF application markedly increases RF lesion size.

Minimally Invasive Surgery Program

Blake OR-Advanced Procedure Room – David Rattner, MD, MGH

1. Room design was tested and finalized through the process of building design mock-ups and the use of Auto Computer Aided Design models. Additional funding was sought and secured by the project leadership that has resulted in Partners HealthCare System making an additional capital commitment of $750,000 to fund the unique construction aspects of

the OR of the Future (ORF). Core funding had already been provided by MGH for the usual and ordinary aspects of the build out. Construction was substantially completed June 2002.

2. Finalized all agreements and statements of collaboration with Industry partners. Ten industry partners have joined the ORF project, along with two companies who have collaborative research and development agreements with CIMIT, Mobile Aspects and Sentinel Wireless. Throughout FY 02 Industry partners worked with the ORF team to identify appropriate technology for the project, arranged delivery, completed installation, integration and training for various technologies in July 2002 (see Table 1).
3. Executive Group created sub-committees with responsibility for specific issues, e.g., Outcomes, Core Equipment, IT, Construction, Staffing and Supply Train.
4. Outcomes template finalized and in place
5. A candidate for the position of Project Manager, Marie Egan, RN, MS, was identified and recruited.
6. A simulation model of various staffing patterns was developed. This modeling: 1) identified a staffing pattern that optimizes the efficiency and utilization of ORF personnel; 2) created new job descriptions that guided the selection of staff to work in the room; 3) catalyzed development of novel policies and procedures to guide practice in this innovative environment. The staff will also contribute to the data collection for the Outcomes Project by participating in job satisfaction surveys both before the room opens and at intervals afterward. The staff (medical, anesthesia, nursing, biomedical and support staff) has been identified and trained.

7. Room opened for training, including mock surgeries, in July 2002. The multi-disciplinary team collaborated to develop surgical scenarios that were then acted out. These scenarios included cases from each of the three surgical specialities operating in the ORF, General Surgery, Gynecology and Genito-Urinary surgery. Lessons learned form each mock case were integrated into future iterations. The room opened for surgery in August 2002. Four Gynecology cases were performed in a smooth, safe fashion.

Patient Monitoring and Communications – Nathaniel Sims, MD, MGH

Over the past year, a sustainable research and development infrastructure has been created at MIT and Massachusetts General Hospital. An innovative concept and development plan has been created and articulated through papers, prototype demonstrations, and multi-media presentations. There have been significant successes in sourcing and aggregating custom sensors, components, and software modules. Key clinical and research partners have been identified by a variety of means. Sustainability has been achieved through the incremental recruitment of clinicians and advanced degree students to the effort. Two flagship projects, exemplary of the power and promise of this initiative, the Patient-Centric Network (described in the quarterly report) and the Mitral Valve Prolapse Detector, described below, are in advanced stages of development. Finally, two avenues of major additional funding have been obtained to support related work. Publications and patent applications are in draft form.

Robotics in Cardiac Surgery – David Torchiana, MD, MGH

Laboratory studies over the last year were limited because of a delay in acquiring DoD animal approval. We have acquired a robotic system upgrade with microwrist instruments. The use of articulating instruments increases surgeon dexterity from five to six degrees of freedom. The Hermes system has been installed allowing the surgeon central control of the operating room

through voice and touch screen displays. Since the last quarterly report, Computer Motion has assigned a fulltime engineer to our laboratory to assist with the use of the new robotic interface.

Gallbladder Extraction Device – David Whittaker, MD, MGH
Over the past year, our key results include: 1) Preliminary Patent Application with the Patent and Trade Office, 2) Ethicon Endo-surgery deferred further involvement until they can evaluate a working prototype, and 3) Currently seeking a contract with outside vendors to manufacture a prototype.

Laparoscopic Ultrasound – Kirby Vosburgh, PhD, MGH
Over the last year, the CIMIT team has developed a surgical navigation system that may enable physicians with limited ultrasound experience to use laparoscopic ultrasound (LapUS). We have filed an invention disclosure that describes our system with the Massachusetts General Hospital licensing office and submitted an abstract based on our preliminary experimental results for the Society of American Gastrointestinal Endoscopic Surgeons 2003 meeting. We have also made significant progress in our core technology research, including: 1) determining image based US-CT registration techniques are not feasible without an image processing step that accounts for the inherent differences in how US and CT images are acquired; 2) establishing an agreement with our corporate collaborators to construct a second generation tracked laparoscopic ultrasound that fits through a standard 12mm laparoscopic port; and 3) setting up 3DUS software in our lab for ongoing visualization and registration experiments.

Image-Guided Therapy Program

Cellular Resolution Endoscope – Brett Bouma, PhD, MGH
The CIMIT team has developed a novel broadband light source based on dispersion compensating mirrors and nonlinear propagation in optical fiber. The source provides high-brightness light and enables high-resolution imaging over a large field of view. We have demonstrated that digital signal processing can be used to overcome image blurring that results from unbalanced dispersion and from non-Gaussian spectral distributions. These advancements have been combined with the development of a novel hand-held imaging probe that provides unprecedented resolution and field of view and have used this probe for imaging tissue *in vitro*.

Automated Segmentation of Anatomy from CT and MRI – Carl-Fredrik Westin, PhD, BWH
This year, the team has been focused on developing a user-friendly software module, based on our optimized libraries developed last year, in the 3D Slicer. The 3D Slicer is a visualization tool developed as a joint effort between our laboratory and the AI laboratory at MIT (Cambridge, MA [http://slicer.org]). In addition, the team has focused on a novel method for extraction of vessel centerlines. Preliminary results were recently presented in [Krissian02]. The method has sub-voxel accuracy and is based on the gradient, and the eigenvalues of the Hessian matrix to interpolate the zero-crossing of the gradient vector in the cross-sectional directions. The method is fast and efficient. It takes about 4 min on a standard workstation or PC to process a PCA-MRA data set of size 256x256x122. The method is currently tested on cardiac CTA data. The team has also developed a novel approach to correct flow data from phase contrast angiography (PCA) [Watanabe02a], [Watanabe02b]. The method is based on combining computational fluid dynamics (CFD) and segmentation in a level set framework.

Tissue Engineering Program

Polymeric Nanoparticles for High Efficiency Gene Transfer – Robert Langer, ScD, MIT
The team has continued development on the first accelerated discovery approach for finding synthetic transfection vectors. Several new polymers discovered through this approach have higher transfection efficiencies than existing synthetic vectors in cell-based assays. We have also modified several factors in the synthetic procedure that will allow for much larger libraries, containing thousands of structures, to be synthesized using a semi-automated, high-throughput system.

Vascularized Tissue in vitro for Implant – Jeffrey Borenstein, PhD, Draper
This year the CIMIT team has made significant progress in the following areas:

- Novel mathematical model for the angiogenesis process has produced physiologically viable capillary beds
- New, proprietary approach has been developed for the design of three-dimensional vascularized tissues with very high capillary densities
- High resolution features micromachined in industry-standard biodegradable polymer (PLGA), with minimum features 2 microns in size, and resolution of 0.02 microns.
- Multi-layer PLGA films (up to 6) integrated into a scaffold construct in a single step
- New biodegradable polymer from MIT (bio-rubber) micromachined at high resolution to form scaffolds which should have greatly reduced inflammatory response
- Formation of capillary wall membrane in microfluidic culture has been demonstrated using self-assembling peptides in a joint Draper-MIT-MGH project

Medical Simulation Program

Enabling Technologies for Medical Simulation – Steven Dawson, MD, MGH
Among the most notable accomplishments in the past year, the CIMIT team:

- Filed patents to protect the intellectual property in the VIRGIL Chest Trauma Training System;
- Secured trademark rights to the VIRGIL name for the training system;
- Began commercialization discussions for the VIRGIL system;
- Filed four new invention disclosures for existing research projects;
- Initiated a new collaboration with USUHS and the National Capital Area Simulation Center;
- Began validation studies comparing the VIRGIL system to existing accepted animal training models;
- Presented our vision of medical simulation in a keynote address to the leadership of the American College of Surgeons;
- Participated in drafting a white paper for a new thrust in simulation research by the American College of Surgeons;
- Submitted the Medical Simulation Training Initiative (MSTI) as a STO to the Defense Department, under the sponsorship of COL Robert Vandre; and
- Demonstrated the VIRGIL system to GEN James Peake, Surgeon General of the Army, GEN Lester Martinez-Lopez, Commanding Officer of USAMRMC, and COL Jeffrey Roller, Commander of TATRC.
- See Section 1.3: Annual Report Cover Project on page 15.

Biodetection Program

Real Time Blood Assay – Christopher Dube, PhD, Draper

Two of the key milestones of the past year include: 1) Detection of the microbial pathogen *E. coli* O157:H7 using individually functionalized μCANARY elements. This represents a major achievement in that it demonstrates rapid, sensitive detection of an important human microbial pathogen with flexural plate wave technology, and 2) Completion of assays of four different E. coli organisms to compare affinity ligand reagent specificity for E. coli. The organisms include DH5-α, O157 knockout, O55, and O157 knockout gene reinserted. The standard antibody for all assays was anti-O157H7. These results showed that our assay, based on the anti-O157:H7 antibody, is sufficiently selective to differentiate between these organisms. The O157 knockout (the gene that is responsible for expression of the O157 epitope, or outer surface feature of the bug, was deleted and as a result the O157 feature was not expressed) organism previously showed no binding to the anti-O157:H7 antibody. That result was tested again, as well as a version in which the O157 gene was reinserted, and the O157 feature should be expressed again.

FAIMS Analyzer for the Detection of Bacillus Spores – Jeffrey Borenstein, PhD, Draper

During this first year of the project, a complete Pyr-PFAIMS system was assembled by coupling a commercial pyrolyzer with the PFAIMS prototype. A pyrolysis protocol was obtained from the manufacturer of the pyrolysis system; this protocol was evaluated and optimized using Ion Trap Mass Spectrometry. The protocols were tested with dipicolinic acid (DPA), picolinic acid (PA) and pyrolyzed *Bacillus subtilis* samples (as a simulant for *B. anthracis*.) Pyr-PFAIMS protocols have been developed, and test data has been obtained for pyridine, PA and DPA.

Combat Casualty Care Program

RAFTS/Bioglove – Geoffrey Ling, MD, PhD, USUHS

For the Bioglove, a first prototype was constructed using the component parts previously identified. Animal testing was initiated over this reporting period. This device was used to EKG in 4 anesthetized pigs. The Bioglove was placed on the anterior chest over the heart. For RAFT, collection of normal baseline data of 15 normal human subject volunteers was completed. Data was obtained and processed of their chest, chest and leg using methods previously described. The collected information was obtained and processed as previously described. In brief, following informed consent, the RAFT antenna was held 6 cm away from each subject. Raw data was collected using a network analyzer. Data was processed using the MUSIC algorithm and the MATLAB computer program. The data was displayed as amplitude or phase as a function of radio frequency. Both real and imaginary data were used. Investigators analyzing the raw data were blinded to the treatment.

Parallel Processing in Medical Monitoring – William Wiesmann, MD, Harvey Mudd

The 2001/2002 Harvey Mudd College CIMIT team designed and implemented a distributed computing architecture to serve as the foundation for a research tool to investigate the benefits of implementing a real-time patient monitoring system.

Vulnerable Plaque Program

Vulnerable Plaque - James E. Muller, MD, MGH
This past year, the CIMIT Vulnerable Plaque Program was established in the former CIMIT Central Office space of approximately 2200 sq. ft. at Charles River Plaza. The space houses 12 VPP investigators including cardiologists, radiologists, Ph.D. scientists, post-doctoral fellows and students. This stimulating environment has critically enhanced the success of the Vulnerable Plaque Program. In additional to scientific progress, the Vulnerable Plaque Program has initiated a strategic planning process under the leadership of Lynn R. Osborn, MBA.

Characterization of Vulnerable Plaque – Thomas Brady, MD, MGH
Using cadaveric coronary, aorta and carotid specimens, we have developed criteria for plaque characterization and have tested these criteria against histopathology in a blinded study.

Detection of vulnerable plaques with radionuclide technology – Alan Fischman, M.D., MGH
This past year, the CIMIT team employed an animal model of atherosclerosis, in which macrophage-rich atherosclerotic plaques were induced in New Zealand rabbits by balloon de-endothelialization of the infradiaphragmatic aorta followed by a high cholesterol diet.

Magnetic Resonance Compatible Devices - Jerome Ackerman, PhD, MGH
During the past year, the CIMIT team has largely accomplished Specific Aims 1 and 2. Special pulse sequence software that was installed on the cardiac MR scanner by the manufacturer is suitable for RF coil tracking, and has fulfilled the requirements of Specific Aim 3. We requested and were granted a no cost extension to March 1, 2003, in order to complete the building of several intravascular coils and to characterize their performance. Commercial software for numerical simulation of coil electromagnetic fields is up and running and producing results. We have written our own codes for analytic simulation of coil inductance and resistance. The software also produces masks for coil photolithography (Specific Aim 1). We have constructed a coil tuning box that works with a wide variety of interchangeable intravascular coils; produced and tested several coils; and compared their experimentally measured parameters with the numerical and analytic predictions, obtaining excellent agreement (Specific Aim 2). A means of external electronic coil tuning has been devised and tested. Both proton images and phosphorus-31 spectra have been obtained with the appropriately designed coils.

Stroke Program

MGH XMR Suite – R. Gilberto Gonzalez, MD, PhD, MGH
Work is continuing on the xMRpm software package to develop models for physiological probability maps within the xMR environment. The XMR suite at MGH is scheduled to be open for acute stroke diagnosis and treatment in December 2002.

Technology Assessment and Outcomes Analysis Program

Technology Assessment Program Core – G. Scott Gazelle, MD, PhD, MGH
The CIMIT team has succeeded in establishing a large and capable group of investigators. These investigators have developed a rich network of collaborations throughout CIMIT. We have collaborated and/or consulted with other CIMIT investigators on issues such as project feasibility, study design, endpoint determination, and approaches to data analysis. We have also

assisted with primary data collection and analysis. This work complements other more traditional laboratory and/or clinical research being carried out by individual CIMIT investigators or within the context of major CIMIT Programs.

Operating Room of the Future (ORF) Outcomes - G. Scott Gazelle, MD, PhD, MGH
Over the past year, the preliminary ORF simulation model was expanded to incorporate multiple operating rooms using either standard anesthesia procedures, the proposed two anesthesiologist handoff model, or a combination of both. This model has been populated and verified with process data from the MGH department of surgery's dynamic scheduling system and the hospital cost accounting database (TSI). Using the model, analyses are ongoing, and this work is carried out in collaboration with the ORF Project team.

Vulnerable Plaque Outcomes - G. Scott Gazelle, MD, PhD, MGH
Over the past year the development of the cardiovascular disease model has proceeded in steps that correspond with management decisions in cardiac disease. We have continued to make progress on the development of a model with which to analyze the effect of vulnerable plaque detection with a new catheter-based technology, including treatment of the plaque with percutaneous coronary interventions.

1.2 Projects awaiting Animal and/or Human Use Approval

Atrial Fibrillation Ablation with MR Guidance – David Keane, MD, MGH
The CIMIT team, lead by Dr. Keane, is awaiting animal use approval before initiating this project.

Non-Invasive, Image-Guided Blood-Brain Barrier Opening – Kullervo Hynynen, PhD, BWH
The CIMIT team, lead by Dr. Hynynen, is awaiting animal use approval before initiating this project.

Vascular Systems and Angiogenesis - Joseph Vacanti, MD, MGH
The CIMIT team, lead by Dr. Vacanti, is awaiting animal use approval before initiating this project.

Three-Dimensional Tissue Design - Joseph Vacanti, MD, MGH
The CIMIT team, lead by Dr. Vacanti, is awaiting animal use approval before initiating this project.

Treatments for Ovarian Cancer – David MacLaughlin, PhD, MGH
The CIMIT team, lead by Dr. MacLaughlin, is awaiting animal use approval before initiating this project.

Continuous Monitoring of Stroke with Diffuse Optical Tomography – David Boas, PhD, MGH
The CIMIT team, lead by Dr. Boas, is awaiting human and animal use approval before initiating this project.

1.3 Annual Report Cover Project

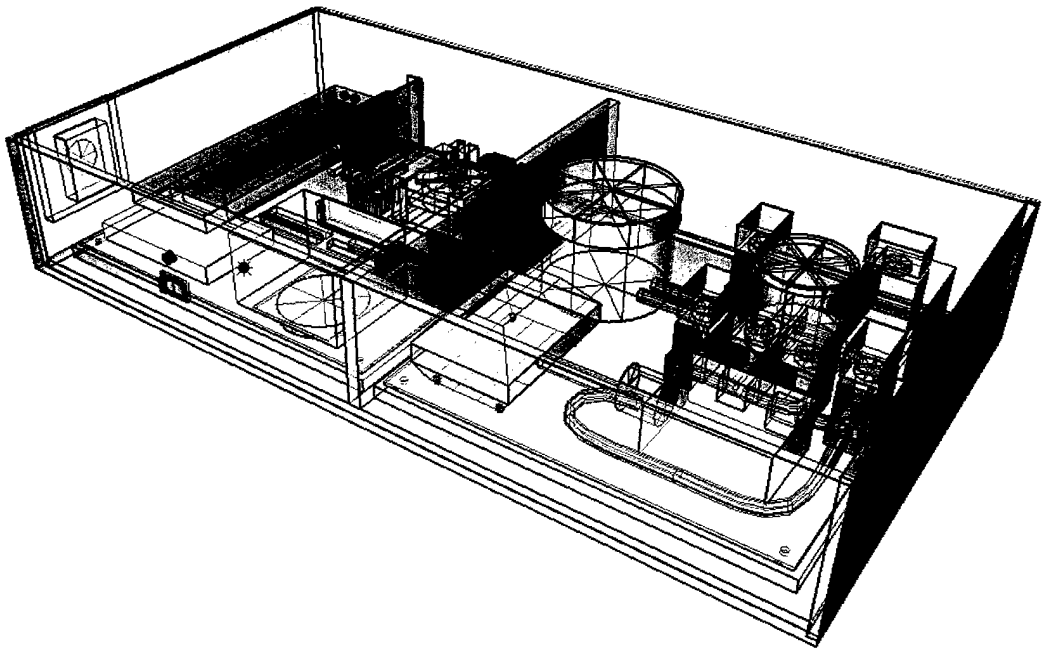
VIRGIL™ Chest Trauma Training System
Principal Investigator: Steven Dawson, M.D., MGH

CIMIT team with VIRGIL™

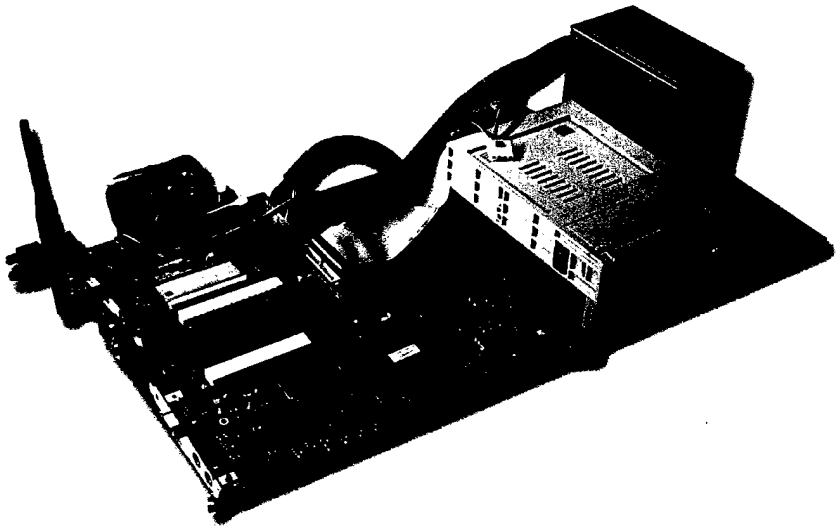
The VIRGIL™ system continues to undergo design refinements that will increase robustness and reliability. We have obtained hardwired PC boards from Ascension Corporation to permit streamlining of the system and reduce the number of fragile electronics components. The Graphical User Interface design has been reconsidered and is being transferred to a Java Server Pages (.jsp) format, in order to allow greater flexibility and modular scene-specific presentations, which were not possible under the previous FLASH-based architecture. The enclosure for the control elements has been redesigned to accommodate the smaller footprint of the hardwired systems more efficiently. In collaboration with the trials at USUHS (see *Validation*, below), we are considering a simpler design of a classroom-style training system, which would lack some of the elements of realism incorporated into the alpha version of VIRGIL at the request of the Special Forces. We have begun a pre-commercialization redesign of the portals, in collaboration with Limbs and Things, Inc. in order to permit mass production and cost-savings that would result from large scale manufacturing.

Lastly, in August 2002, we were requested to provide General James Peake, Surgeon General of the Army, with video records of the VIRGIL™ system in use so that he could present the system as part of his annual Science and Technology brief to the Army Chief-of-Staff General Eric Shinseki.

The CIMIT team will continue with the transition to a hard-wired electronics system, allowing better field use and transportation. We will complete modifications of the GUI to the .jsp format. We will also continue design plans for transition of VIRGIL™ to an ATLS compatible simulation system, suitable for both military and civilian training.



CAD design of third version of VIRGIL control system unit, with ruggedized construction permitting field deployment.

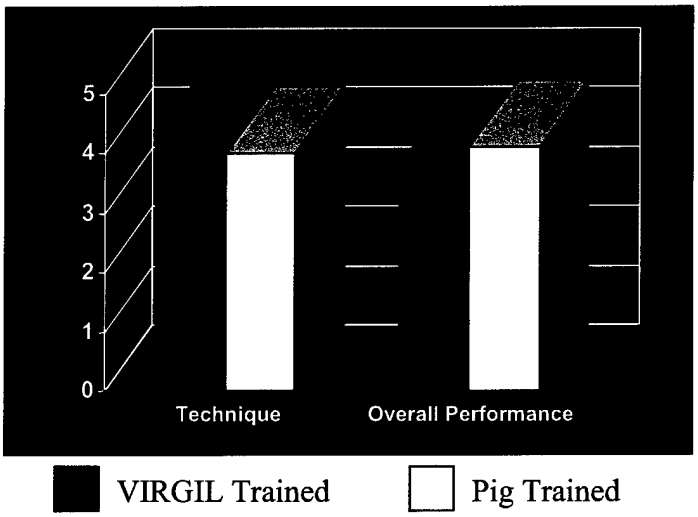


Hardwired workstation that replaces previous VIRGIL laptop, incorporating a 2.2 Ghz Pentium IV processor and remote wireless access. The later feature allows performance results to be accessed remotely from a separate "control" PC while training is underway.

Validation

During the past year, we began validation studies of the VIRGIL system. Our initial sessions were done in collaboration with the annual recertification of the Boston MedFlight EMT's. Although this group is fully qualified in advanced trauma life support (ATLS) they had never before been able to practice chest tube insertion with direct feedback as to individual performance. These studies showed that the VIRGIL system was able to discriminate between

experienced and novice EMT's and personnel with no medical knowledge. Our initial tests at USUHS showed that the VIRGIL system performed at least as an equivalent model to the existing pig training models.



USUHS faculty evaluation of student's technique and overall performance following animal and VIRGIL training, August 2002: *Following training on VIRGIL or pigs, technique and performance are equivalent in both the animal trained and the simulator trained groups. The studies performed at USUHS show that simulation training can serve as an animal equivalent.*

Summary

The USUHS studies will continue. Additional training sessions are scheduled for October and December, allowing training and testing of the entire third year medical class. Longitudinal studies will be conducted to assess retention of knowledge and skills. We are in discussions with the USUHS faculty to examine VIRGIL in the setting of an ATLS curriculum.

1.4 Highlight Project

Cardiomyocyte repopulation for congestive heart failure

Principal Investigator: Craig Thompson, M.D., MGH

Congestive heart failure is a terminal pathophysiologic manifestation of ischemic, myopathic, valvular, and various extracardiac disease states, and accounts for a majority of morbidity, mortality, and health care expenditure in the developing world. Despite advances in preventive, medical, and mechanical approaches to maintain or restore lost cardiac function, many patients remain inadequately treated. Orthotopic cardiac transplantation is limited by donor supply, its highly invasive nature in this compromised patient subset, and need for chronic immunosupression. It is unlikely that donor organ supply will ever meet demand in this disease. Xenotransplantation and artificial hearts, despite decades of investigation, remain limited by biocompatibility, infection, and bleeding.

Our group and others have been interested in adapting principals of replacement biology to develop a mechanism to implant a tissue-engineered progenitor cell substrate via minimally invasive methods that will result in *de novo* angiomyogenesis and restore function to the failing

heart (Thompson CA, Oesterle SN. "Biointerventional Cardiology"; *Vascular Medicine* 2002, in press; Cox ID, Thompson CA, Oesterle SN, "Biointerventional Cardiovascular Therapy"; *European Heart Journal* 2002, in press.). During previous CIMIT funding periods, our group developed and performed the seminal testing of a novel trans(coronary)venous method for direct myocardial cell delivery, explored the interactions of various cell sources and biogel polymers, developed a porcine model for myocardial infarction/ischemic heart failure, and isolated/characterized an enriched progenitor cell source from autologous adult porcine bone marrow.

The CIMIT team is currently evaluating the angiomyogenic potential of this cell source percutaneously delivered to a porcine heart failure model. Our goal for fiscal year 2003 is to complete this series of experiments, to understand electromechanical and arrhythmogenic potential of the cell grafts, and develop a method for *in vivo* cell imaging, as a function of regional performance, to set a standard by which our group and the international community may optimize this method ultimately for the successful treatment of patients.

(1)

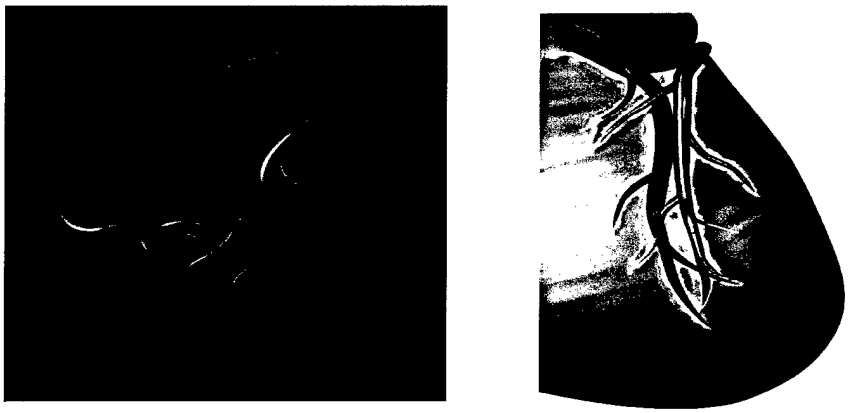


Figure 1. Concept of direct myocardial access using the coronary venous system. The myocardium can be accessed by direct needle puncture under intravascular ultrasound guidance. A microinfusion catheter may be advanced to the area of interest for targeted, quantitative cell delivery. (courtesy TransVascular, Inc., Thompson CA. ACC 2002)

(2) Endocardial and epicardial electromechanical mapping (Figure 2) with CARTO system, and ventricular stimulation to evaluate the electromechanical properties and arrhythmogenic properties of cardiac cell grafts. Electromechanical properties of cell grafts and arrhythmia substrate has not been studied in large animal models. We believe that this line of investigation is critical to establish safety profiles for cardiac cell transplantation in humans.

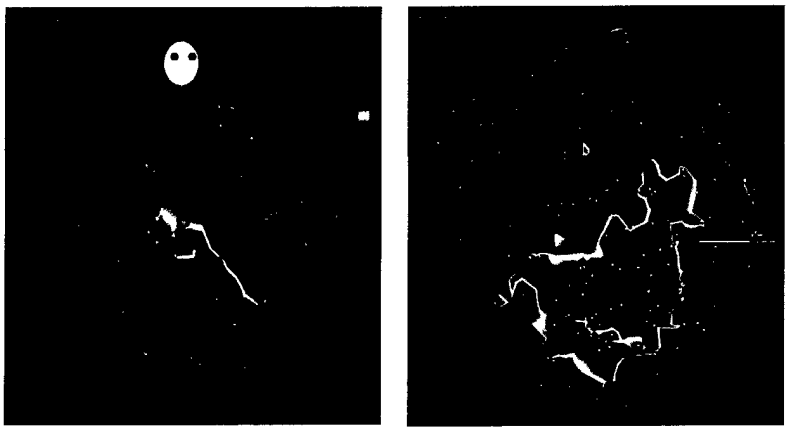


Figure 2. Endo-(left) and epi-cardial (right) electromechanical voltage maps of chronic porcine myocardial infarction model provided by the experimental electrophysiology laboratory. (courtesy Vivek Reddy)

(3) Develop a method for non-invasive, *in vivo* cell imaging using labeled cells and magnetic resonance technology and positron emission tomography. These technologies will provide us, and the medical research community, a method to quantitatively track cell fate in living animals, and correlate to regional function, blood flow, viability, thus providing the means to truly optimize this therapy for clinical use.

Several milestones have been achieved since this project's inception several years ago:

(1) The first series of percutaneous, transcoronary venous direct myocardial cell delivery (Thompson CA, et. al. ACC 2002. Manuscript pending) (Figure 3)

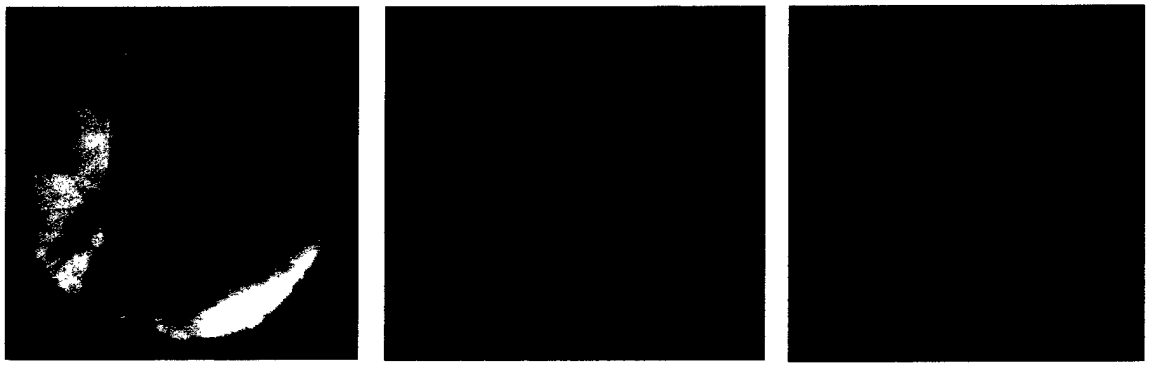


Figure 3. Example from first (feasibility) series of percutaneous, transvenous cellular cardiomyoplasty in normal porcine myocardium. (Far left) fluoroscopy of transvenous myocardial cell delivery enhanced with contrast (center) cell-biogel tissue engineered substrate (right) phcyoerythrin immunostaining (vs GFP, red fluorescence) demonstrating GFP uptake in elongated tubes morphologically similar to surrounding myocardium (hypothesis generating; this study was not designed a priori to evaluate differentiation potential) (Thompson CA, ACC 2002)

(2) Characterization of mesenchymal stem cells in porcine myocardium

(3) Optimization of green fluorescence protein mesenchymal stem cell labeling using pseudotyped retrovirus in several small/large animal species (Nasseri, BA, et. al) and cell membrane labeling techniques suitable for developmental identification and analysis (Figure 4).

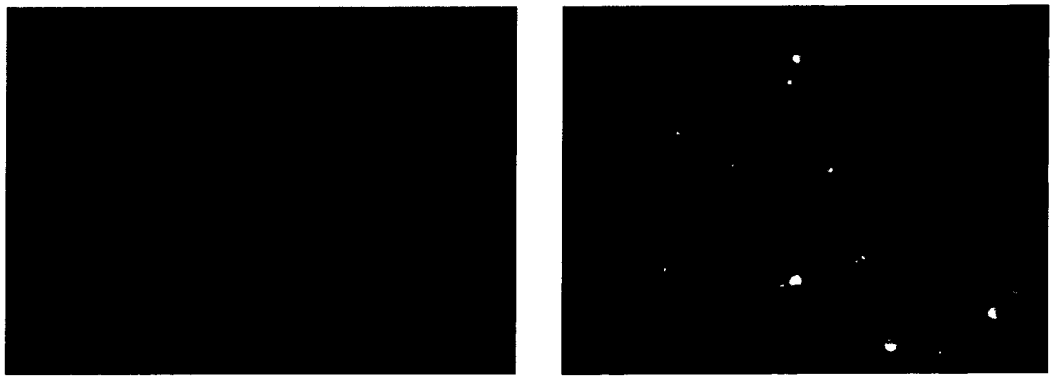


Figure 4. (left) Green fluorescence protein labeling of mesenchymal stem cells/bone marrow adherent cells transduced with psuedotyped vesicolstomatitis virus and (right) purified, enriched mixed progenitor bone marrow cell population labeled with PKH-26GL cell membrane label (rhodamine conjugation) 20x magnification. (Thompson CA MMVR 2002, Thompson CA ACC 2002)

(4) Development of immunohistochemistry methods to discriminate cell/polymer biogel donor-host relationships (Figure 5)

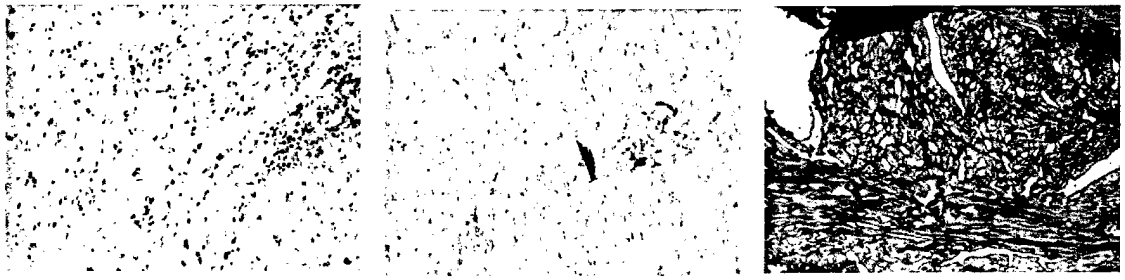


Figure 5. Immunohistochemistry of cell/biogel substrate at 2 week timepoint (20 x magnification, DAB conjugate), (left) negative control (center) positive control with cells and biogel in the same field, (right) positive control (GFP transgenic mouse myocardium). (Thompson CA ACC 2002)

(5) Evaluation of biogel polymer/mesenchymal stem cell interaction and catheter biocompatibility testing
(6) Isolation/characterization of adult porcine bone marrow, purified/enriched progenitor cell population suitable for hypothesis testing
(7) Development of reproducible, porcine myocardial infarction/chronic heart failure model
(8) *Ex vivo* characterization of transvenous microcatheter substrate delivery using MRI
(9) Performing percutaneous progenitor cell delivery in heart failure model (current protocol) with functional, electromechanical, hemodynamic, and biologic endpoints.

The cell transplant program's infrastructure is reaching maturation to pursue various areas of hypothesis testing (see investigational plan). Dr. Thompson has actively engaged in collaboration with Drs. Mark Fishman and Ashok Srinivisian at the Cardiovascular Research Center (Charlestown, MA) in the cell discovery/characterization/labeling process to optimize the implantable substrate and Dr. Vacanti for biopolymer "delivery vehicles" and theory of replacement organogenesis. Drs. Stuart Houser and Tom Aretz provide histopathology core laboratory services. Dr. Vivek Reddy, Director of Experimental Electrophysiology at MGH, will provide intellectual and technical support for electromechanical evaluation and arrhythmogenesis. Dr. Motoya Hayase, Director of the Cardiovascular Laboratory for Integrative Physiology and Imaging (CLIPI) at MGH, Ms. Jennifer MacGregor and Mr. Luis Guererro will assist in animal procedures and animal care/welfare. Drs. Farouc Jaffer, Fred Holmvang, and Ralph Weisleder are available for assistance for MR imaging applications and Dr. Alan Fischman for PET imaging.

"In house" services for conduct of these experiments include:

(1) CLIPI lab (Herman K. Gold, Craig A. Thompson, collaborators: Motoya Hayase, Farouc Jaffer, Jennifer Macgregor, Luis Guererro)– a large animal device testing facility with integrative equipment for physiologic assessment, including a fully functional, state-of-the-art digital Siemens cardiovascular catheterization laboratory, a 1.5 Tesla short bore MRI scanner (General Electric), pre-post procedure animal care area, and office space.

(2) Experimental electrophysiology laboratory (collaborator: Vivek Reddy)– inclusive of dedicated assessment of endo- and epicardial electromechanical activity, ventricular arrhythmia.

(3) Histopathology core laboratory (collaborators: Stuart Houser, Tom Aretz) – histopathologic processing of tissue sections, immunohistochemistry, confocal microscopy

(4) Cardiovascular Research Center (Craig A. Thompson, collaborators: Mark C. Fishman, Ashok Srinivisan) – 10,000 sq.ft. space with capabilities for cell assessment, characterization, flow cytometry, sorting (FACS/gradients/centrifuge), cell culture, and ancillary supplies.

(5) Wellman Surgical Laboratories/Tissue Engineering Laboratory (collaborator: Joseph P. Vacanti (Co-PI)) Cell culture/storage

(6) Cardiovascular Tissue Engineering Laboratory (Craig A. Thompson) Cell characterization, sorting, culture, biopolymer processing, catheter modification/engineering (also in collaboration with Transvascular, Inc, Menlo Park, CA) computer hardware/software

(7) Knight Center for Cardiovascular Interventional Therapy (Herman K. Gold, Eugene Pomerantsev, Craig A. Thompson): processing of digital images, subtraction software for large and small/capillary vessel quantitative assessment, quantitative angiography

(8) MGH Positron Emission Tomography Center (collaborator: Alan Fischman) *in vivo* cell graft imaging, wall motion, blood flow, and viability assessment

*All animal procedures/care to be performed in accordance with accepted institutional animal welfare standards and subject to MGH IRB and DoD approval.

Key Results: The key results over the past year are as follows:

- Development of a reproducible, myocardial infarction heart failure model.
- Reliable cell labeling system for histologic evaluation of cell grafts.

- Refinement of transvenous, direct myocardial cell delivery.
- Refinement of endo- and epicardial mapping techniques to evaluate cell graft arrythmia and electromechanical properties in a large animal model.
- Preliminary data suggest electrical normalization of epicardial potentials compared to endocardial potentials. We hypothesize that cell grafts have a proclivity for maturation with proximity to the epicardial surface its robust vascular network.

Specific Aim 1: Evaluate procedural safety and feasibility of trans(coronary)venous myocardial cell delivery to infarcted and ischemic myocardium in porcine chronic infarction model.

Progress: Final approval from the Animal Use Committee at DoD was received in June 2002. The CIMIT team will now initiate the following:

(1) Coil embolize proximal/mid left anterior descending artery of 16 Yorkshire swine and survive animals to 30 day timepoint (using intracoronary and intravenous antiarrhythmic strategies developed during current CIMIT funding period 2002 to maximize survival and precipitate systolic dysfunction).

(2) Harvest autologous bone marrow (~200cc) at 30 day timepoint, purify/enrich for previously characterized mononuclear cell population and label with PKH-26GL (figure 4) [method developed during CIMIT funding period 2002)

(3) Perform percutaneous myocardial cell transplant with TransAccess delivery system (figure 6) (developed and tested CIMIT funding period 2001-2002) of bone marrow progenitor cells (~2 x 10^7/cc) vs. control (phospho-buffered saline); 40 injections distributed in anterior, lateral, apical, and septal walls.

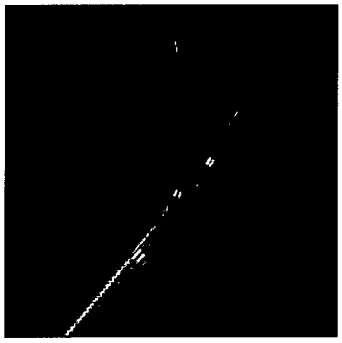


Figure 6. Crosspoint TransAccess® catheter with microlume delivery system. This is a composite catheter combining a phased array intravascular ultrasound transducer to provide targeted puncture of a sheathed, extendable nitinol needle at the tip. The microlume catheter may then be projected through the needle tip and tunneled to the area of interest in the myocardium. Courtesy TransVascular, Inc., (Thompson CA MMVR 2002, ACC 2002)

(4) Reassess regional wall motion by biplane ventriculography at day 60 (1 month post transplant) and hemodynamics.

Endpoints: mortality, evident cardiac tamponade, procedural arrhythmia at time 0, 30, 60 days.

Specific Aim 2: Evaluate angiomyogenesis potential and performance characteristics of percutaneous cellular cardiomyoplasty

Progress:

(1) Procedure as specific aim 1.

(2) Quantitative angiography including biplane ventriculography/regional wall motion score, primary, secondary, and tertiary vascular branching counts, and capillary (subtraction software) blush score at times 0 (pre and post MI), 30, and 60 days. High powered field vessel count per histology as well. Power calculations for these measurements are on expected difference of 5% between treatment groups, and two tailed P = 0.05.

(3) Identification of "donor" labeled bone marrow cells at sacrifice (day 60) by direct red immunofluroescence (with correlation to injection sites defined by typical echo/spect protocols, e.g. Basal, mid, and apical regions subdivided into anterior, lateral, apical, and inferior/posterior segments). The donor bone marrow cells will be confirmed by DAB conjugated immunostaining, and counterstaining with cardiac specific markers (troponin I, connexin) will be performed to evaluate differentiation potential.

(4) Hemodynamic assessment at time 0 (pre and post MI), day 30 (transplant vs. control procedures), and day 60 (sacrifice) will include heart rate, aortic pressure, left ventricular end-diastolic pressure, dP/dT, dP/dT/P.

Specific Aim 3: Evaluate endo- and epi-cardial electromechanical ventricular potentials and inducibility of malignant ventricular arrhythmia (sustained ventricular tachycardia or ventricular fibrillation).

Progress:

(1) Procedure as specific aim 1.

(2) At day 60 (1 month post transplant vs control injections/time of sacrifice), endo- and epicardial electromechanical mapping with be performed with CARTO mapping system.

(3) After the mapping procedure, ventricular stimulation for arrhythmia will be performed using convention right ventricular stimulation with repetitive, successively accelerating source trains.

(4) Both mapping for infarct, ischemia, and normal potentials, and ventricular arrhythmogenesis will be analyzed with calculations of expected 5% difference between treatment groups and two tailed P = 0.05.

Specific Aim 4: Evaluate the role of biogel delivery vehicles for acute cell retention and trafficking of catheter-delivered cells using MRI.

Progress:

(1) Infarct procedure as specific aim 1 (N=3 per arm).

(2) At 21-30 days, bone marrow cells will be harvested and labeled with intracellular iron.

(3) Catheter-based cell delivery with and without collagen (Cellagen) biogel will be performed.

(4) Immediate post-procedure and 24 hour cardiac MRI will be performed (1.5 T GE MRI magnet in CLIPI lab) and animals sacrificed.

(5) Intensity (quantitative subtraction), distribution (per echo/spect protocol listed above), will be evaluated between the two groups.

Plan: During the next quarter and beyond, the CIMIT team plans to further develop a minimally invasive method to deliver a tissue-engineered progenitor cell substrate to restore lost myocardial

function by the proposed mechanism of *de novo* angiomyogenesis, that is, the creation of new cardiac contractile muscular units that are capable of growing (vasculogenesis) and/or recruiting (angio/arteriogenesis) their own blood supply. Current minimally invasive delivery methods are limited by lack of specificity (shunting in the case of coronary arterial and venous injection) and targeting accuracy and cell retention (endoventricular needle injection). We are developing a method using the coronary venous system as a "roadmap" for the heart to facilitate direct myocardial access for targeted cell delivery (Figure 1). Angiomyogenesis has been actively pursued by many groups over the past decade, with equivocal results at best in small animal models. To date, convincing evidence is absent in large animal pre-clinical models.

1.5 Highlight Activities and Events

A. Scientific Advisory Board

In May, the CIMIT Scientific Advisory Board Review was completed with the visit of **Richard J. Johns, M.D.,** Distinguished Service Professor, Biomedical Engineering from Johns Hopkins Medical Institutions. The other members of the board are:

- **Eugene Braunwald, M.D.**
  - Chair, CIMIT Scientific Advisory Board
  - Chief Academic Officer, Partners HealthCare System
  - Distinguished Professor of Medicine, Harvard Medical School
- **Warren S. Grundfest, M.D., FACS**
  - Professor of Electrical Engineering, Professor of Surgery
  - The Henry Samueli School of Engineering & Applied Science
  - University of California at Los Angeles
- **James T. Willerson, M.D**
  - President, University of Texas Health Science Center at Houston
- **Thomas J. Fogarty, M.D.**
  - Professor of Surgery, Department of Surgery, Division of Vascular Surgery
  - Stanford University School of Medicine
- **Stanley Baum, M.D.**
  - Department of Radiology
  - University of Pennsylvania Medical Center

Initial feedback from the board members was highly positive, although it was stressed that CIMIT should develop and maintain long term metrics to demonstrate its success.

B. Col Robert Vandre visit

On May 23, 2002, Col Robert Vandre of US Army Medical Research and Materiel Command visited CIMIT to initiate a new $5M program in Combat Casualty Care. This program will emphasize advanced simulation for medical training (building on the successful CIMIT Simulation effort), and a new effort in wireless physiological monitors.

C. ISN Award

The United States Army has selected MIT as the home of the Institute for Soldier Nanotechnologies (ISN). This institute will create lightweight molecular materials to equip foot soldiers of the future with uniforms and gear that can heal them, shield them and protect them against chemical and biological warfare. The ISN's role is one of basic and applied research, with a primary goal of creating an expansive array of innovations in nanoscience and

nanotechnology in a variety of survivability-related areas that will be harvested by the industrial partners for future Army application. The research will integrate a wide range of functions, including multithreat protection against ballistics, sensory attack, chemical and biological agents; climate control (cooling, heating, and insulating), possible chameleon-like garments; biomedical monitoring; and load management. The objective is to enable a revolutionary advance in soldier survivability through the development of novel materials for integration into the future warrior systems. CIMIT is a founding partner of the Institute; CIMIT scientific and leadership staff are playing key roles in organizing the technical work and leading the medically related activities.

D. CIMIT Research Awards

The internal evaluation of the submitted proposals for the fiscal year starting 1 October 2002 has been completed. 78 proposals were received and the CIMIT Scientific Review Committee has approved 43. Included in this packet are 38 of the 43 approved (which includes some projects in Trauma Critical Care). As you review these proposals, the "approval" consists of 2 categories:

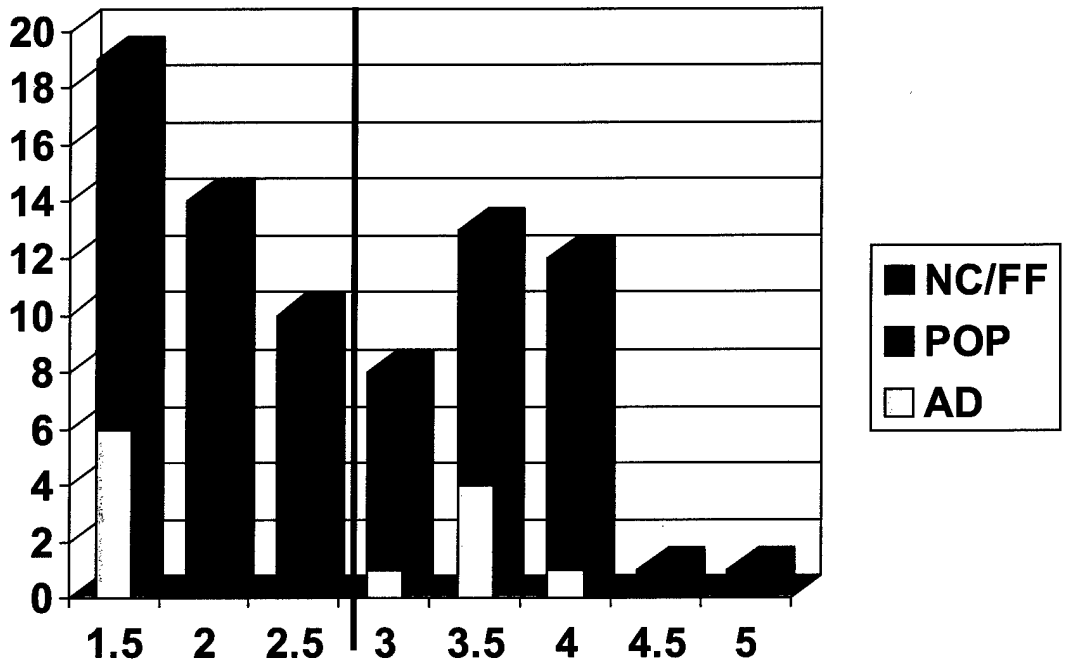
- ❖ Approved as submitted
- ❖ Accept with revisions.

Prior to the CIMIT Scientific Review meetings, the Application Development and Proof of Principle applications were given blinded outside peer review evaluations. A primary and secondary internal reviewer were selected to present the project and its reviews to the full CIMIT Scientific Review Committee, which discussed the project in detail and scored it. Each project attribute was given an absolute rank using the criteria and ranking scales. Each project was then given a relative rank which was near, but not necessarily equivalent, to the average of the attribute scores, since the ranking criteria hold different level of importance. Considerable effort was made to cross-compare rankings so that each project received equal and fair consideration.

While the process was similar to a typical NIH "Study Section," a significant difference is that the review committee would occasionally "accept with revisions" a project proposal. In these cases, the original proposal and the CIMIT review are given herein.

The following Figure gives statistics on the review process. Note that some projects in Trauma/Casualty Care were included in the internal review process, but are not included in this proposal since they are funded by a different Cooperative Agreement.

Payline score/CIMIT Scientific Review/July 2002 for October 2002 funding



Result:
43 of 78 grants approved (55% of applications)
20 AD -> 6 Funded as AD, 8 downgraded to POP -> 6 AD
33 POP -> 15 Funded as POP, 4 downgraded to NC/FF ->23 POP
25 NC -> 10 Funded ->14 NC/FF
$4,050,228 of $10,616,625 awarded (38% of requested)

E. Annual Stakeholders Meeting and Industry Advis ory Board Meetings
In October 2001, CIMIT hosted its Annual Stakeholders Briefing, a networking opportunity during which more than 150 attendees were introduced to some of the most promising MIT-based collaborations and saw exciting demonstrations of CIMIT's work in a "science fair" setting.

CIMIT also hosted spring and fall meetings with CIMIT's Industry Advisory Board (IAB), a panel of 11 industry leaders who provide valuable insight and direction to CIMIT's leadership. The spring meeting provided a forum for discussing CIMIT's five-year plan in light of future trends in the technology development industry. The fall meeting focused on the status of CIMIT's industry programs and research portfolio and on CIMIT's National Response Plan, designed to fast track or redirect and enhance CIMIT's current activities in order to provide deliverables to improve national crisis response and treatment.

Industry Members include:
John Abele, Founder and Chairman, Boston Scientific Corporation
Paul Citron, Vice President, Science and Technology, Medtronic, Inc
Cynthia Danaher, Industry Consultant
Ronald Dollens, President and CEO, Guidant Corporation
Scott Donnelly, Vice President, Globel Technology Operations, GE Medical Systems
Alexander d'Arbeloff, Chairman, MIT Corporation; and Founder, Teradyne, Inc.
George Rabstejnek, Vice Chairman, Massachusetts Eye and Ear Infirmary
Frank Samuel, Technology Consultant, Office of the Governor, Ohio
Tom Sommer, President, Mass Medic
John Thompson, Attorney, Nutter, McLennan and Fish, LLP
Josh Tolkoff, President, Seedling Enterprises, LLC

2.0 ENABLING TECHNOLOGIES

2.1 ENDOVASCULAR DEVICES PROGRAM

Task 1: Cardiomyocyte repopulation for congestive heart failure
Principal Investigator: Craig Thompson, M.D., MGH

See Section 1.4: Highlight Project on page 17.

Task 2: Radio frequency ablation with needle-tipped catheter
Principal Investigator: William Stevenson, M.D., BWH

Radiofrequency (RF) catheter ablation has become first-line therapy for supraventricular tachycardia, with a success rate in excess of 95% and very low complication rates. Catheter ablation for ventricular tachycardia, however, remains an important challenge. The reentrant substrate for ventricular tachycardia following myocardial infarction may lie deep to the endocardium, beyond the reach of standard endocardial ablation techniques. We have therefore modified a catheter with a retractable needle at the tip to allow radiofrequency energy application through the needle. A thermocouple has been embedded in the tip of the needle to allow temperature control during RF application.

Our goals have been to determine the feasibility of delivery of deep myocardial RF ablative energy using the needle-tipped catheter, and to gain preliminary insights into its potential clinical utility. Our preliminary work included bench experimentation using *in vitro* bovine myocardium slabs to learn how to apply RF through the needle electrode, and we have now demonstrated the feasibility of this technique *in vivo* in a porcine model. The results of this work were outlined in our previous quarterly report and were reported at the 2002 Scientific Sessions of the North American Society for Pacing and Electrophysiology. The results will be summarized below. In brief, we demonstrated that RF ablation using the needle tipped catheter is feasible, and creates deep lesions. The ablation lesions, however, are narrow and would require very precise positioning for successful ablation, and could be insufficient to interrupt broad reentry circuits. We have therefore carried out further extensive bench research into methods to improve the potential clinical applicability of needle ablation by increasing lesion size.

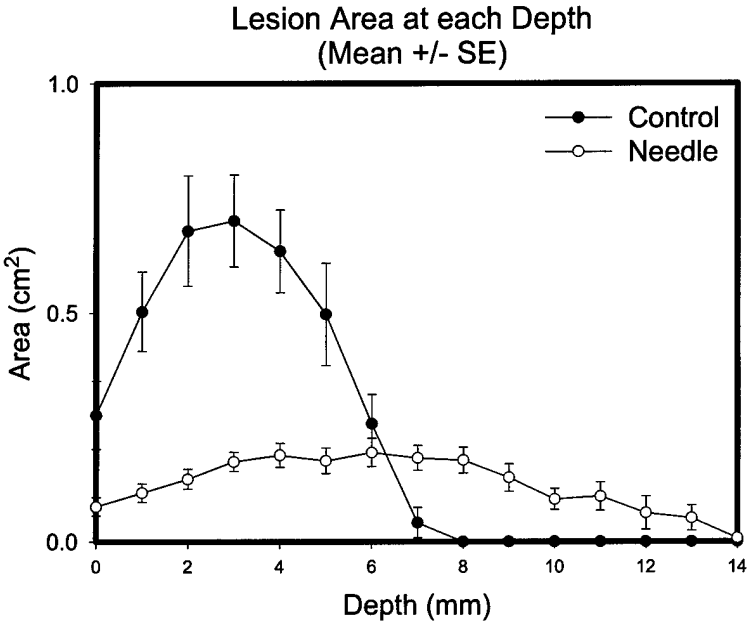
We expect to demonstrate, with further investigation, that modified needle ablation can create substantially larger and deeper lesions than can be achieved with standard techniques. We have determined the major limitations to creation of large lesions using this technique to be small electrode surface area, and high resistance at the tissue-electrode interface, with consequent local heating at low power input, such that only a small volume of tissue is raised above lethal temperatures. By infusing saline into the needle we can create a large "virtual" ablation electrode, dispersing current density away from the electrode and allowing significantly greater power delivery and consequently much greater lesion size. We plan to continue this experimentation in our porcine model.

Key Results: A retractable needle electrode can be imbedded into ventricular myocardium guided by fluoroscopic imaging and used to apply RF ablation current deep to the endocardium. The resulting RF lesions are deep and can be transmural, but are narrow, such that precise

positioning of the ablation needle would be required and would be likely to interrupt only small or narrow reentry circuits. Infusing normal saline through the electrode prior to and during RF application markedly increases RF lesion size.

Specific Aim 1: To determine if application of radiofrequency energy (RF) through a needle electrode guided into the myocardium from an endocardial catheter can produce ablation lesions of sufficient size to potentially ablate intramural arrhythmogenic areas.

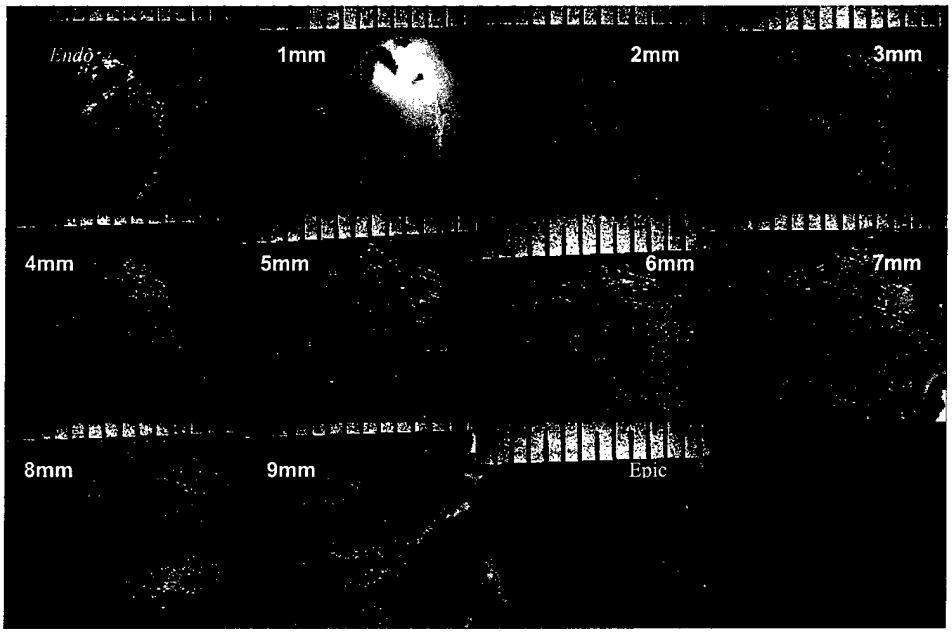
Progress: The CIMIT team has succeeded in our principal specific aim, to determine if application of radiofrequency energy (RF) through a needle electrode guided into the myocardium from an endocardial catheter can produce ablation lesions of sufficient size to ablate intramural arrhythmogenic areas. We have determined that the novel retractable-needle-tipped catheter can be adapted to deliver intramural radiofrequency ablative energy, and that a fully transmural lesion can be created. We have systematically studied our ability to create deep myocardial ablation lesions, and further adapted the needle, embedding a thermocouple within the tip of the needle.



In 3 anesthetized pigs vascular access was achieved and the needle electrode catheter advanced through the aorta into the left ventricle under fluoroscopic and electromagnetic imaging guidance. A series of RF applications was delivered to the needle electrode imbedded into the myocardium (temperature 90 degrees for two minutes). Control lesions (temperature controlled to 60 degrees for two minutes) were created with a standard 4 mm electrode placed at the endocardial surface. Needle lesions were deeper (10.15 +/- 0.77 mm vs. 5.67 +/- 0.37 mm, $p<0.001$) and were more likely to be transmural (77% vs. 11%, $p=0.008$). Needle lesions, however, were long and thin, and of smaller overall volume than control lesions (174.7 +/- 18.6 mm^3 vs. 358.4 +/- 56.2 mm^3) attributable to the much larger cross-sectional area of standard lesions near the endocardium. Standard RF lesions had a mean cross-sectional area of 0.548 +/- 0.04 cm^2 within the first 6 mm of depth, compared to 0.151 +/- 0.01cm^2 for needle lesions. At depths > 6mm, however, the needle electrode lesions had a greater cross-sectional area (0.136 +/- 0.01 vs. 0.005 +/- 0.004 cm^2, $p<0.001$). Intramural temperatures of 90 degrees could be achieved with the needle electrode.

A typical needle ablation lesion is shown in serial cross-section from the endocardium. Note that there is minimal endocardial disruption, and no char or thrombus adhesion. The lesion is concentric around the needle track with distinct margins, and is seen throughout the full depth of

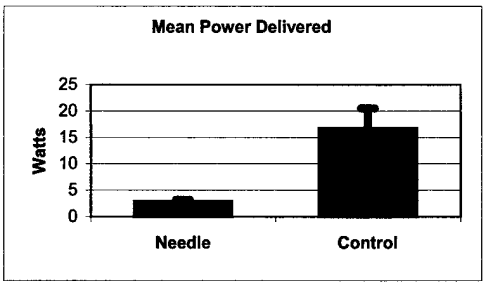
needle penetration. The final image is of the epicardial surface where a small area of ablative destruction can be observed.

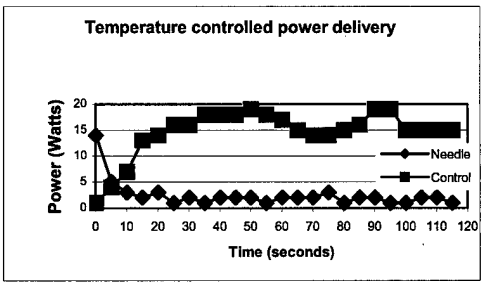


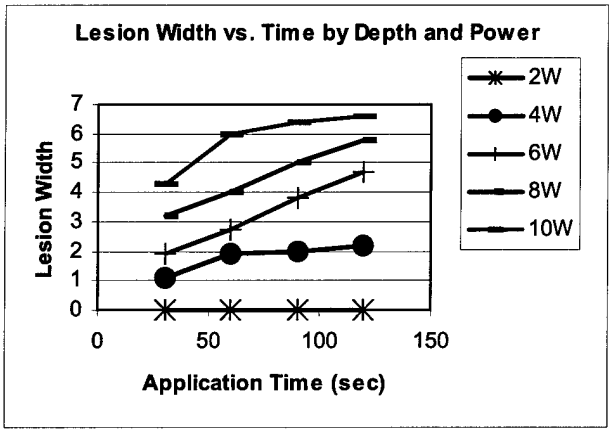
Specific Aim 2: To determine the relationship between RF application time, power, temperature and lesion size.

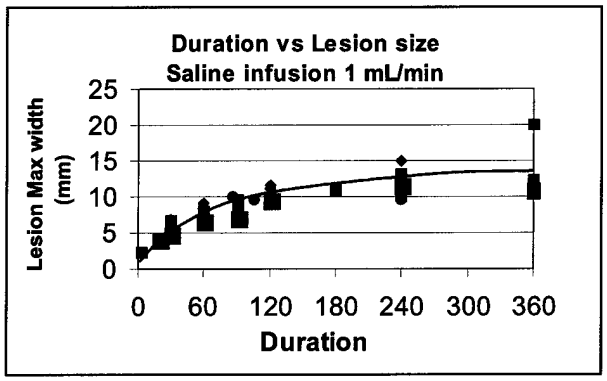
Progress: We have characterized the relationship between RF application time, power, temperature and lesion volume. Lesion dimension varies with power applied and duration of application, leveling off and failing to demonstrate further increases in size after approximately 120 seconds.

In vivo, at power titrated to achieve maximum permissible temperatures (<100°C), the lesions generated are of relatively low volume. Limiting power to that sufficient to heat the catheter/tissue interface to 90° results in mean power output of 2 Watts (see figures below), and is the major limitation to lesion creation by this method. Tissue ablation is a result of resistive heating (which increases with power and tissue conductivity and decreases with the fourth power of the radius from the electrode), and conductive heating through the tissue from the zone of resistive heating. A small tissue-electrode contact surface area results in a very small zone of resistive heating, and a consequently small lesion.







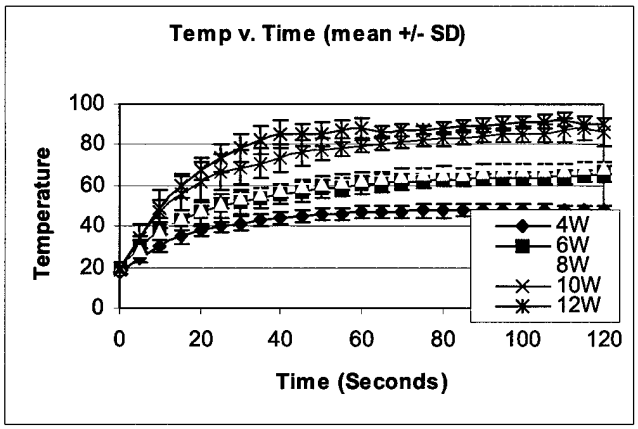


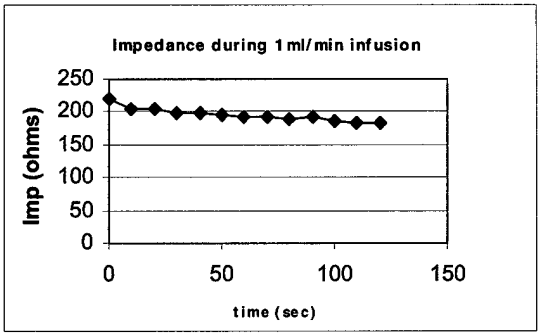
Specific Aim 3: To discover means of increasing lesion width while maintaining depth achieved by needle ablation.

Progress: After determining that *in vivo* needle ablation resulted in lesions that were narrower than would be clinically ideal, and that tissue overheating at low power was the major limitation to increasing lesion size, we investigated methods for increasing tissue conductivity and effective electrode size. Infusing saline into the myocardial interstitium serves to perform both. The effect of saline infusion on tissue impedance is demonstrated in the figure below.

In vitro experimentation in bovine myocardium demonstrated that saline infusion into through the needle permits greater RF energy delivery through the needle ablation catheter and increased lesion dimensions. A range of power applications was investigated to determine the maximal power output which can be achieved without formation of "steam pops". *In vitro*, the optimal power was 10 Watts, which produced no impedance rises or "pops" occurred. At 12 Watts, "pops" did occur, and temperature measured by a plunge electrode 2 mm from the catheter tip occasionally reached temperatures >100° C. (See figure). Lesions created *in vitro* by this method have much greater dimensions than simple needle ablation. Plotting lesion width against RF application time with saline infusion demonstrates that lesion width matures by approximately 120 seconds, but reaches maximal widths well in excess of 10 mm. This is substantially larger than that which can be achieved with simple needle ablation, and the depth (not shown) is much greater than can be achieved with standard surface RF ablation.

In-vivo studies were in 8 anesthetized pigs. Saline irrigation at 1 ml/minute was initiated 1 minute prior to RF application and continued during the application. The resultant lesions are





much larger than we had been able to achieve with either standard (control) endocardial ablation or with simple needle ablation. (See figure) The depth achieved by needle ablation is preserved, yet lesion width is much greater than in the absence of irrigation.

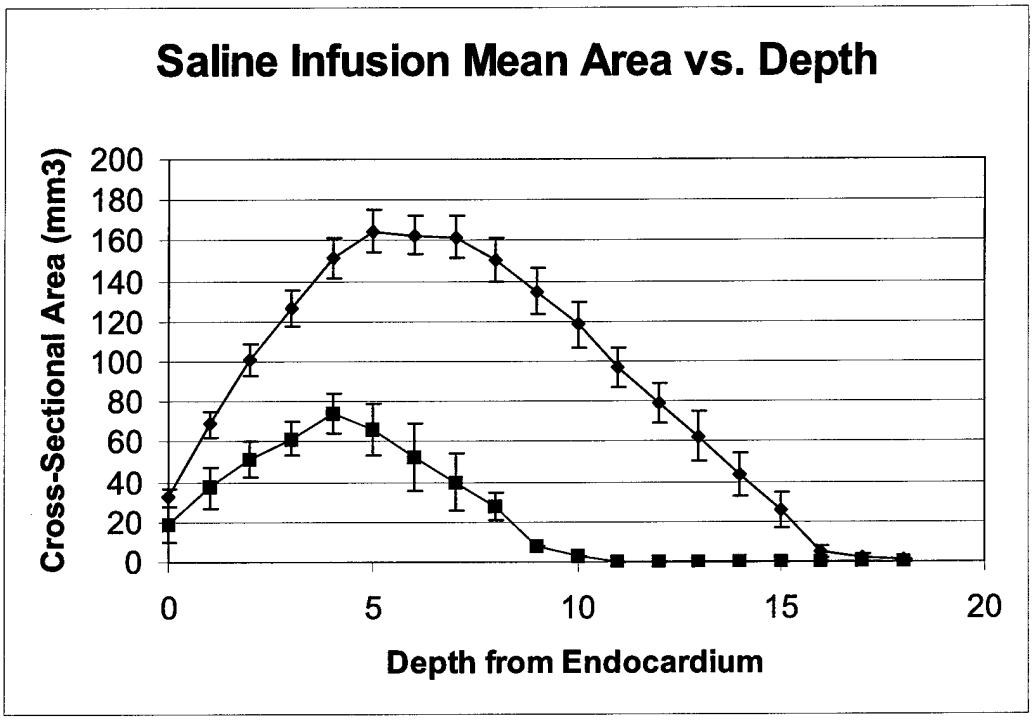


Figure. Graph of cross-sectional ablation lesion area at the endocardial surface (0 depth) and progressively greater distance from the endocardium. With standard RF ablation (squares) lesion area at 10 mm depth is minimal. With saline irrigation of the needle electrode (circles) lesion areas of more than 100 mm are achieved at 10 mm depth.

Significance

Lesion size and depth achieved with saline irrigation RF ablation are impressive. It is possible that this will be sufficient to allow a simplified ablation approach to ablation of scar related ventricular tachycardias, in which the center of the scar is identified based on electroanatomic mapping. Such an approach would be a major advance. Substantial further testing for safety and efficacy is required.

Plan Project completed. We are continuing to seek other funding sources to pursue additional studies in porcine models to optimize saline infusion rates and energy applications. We anticipate pursuing an IDE through Biosense Webster, Inc. for human trials.

Task 3: Atrial fibrillation ablation with MR guidance

Principal Investigator: David Keane, M.D., MGH

The CIMIT team, led by Dr. Keane is awaiting animal use approval before initiating this project.

2.2 MINIMALLY-INVASIVE SURGERY PROGRAM

Task 1: Blake OR-Advanced Procedure Room and Innovation Laboratory, APRIL

Principal Investigator: David Rattner, M.D., MGH

The Massachusetts General Hospital (MGH) Surgical Executive Committee and CIMIT have collaborated over the past year to design and build a unique, integrated operating room that maximizes use of recent or new technologies. This project was put in place due to the limitations placed on innovation by present operating rooms, with regard to room design, function, integration of equipment and people, and ability to capture real time data. Many technologies designed to impact procedural medicine are introduced in isolation and thus frequently fail to improve efficiency, improve safety, or reduce costs. The haphazard introduction of devices into a technologically complex environment may even increase both costs and the risk of adverse events.

The overall goal of the Operating Room of the Future is to develop or modify new surgical equipment, procedures and processes that will result in improved patient outcomes, operating room efficiency, or both. The ORF process has sought to establish links to both industry partners and academic researchers who are developing these new technologies, to maximize the talents and skills of each area to provide or build the optimum integrated operating room. This includes collaboration among industry partners to maximize the integration of modular equipment, new surgical information systems, and new approaches to process flow. It is only when individual high technology components can be integrated into systems that the intended goals can be achieved. The challenge is to improve processes, optimize patient safety, increase throughput and reduce costs.

Key Results:

8. Room design was tested and finalized through the process of building design mock-ups and the use of Auto Computer Aided Design models. Additional funding was sought and secured by the project leadership that has resulted in Partners HealthCare System making an additional capital commitment of $750,000 to fund the unique construction aspects of the OR of the Future (ORF). Core funding had already been provided by MGH for the usual and ordinary aspects of the build out. Construction was substantially completed June 2002.
9. Finalized all agreements and statements of collaboration with Industry partners. Ten industry partners have joined the ORF project, along with two companies who have collaborative research and development agreements with CIMIT, Mobile Aspects and Sentinel Wireless. Throughout FY 02 Industry partners worked with the ORF team to identify appropriate technology for the project, arranged delivery, completed installation, integration and training for various technologies in July 2002 (see Table 1).
10. Executive Group created sub-committees with responsibility for specific issues, e.g., Outcomes, Core Equipment, IT, Construction, Staffing and Supply Train.
11. Outcomes template finalized and in place
12. A candidate for the position of Project Manager, Marie Egan, RN, MS, was identified and recruited.
13. A simulation model of various staffing patterns was developed. This modeling: 1) identified a staffing pattern that optimizes the efficiency and utilization of ORF personnel; 2) created new job descriptions that guided the selection of staff to work in the

room; 3) catalyzed development of novel policies and procedures to guide practice in this innovative environment. The staff will also contribute to the data collection for the Outcomes Project by participating in job satisfaction surveys both before the room opens and at intervals afterward. The staff (medical, anesthesia, nursing, biomedical and support staff) has been identified and trained.

14. Room opened for training, including mock surgeries, in July 2002. The multi-disciplinary team collaborated to develop surgical scenarios that were then acted out. These scenarios included cases from each of the three surgical specialities operating in the ORF, General Surgery, Gynecology and Genito-Urinary surgery. Lessons learned form each mock case were integrated into future iterations. The room opened for surgery in August 2002. Four Gynecology cases were performed in a smooth, safe fashion.

Specific Aim 1: To design and build a novel Operating Room (OR of the Future):

- Team formation
- Finalizing goals
- Establishing Industry Collaborators
- Testing, Finalizing Room Design
- Identifying Needs, Methods of Tracking Equipment and People
- Identifying Needs and Facilitating Design of Information Integration

Progress: Team formation

The Massachusetts General Hospital (MGH) Surgical Executive Committee and CIMIT formed a team to design and build a novel Operating Room (OR of the Future). The team grew to include over 25 members with backgrounds in Surgery, Anesthesia, Nursing, Architecture, Construction, Information Systems, Biomedical Engineering, Operating Room Management and Administration, Engineering, and Outcomes Measurement. This "Large Group" meets biweekly and has responsibility for evaluating and directing the "big picture".

In Fall 2001 it became clear to the group that a number of smaller sub-committees would better meet the management and organizational needs of various key aspects of the project. The sub-committees formed included Core Equipment, Supply Chain, Staffing and Patient Flow, Outcomes, Construction, and Information Technology. These six sub-committees meet on a schedule established by their memberships and are over seen by the ORF Executive Group. This Group comprises key senior leadership who meets as a group weekly and is responsible for oversight of the entire project.

During FY02 a candidate for the position of Project Manager, Marie Egan, RN, MS, was identified and recruited. This position is jointly funded by CIMIT and MGH Department of Nursing and functions as an essential interface between the MGH operating room leadership and staff and CIMIT.

The ORF team continues to guide the purpose and function of the ORF. Membership of the team is modified to meet the evolving needs of the project, e.g. Architecture and Construction no longer have full time representation on team. Clinical and scientific membership is expanding as room utilization increases.

Plan: Going forward, the focus of the ORF team will be to develop and refine processes for the integration of new technologies, data collection and analysis, team building, patient flow and

work flow. In collaboration with the Simulation Center we will design two, six-hour modules to be used twice during the first year of operation of the ORF. Scenarios will be created to put team members in challenging situations that demand good teamwork for success. The program will include realistic simulations, a short didactic session on principles of crisis management and teamwork, debriefing of the video taped session, followed by other scenarios and debriefing. Each team member will experience both modules during the year.

Progress: ***Finalizing goals***
Four goals were established by the ORF team. 1) To create an operating room with integrated and automated information/communication systems to allow effortless data collection and measurement 2) To reduce "technology crowding" around the patient by the use of boom systems and a control room 3) To reduce turnover time in order to increase efficiency and productivity of the ORF and 4) To create the infrastructure to formally evaluate the impact of these technologies and design changes on patient care.

Plan: Project completed.

Establishing Industry Collaborators
Progress: Industry participation was seen as an essential element to the success of designing this Beta site room, with a goal to maximize the functionality and integration of state of the art technology. There are now a total of 10 Industry partners involved in ORF along with two companies who have collaborative research and development agreements with CIMIT, Mobile Aspects and Sentinel Wireless.

These companies were selected because they were felt to represent "best of breed" technologies and to have a requisite corporate attitude of collaboration and willingness to work with other industry partners. Each company signed an agreement with CIMIT to be a partner in this development, and each contributed not only state of the art technology to be integrated into this room, but also ongoing technical and engineering expertise. The industry proprietary information was protected, but new models for integrating equipment from different companies were considered a work product of this project.

The work of this past year was to finalize and complete industry agreements and to have them enacted. At the close of this past year project partners have successfully installed an initial iteration of their products, assisted in the training of the multi-disciplinary team and achieved a degree of integration with each other's technology. The contributions of these partners are detailed in the table below.

- Anesthesia Companies: Drager Medical Systems, GE Medical Systems
- Infusion Devices; Harvard Clinical Technologies
- EndoSurgical Companies: Karl Storz Endoscopy, J&J Ethicon Endo-Surgery; Pentax Precision Instruments
- Inventory Management and tracking technologies: Omni cell, Mobile Aspects, Sentinel Wireless
- Imaging technology: BK Medical
- Equipment booms, OR lights, sterilizer, blanket warmers: Getting Castle
- Patient transport system and operating table; Maquet, now part of Getinge Castle

Plan: The ORF team will hold a series of meetings with Industry partners, both separately and collectively, to establish mutual goals for the development and further integration of their technologies in the coming year. Both groups will work closely with the Outcomes team to facilitate the collection and analysis of data.

CIMIT/MGH BLAKE ORF INDUSTRY PARTICIPANTS

Table 1

Industry	**Terms of Agreement**	*Equipment In Kind*	**$ Value of Equipment**	**Membership Fee**	**Value**
Laparoscopic Cameras:					
Karl Storz	5 years	OR 1 System, - integration of cameras, light sources, monitors, and insufflator controlled by one screen	$335,000		$335,000
Laparoscopic Equipment:					
Pentax	TBD	One gastroscope One colonscope	$50,000	$15,000	$65,000
Booms/Lights:					
Gettinge Castle	1 year	Boom and cart system moves equipment off floor, eliminates cables	$412,000		$412,000
Energy Delivery Systems:					
J&J Ethicon Endosurgery	1 year	Best ultrasonic system (Harmonic), most integrated RF (Pegasys)	$80,000	$50,000	$130,000
Anesthesia/ Monitoring					
Draeger	3 years	3 anesthesia machines, booms, anes. record keeping and IS system	$165,000		$165,000
GE Medical Systems	3 years	Networked physiologic monitors for 3 patient locations/continuous monitoring	$75,000		$75,000
Asset Tracking:					
Sentinel Wireless	Collabor-ative	Active tracking of surgical objects and people			
Mobile Aspects	Collabor-ative	RF tagging for passive inventory control (instruments, scopes)			
Omnicell	1 year	Automated storage cabinets for nursing, anesthesia supplies with expected 20% reduction in disposables	$412,000	$50,000 (yr1) $50,000 (yr2)	$512,000
Patient transport system/OR table:					
Maquet (not part of Gettinge)	1 year	3 bed transport system, one bed post and accessories			
IV Drug Delivery Systems:					
Harvard Clinical Technology	1 year	Infusion pumps with automatic drug recognition & drug library capabilities	$50,000		$50,000

Imaging Systems					
BK Medical		State of the art colour Doppler ultrasound machine and 3 probes	$100,000	?	?
SUBTOTALS			$1,679,000	$165,000	
GRAND TOTAL $1,844,000					

Testing, Finalizing Room Design
Progress: Room design was tested and finalized through the process of building design mock-ups and the use of Auto Computer Aided Design models. This proved to be an essential part of the design process as issues arose in the evaluation that had not been anticipated until that point. The team of surgeons, nurses, anesthetists and engineers worked with the architects to achieve the aforementioned 4 goals. The process of anesthesia induction prior to surgery, and then emergence/extubation post surgery can be a prolonged process that delays use of the operating suite for the next patient.

The team designed both an architecture and a work flow system that allows for induction and emergence in an ante room equipped with anesthesia equipment and personnel. This flow model was tested through a computer simulation, and refined accordingly. With this simulation process evaluated by the clinicians who will use this room, the actual design was modified to maximize the flow and efficiency. The computer simulation also modeled different schemes for equipment placement and interaction. Finally, a mock up was created based on the computer simulations and further design modifications were made. Critical to this plan was identifying a patient bed that the patient could be placed on prior to surgery, stay on during the procedure, and then during recovery. This equipment was located (Maquet Bed), and facilitated the actualization of this design.

The room became operational in August 2002 and the benefits of having performed mock-ups and using CAD became clear. The patient flow worked very effectively from the first day. The team has adapted to the new flow and becomes more proficient with every operating day. There were still some design issues that did not become apparent until the room became a physical reality – the critical importance of ceiling height when using booms was well understood but the actual construction of ORF and the installation of the enormous amount of infrastructure required in the ceilings resulted in a sub-optimal ceiling height. The booms did not have sufficient clearance. The Construction Committee worked closely with Industry and the end-users to resolve the problem in a creative manner – the area where the main boom is mounted to the ceiling was recessed a crucial 7 inches and the booms had sufficient clearance.

Plan: Ongoing evaluation of how room design meets needs for flexibility and adaptability as additional technology is integrated into the environment.

Identifying Needs, Methods of Tracking Equipment and People
Progress: Project completed.

Plan: Installation, implementation and evaluation of tracking technology will take place as soon as Industry partners are ready to advance. We will investigate the use of a passive wireless

tracking system for two major purposes. First we will attempt to determine the optimal RFID tag to track laparoscopes. Once this is accomplished we will make efforts to track other equipment necessary to perform surgical procedures. Since RFID has potential to greatly improve patient safety we will also conduct feasibility studies to determine the type on information most commonly associated with adverse events and study where access to critical information is needed and at what time in the process of providing care. We will then study feasibility on an inanimate model by creating software that will allow tracking information within the OR environment and matching patient information to pre existing data bases such as drug-drug interaction software.

In FY03 refinements to the tracking system will be optimized and the system will be deployed in the ORF and other areas of the operative environment (e.g. PACU, hallways). Tags will be issued to all ORF staff members (possibly embedded in footwear) – the goal is to provide a single technological solution that makes end-user compliance effortless. Data collected will be utilized to support workflow process reengineering as well as being a key data source for the Outcomes project.

Identifying Needs and Facilitating Design of Information Integration

Progress: Initial installation of information systems complete. A major goal of this project is to measure outcomes. In order to do this, IS infrastructure necessary to support the goals articulated above was identified. The complexity of integrating different databases from multiple sources became apparent and allowed us to identify the links that need to be created. As a result we have identified the resources from within IS that will be needed to work on the project as it moves forward.

Plan: To continue to design and build information systems to meet the evolving needs of the ORF project.

Specific Aim 2: To develop and utilize computer simulation models in order to evaluate the complex and changing systems of the Operating Room of the Future.

Progress: Project completed.

Plan: Computer simulation models will continue to be used to evaluate the impact of innovative change before it is implemented in the surgical environment. - In FY 03 we will work closely with the Outcomes group to expand preliminary discrete event simulation model into a comprehensive and robust model of the entire surgical suite. We will develop additional plans for data acquisition and verify the model against published literature and existing databases. Concurrently we will determine patient clinical (e.g., procedural success, morbidity and mortality) and process outcomes (e.g., waiting time, flow time, resource/staff utilization) associated with the use of the ORF, compare different staffing scenarios with regard to clinical and process outcome, and investigate the effect of surgical technologies and processes on the occurrence and type of medical errors. As part of this analysis we will identify opportunities for further technology/process development in order to guide resource allocation and optimize the development process. In addition we will investigate the effect of surgical technology and process change on staff efficiency, satisfaction and burnout.

Our ultimate goal is to use data mining techniques on large intra-op and peri-operative data sets to establish algorithms that will identify high risk situations with the aim of alerting clinicians when dangerous conditions exist. In FY03 we will apply existing methods to large data sets that describe a standard static problem, with a single database record describing a case for which a prediction will be made. We will then extend this work to data sets with a significant temporal component, such as temporal sequences of a patient's vital signs. We will investigate the inclusion of expert medical knowledge into the machine-learning algorithm.

Task 2: Patient monitoring and communications

Principal Investigator: Nathaniel Sims, M.D., MGH and John Guttag, Ph.D., MIT

Medicine centers on gathering information about the state of a patient, and then using that information to choose interventions intended to improve the patient's state. Using a plethora of devices, clinicians collect a broad variety of data when treating patients. Typical devices include: stethoscopes, electrocardiogram machines and blood pressure monitors. Meanwhile, it has been widely reported that preventable medical error causes between 50,000 and 100,000 accidental deaths per year in the United States. While testifying before the U.S. Senate in February 2000, Dr. Dennis O'Leary, President of the Joint Commission on Accreditation of Healthcare Organizations said, *"I would like to stress that medical error reduction is fundamentally an information problem. The solution to reducing the number of medical errors resides in developing mechanisms for collecting, analyzing, and applying existing information."*

With upwards of fifty microprocessors in every hospital operating room, computing already pervades medicine. Processors can be found in electrocardiogram machines, blood pressure monitors, drug pumps, and even stethoscopes. Each device greatly facilitates medicine's fundamental process of gathering information about the state of a patient and then using that information to chose interventions intended to improve the patient's state.

The objective of this task, "Patient Monitoring and Communications", is to aggregate expertise from academia, industry, and government to create and disseminate novel solutions in this arena to reduce medical error and improve the quality of care. The quarterly progress report described one such innovation, creation of a "Patient-Centric Network: An Architecture for Physiologic Sensors". The description below further defines the approach taken by this group towards creating and sustaining such solutions and the progress to date.

Key results: Over the past year, a sustainable research and development infrastructure has been created at MIT and Massachusetts General Hospital. An innovative concept and development plan has been created and articulated through papers, prototype demonstrations, and multi-media presentations. There have been significant successes in sourcing and aggregating custom sensors, components, and software modules. Key clinical and research partners have been identified by a variety of means. Sustainability has been achieved through the incremental recruitment of clinicians and advanced degree students to the effort. Two flagship projects, exemplary of the power and promise of this initiative, the Patient-Centric Network (described in the quarterly report) and the Mitral Valve Prolapse Detector, described below, are in advanced stages of development. Finally, two avenues of major additional funding have been obtained to support related work. Publications and patent applications are in draft form.

Specific Aim 1: To create sustainable research and development infrastructure to support the design and development of advanced medical systems technologies, such as the "Patient Centric Network: An Architecture for Physiological Sensors."

The infrastructure is necessary to facilitate collaboration among Boston area clinicians, researchers from MIT's Laboratory of Computer Science, CIMIT, and Massachusetts General Hospital's Biomedical Engineering Unit. This collaboration will promote desired outcomes, such as publications, patents and dissemination of provocative breakthrough ideas, creation of device prototypes, medical product development, clinical research projects and recruitment, training and education of promising engineers and clinicians towards careers in physiologic signal processing and medical technology.

Progress: Dr. Sims of Massachusetts General Hospital, Dr. Reuben Mezrich of CIMIT and Prof. John Guttag established a research group (named "ORNET") based at MIT's Laboratory of Computer Science to articulate and develop the Patient Centric Network concept and to undertake a limited number of major projects appropriate in scope and pace to the academic engineering environment. In parallel, the Advanced Biosystems Group was established at Massachusetts General Hospital to conduct advanced scouting/scavenging for technology, customers, applications, and to engage in rapid-response "concept engineering." The latter organization, based in MGH's Biomedical Engineering Unit, works to mobilize resources within the clinical, industrial, and governmental circles to address patient care technology problems and opportunities relevant to acute care settings.

Plan: The synergy between the work of these two groups will be promoted and developed so that further collaborations and aggregation of expertise can be supported. The Advanced Biosystems Group will be establishing satellite offices within CIMIT's Lansdowne Street site to enhance the synergy between the efforts of this group and those of CIMIT. Proximity will strengthen the capacity of the individuals within the group to tap into CIMIT's expertise in the areas of industrial relations, technology transfer, outcomes assessment, and regulatory affairs. Duplication of effort will also be avoided.

Specific Aim 2: To conceive and promulgate a concept and research and development plan for Patient Centric Networking.

Progress: This was accomplished by February 2002 with the completion, and submission for publication, of "Patient-Centric Network: An Architecture for Physiological Sensors." The publication is currently in 'white paper' form and attached to this document. A video on the "Patient Centric Network" was created. The work was presented at numerous forums, including the Boston Sensor Expo this fall.

Plan: Additional publications are in process. The concept and R&D plan will evolve based on feedback from these communication forums. Considerable future work remains. The most important areas are reliability and fault tolerance. Other areas of focus include: the way in which clinicians connect and configure proxies, methods to combine and archive data, especially time-series data streams.

Specific Aim 3: To identify and source digitized multiparameter physiologic data streams, custom sensors, actuators, and thin data clients that can be used to develop and to test prototype

advanced signal-processing algorithms and to create "end-to-end arguments" that illustrate achievement of higher level goals, and novel use models, for patient centric networks.

Progress: Four sources of digitized physiologic data have been sourced and used to create signal processing applications. First, the MGH/Marquette Hemodynamic Waveform Database archives were tapped to create a synthetic prototype network "end to end argument" involving detection, diagnosis, and annunciation of cardiac arrythmias.

Second, in collaboration with Children' Hospital Boston, electroencephalographic (EEG) recordings from children with intractable seizures were sourced for development of an automated "Patient Specific Epileptic Seizure Onset Detector". Third, in collaboration with MGH's Cardiology Unit, a collaboration was established to acquire public domain library acoustic/ECG cardiac recordings of patients with mitral valve prolapse (MVP) to support development of software to distinguish benign murmurs from MVP.

Relative to custom sensors/data acquisition systems/actuator/thin clients, the teams have sourced, adapted, or created a variety of sensors and actuators adaptable to Patient Centric Networks, including conventional electronic stethoscopes, custom piezoacoustic sensors/microphones/accelerometers, commodity and custom ECG front end electronics, and novel low-power optical means for acquiring plethysmographic waveforms and determining oxygen saturation. In some cases these have been incorporated into inexpensive but capable data acquisition systems based on commodity computing devices, for example an acoustic sensor and ECG front end have been coupled to a Compaq IPAQ that has been modified to expose two line input connections to the digital-to-analog signal converter. A representative medical actuator (fluid delivery module from a drug infusion pump) has been sourced from a medical device company (Harvard Clinical).

Plan: Several additional sensor and actuator technologies are in the "pipeline" for use by the teams.

Specific Aim 4: To find clinical research partners, potential customers, potential licensees, and begin or implement significant proposals/projects with several of these.

Progress: Key clinical and research partners have been identified by a variety of means. The efforts currently structured around the MIT ORNET Group include the following:

- Division of Epilepsy & Clinical Neurophysiology at Children's Hospital Medical Center (Boston) [Dr. Blaise Bourgeois - Seizure Onset Detection – unfunded collaboration];
- the Cardiac Unit of the Massachusetts General Hospital [Drs. Francesca Nesta and Robert Levine – Cardiac Auscultation and Mitral Valve Prolapse Detection - funded collaboration];
- the Decision Support Unit and Emergency Services of the Brigham and Women's Hospital [Drs. Linda Ohno-Machado and Robert Greenes – Ambulatory Physiologic Monitoring and Principled Alerting Systems for Emergency Services – grant application filed].
- The efforts currently structured around the MGH ABG Unit include the following:
- the US Army Research Institute for Environmental Medicine [USARIEM – Reed Hoyt, PhD – Warfighter Life Signs Detection – funded collaboration], the US Army Institute for Surgical Research (USAISR – Col. John Holcomb, MD;

- Victor Convertino, PhD – Warfighter Life Signs Detection, Physiologic Status Monitoring, and Trauma Triage – funded collaboration).
- Unfunded relationships are in place with several industrial partners, including Motorola, Meditron NA, Harvard Clinical Technology, Dolphin Medical, and several others.

Plan: The present relationships constitute sufficient activity for the teams at this time. Additional relationships will likely evolve as required.

Specific Aim 5: To incrementally grow the MIT ORNET group to include additional MS and PhD candidates, and clinician participants as appropriate to the academic/development opportunities; incrementally grow the MGH ABG Core Group as appropriate to the funded projects and clinical needs of the Hospital.

Progress: Several additional undergraduates and one PhD candidate have recently been added to the MIT team. One undergraduate, Ali Shoeb, has declared his intention to apply to the HST Medical Engineering and Medical Physics Graduate Program. Additional physicians are now being added to the MIT ORNET group.

Plan: Recruit additional candidates as required.

Specific Aim 6: In the first year of the ORNET, complete at least one significant exemplary project to the point of clinical implementation, patentability, and/or publication.

Progress: In addition to the Patient Centric Network core project, another exemplary project has been completed: the Mitral Valve Prolapse Detector System. In brief, two forms of the detector were developed in a 'competition' between MIT and ABG. Public domain library acoustic recordings with ECG were acquired with Mitral Valve Prolapse or related conditions including controls. The signal processing teams recognized that patients with MVP display increased acoustic energy just before S2 in the higher frequency bands. Both teams implemented algorithms for S1 and S2 detection, average beat calculation, and Time-Frequency analysis, using slightly different approaches. Both experienced significant success in classification of normal/benign murmurs vs MVP and in classification of MVP vs. other systolic murmurs.

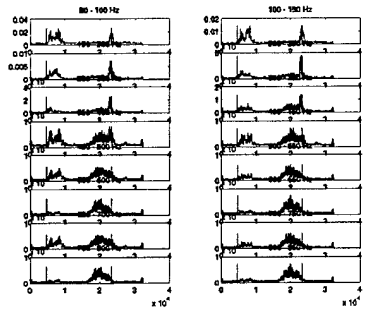
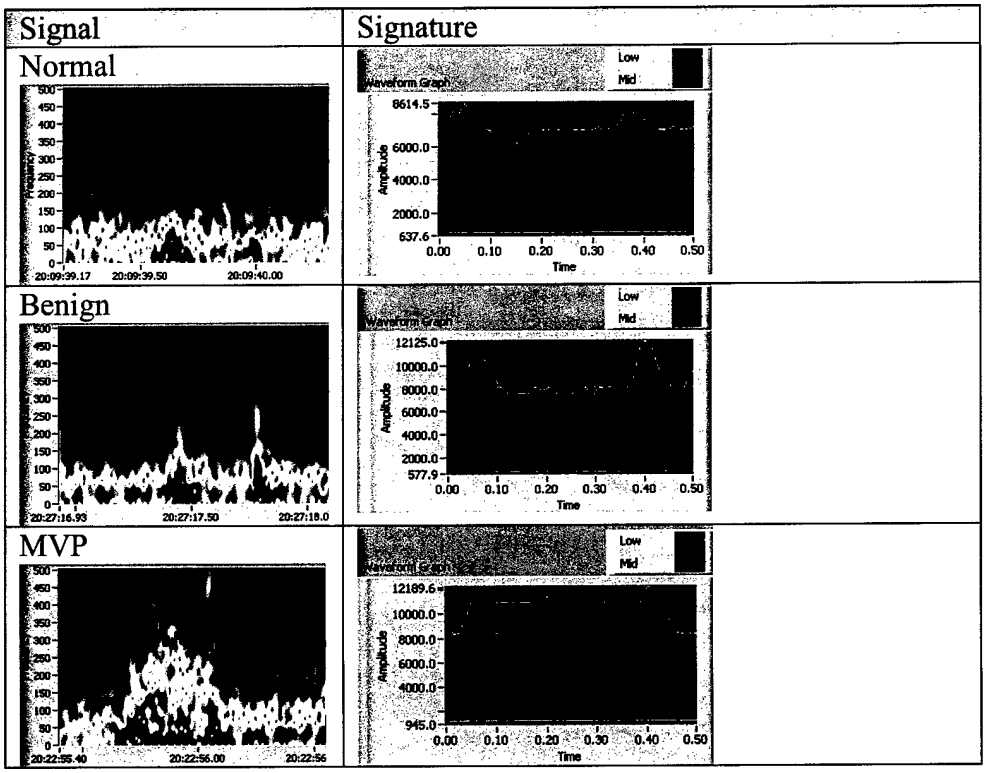
	Figure 1. "MIT" Mitral Valve Prolapse Detector: an average beat from a recording of a patient is passed through a filter bank with bands spanning 50Hz intervals from 50 Hz to 850 Hz. Fiducial marks are present for S1 and S2. Increased energy is seen just before S2 in the higher energy bands (lower portions of the table).
Figure x. MIT Mitral	Figure 2. "MIT" Mitral Valve Prolapse Detector: normal control.

Figure 3. "MGH ABG" Mitral Valve Prolapse Detector: recordings from three patients illustrating aspects of signal depiction and signal processing.



Significance of Mitral Valve Prolapse Detector (as an exemplary effort): In one aspect, it is a modular end-to-end argument (from novel acoustic sensor to body surface to sensor fusion to advanced signal processing to internet dissemination of an automated report). In another aspect it is a multidisciplinary international collaboration. In a third aspect it is an exemplary "health state assessment engine". In a fourth aspect it is an element of a novel use model for distributed health care (affordable advanced diagnosis in primary care). In a fifth aspect it is an example of health care cost reduction (tool to reduce unnecessary cardiology referrals and ultrasound examinations for benign murmurs). In a sixth aspect it is a likely first candidate for technology transfer from MIT and MGH to third parties for implementation – two entities have expressed interest in evaluating the technology for commercialization.

Plan: Much additional work remains to be done to perfect, implement, and validate the MVP Detector. The process by which this will be accomplished will be determined by the teams and by the sponsor, Robert Levine, M.D.

Specific Aim 7: To generate significant publications and patent applications.

Progress: See below attached "Patient Centric Network: An Architecture for Physiological Sensors" – Harfst, Guttag, Curtis, Sims, Mezrich – submitted for publication. Also: "Mitral Valve Prolapse Detection Sensor" - Ames, Sims, Levine – in draft. Also: Video: "Patient Centric Network" – Guttag, Mezrich, Sims.

Plan: Ongoing work will culminate in future publications and patent applications as appropriate.

Specific Aim 8: To attract additional funding for sustainability.

Progress: MGH ABG was funded August, 2002 – September 30, 2003 through CIMIT from the DOD – (US Army/Combat Casualty Care/USARIEM) for work on Warfighter Life Signs Detection Systems. MIT ORNET expects receipt of a portion of a grant from the National Library of Medicine to Brigham and Women's Hospital Decision Support Group for engineering development activities in principled alerting systems for ambulatory monitored patients.

Plan: The teams would appear to be at maximal capacity under the current efforts at this time.

Task 3: Robotics in cardiac surgery
Principal Investigator: David Torchiana, M.D., MGH

This project involves laboratory development of a robotic interface in cardiac surgery. Since the project's initiation in 1999, endoscopic coronary artery bypass ("E-CABG") using the robotic interface ("Zeus", Computer Motion, Inc.) has been performed in seventy-five laboratory animals. During the same period the principal investigator/cardiac surgeon has been participating in a multi-center clinical trial to investigate the use of the device as an aid in harvesting the internal mammary artery.

In humans the internal mammary artery tends to course deep in the transversus thoracis muscle and may be out of the thoracoscopic view of the surgeon. In an attempt to simplify mammary

mobilization, a technique for using CT-image guidance has been developed in conjunction with Professor Howe in the Harvard Dept of Engineering.

Key Results: Laboratory studies over the last year were limited because of a delay in acquiring DoD animal approval. We have acquired a robotic system upgrade with microwrist instruments. The use of articulating instruments increases surgeon dexterity from five to six degrees of freedom. The Hermes system has been installed allowing the surgeon central control of the operating room through voice and touch screen displays. Since the last quarterly report, Computer Motion has assigned a fulltime engineer to our laboratory to assist with the use of the new robotic interface.

Specific Aim 1: To develop closed-chest video endoscopic coronary artery bypass using a robotic interface in the laboratory while transferring the technology into the clinical setting in phases. The transfer of techniques into the operating room is contingent on FDA approval. Laboratory studies directed towards device development and training of the surgical team will continue throughout all phases.

Proximal anastomosis with mechanical device
The proximal anastomosis device ("Symmetry", St. Jude Medical, Inc.) was modified to allow successful endoscopic deployment and provide a hemostatic connection of a saphenous vein to the ascending aorta in a large animal model. A new technique involving direct cross-clamping of the ascending aorta and the direct administration of cardioplegia into the aortic root eliminated the need for fluoroscopy to position the catheter.

Novel method of cardioplegia delivery and venting
A novel method of cardioplegia administration using the saphenous vein as the conduit for delivery was successfully carried out in a large animal model. A new means of aortic root venting was performed using a catheter cannulating the saphenous vein. These findings were presented this year at the major cardiac surgical meeting focused on minimally invasive therapies.

Computer-guided LIMA harvesting
In an effort to improve the safety and efficiency of LIMA harvesting, the laboratory has undertaken a study in a large animal model to use pre-operative CT to "map-out" the course of the artery prior to surgical procedure. The surgery is then conducted using the robotic interface under the guidance of data collected from this pre-operative image. This work is described in detail in the following:

This study has unsuccessful in that it has not been possible to register anatomical landmarks and locate the instrument tips to the level of precision needed. Although the concept remains attractive and the potential for added significance great, the next steps in the project have yet to be defined.

Algorithm-based Port Placement
The laboratory conducted a study in conjunction with Boston University School of Engineering faculty to develop a port placement optimization model using an algorithm designed to increase surgeon dexterity and decrease procedure duration. The potential clinical applicability of the port placement system will be to overcome the effects of variation in human anatomy in port

placement. The system may also serve as a useful training model for surgeons learning to perform minimally invasive procedure.

Plan: The cardiac surgeon/ principal investigator will continue to perform E-CABG procedures in a large animal model in the laboratory to investigate methods and instrumentation, such as image-guided surgery, to support minimally invasive cardiac surgery while providing a training ground for specialized surgical skills.

Task 4: Gallbladder extraction device
Principal Investigator: David Whittaker, M.D., MGH and David Rattner, M.D., MGH

Laparoscopic surgery has become an impressive tool in a surgeon's arsenal. It has allowed minimally invasive approaches to once invasive procedures. Laparoscopic cholycystectomy is one of the most commonly performed laparoscopic procedures in the US (approximately 750,000 cases/year). The average dissection time is 45 minutes for an uncomplicated case. Frequently, however, surgeons encounter difficulty removing the actual specimen from the body due to an inflamed, edematous, stone-filled gallbladder that will not fit through a small laparoscopic incision. The surgeons will spend an additional five to twenty minutes on this portion of the procedure. Many techniques are available to extract the gallbladder including shear force, the use of crushing clamps and bags; and widening of the skin and facial incision. These techniques are often associated with the loss of stones or tissue into the abdomen and resultant risks of abscess formation. Additionally, there is the risk of wound infection from dragging the infected specimen through the wound. The CIMIT team has designed a device to provide a controlled means for encomp0assing the gallbladder and its contents in a secure fashion, compressing it and allowing easy and efficient removal through the trocar site.

The project has seen slow, but steady advances over the past year. From the Subcommittee on Research Animal Care (SRAC) and the Department of Defense (DoD) animal studies approval, to the Preliminary Patent Application (PPA) and communications with outside vendors including Ethicon Endo-surgery, the project continues to make progress.

We had hoped to involve Ethicon in the development of the prototype to help defray costs and streamline its introduction to industry. Ethicon, however, eventually decided to defer further involvement until they can evaluate a working prototype. Unfortunately this decision process resulted in a significant loss of productive time. Furthermore, we are once again faced with the full financial burden of the product R&D. Therefore, we have returned to our initial intent to manufacture a working prototype and then re-approach our industry contacts. We are currently seeking a contract with an external vendor to manufacture a prototype.

It appears as though a prototype could be produced by late November which should allow for testing in December or January. Of the original $25,000 award, there is still ~$22,000 remaining. This should be sufficient for the prototype production and testing as outlined in the original budget. In order to facilitate this aspect of the project, we have requested a no-cost, one-year time extension for the CIMIT award. We remain committed and confident that a successful device can be produced that will be intriguing to the laparoscopic device industry.

Key Results: Over the past year, our key results include: 1) Preliminary Patent Application with the Patent and Trade Office, 2) Ethicon Endo-surgery deferred further involvement until they can evaluate a working prototype, and 3) Currently seeking a contract with outside vendors to manufacture a prototype.

Specific Aim 1: To establish a working relationship with Johnson & Johnson's Ethicon Endo-Surgery division for the continued research and development of this device.

Progress: As outlined above, this has proven to be a very slow and time-consuming process.

Plan: To establish a working relationship with Johnson & Johnson's Ethicon Endo-Surgery division for the continued research and development of this device.

Specific Aim 2: In the event that the discussions with EES fall through, we will either address different industry contacts or contract with an outside vendor for device development.

Progress: The CIMIT team is in the process of establishing the initial protocol and legal framework for non-disclosure agreements.

Plan: Dr. Whittaker returned to the U.S. Navy in July, arrangements are being made for continued, ongoing interactions with CIMIT.

Task 5: Laparoscopic ultrasound
Principal Investigator: Kirby Vosburgh, PhD, MGH and James Ellsmere, MD, MGH

Laparoscopic ultrasound (LapUS) has repeatedly been shown to improve the staging of pancreatic cancer. The adoption of LapUS by physicians, though, has been hampered by the difficulty they have in understanding the spatial orientation of the imaging plane. We are developing a system to overcome this visualization problem and establishing a test plan to clearly demonstrate the clinical value of using LapUS to stage pancreatic cancer. Preliminary experiments indicate that our system may be able to help orient physicians to LapUS images of the pancreatic head. At the same time, we are evaluating new technologies to make the system both more robust and less user dependent.

The ultimate goal of the laparoscopic ultrasound project is to enable physicians to use LapUS to improve the staging of pancreatic cancer. Over the last decade several groups have described how LapUS can be used to improve the staging of pancreatic cancer and thus reduce the number of patients who undergo non-therapeutic laparotomies. Despite these reports, currently only select centers are using this modality. Physicians have been slow to adopt LapUS because they find it difficult to understand the spatial orientation of the 2D images. By combining preoperative CT with intraoperative laparoscopy and LapUS, we hope to improve the likelihood of identifying those patients who will not benefit from surgery prior to undergoing a laparotomy.

Key Results: Over the last year, the CIMIT team has developed a surgical navigation system that enables physicians with limited ultrasound experience to use laparoscopic ultrasound (LapUS). We have filed an invention disclosure that describes our system with the Massachusetts General Hospital licensing office and submitted an abstract based on our preliminary

experimental results for the Society of American Gastrointestinal Endoscopic Surgeons 2003 meeting. We have also made significant progress in our core technology research, including: 1) determining image based US-CT registration techniques are not feasible without an image processing step that accounts for the inherent differences in how US and CT images are acquired; 2) establishing an agreement with our corporate collaborators to construct a second generation tracked laparoscopic ultrasound that fits through a standard 12mm laparoscopic port; and 3) setting up 3DUS software in our lab for ongoing visualization and registration experiments.

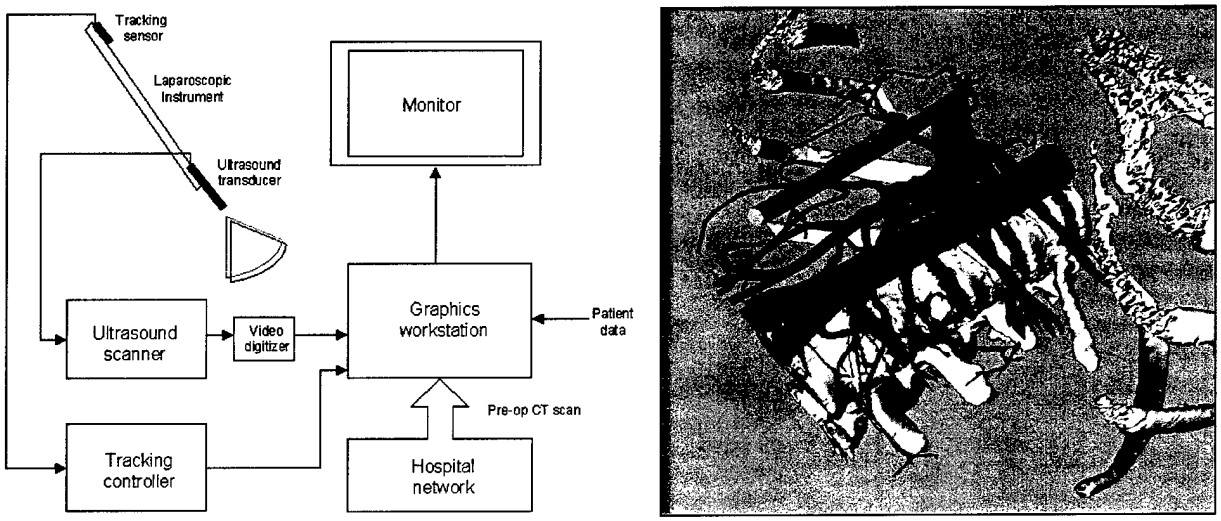


Figure 1. The system shows the laparoscopic surgeon the ultrasound's field of view overlaid on a simulated 3D model of a patient's arterial anatomy.

Specific Aim 1: LapUS Field-Of-View Orientation System

Progress: The system we designed, implemented and validated over the last year uses the miniBIRD magnetic tracking system (Ascension Technology, Burlington, VT) to track the field-of-view of a LapUS (BK Medical, Wilmington, MA)[1]. Building on the open source application, 3D Slicer (www.slicer.org), we created the software necessary to read the six degree-of-freedom position information from the tracking system and display a real time 3D rendering of the ultrasound field-of-view overlaid on a simulated patient's segmented anatomy. The hardware components and 3D view are shown in Figure 1.

For input, the system requires a contrast enhanced CT volume made up of thin axial reconstructions over the volume of interest (upper abdomen from the xiphoid sternum down to and including the lowest ribs). The skeleton and major arteries are then segmented from library CT images using a semi-automated process. Before starting the laparoscopic ultrasound

[1] The miniBIRD transmitter is fixed to the table so that it will be 20 – 200 cm from the receiver during an operation. The receiver is attached directly to the ultrasound transducer. The images from ultrasound system are calibrated to physical space using a "cross wire" technique described in Prager, R.W., et al., *Rapid calibration for 3-D freehand ultrasound.* Ultrasound in Medicine and Biology, 1998. **24**(6): p. 855-869.

examination, the segmented CT and patient may be grossly registered using four ribs as fiducials. The laparoscopic ultrasonographer then performs a LapUS examination of the pancreas and peripancreatic structures. Once the celiac axis and superior mesenteric artery are identified, the system can be updated to reduce the registration error. Typical registration error before updating is 5mm. After updating, the registration error improves to approximately 3mm

This September we submitted an abstract to the Society of the American Gastrointestinal Endoscopic surgeons that describes two validation experiments we conducted. For the first experiment, 3 library images (40X60 mm) of the pancreas and its surrounding structures were reconstructed from a CT based on oblique planes that are typical for LapUS examinations. Physicians (n=6) were asked to specify the position and orientation of these oblique images relative to both the CT angiogram and CT grayscale volume. Speed and accuracy were compared using the nonparametric Wilcoxon signed rank test. For the second experiment, LapUS was performed on a 25 kg pig which preoperatively had a CT angiogram. Physicians (n=4) were asked to identify 4 landmarks (celiac axis, SMA, portal vein confluence, and pancreatic duct) when shown the LapUS image in combination with either the image plane overlaid on the angiogram or laparoscopic video of the peritoneal surfaces. Correct responses were compared using the Chi-square test.

The first experiment showed physicians took less time (77s vs. 155s, $p<0.01$) and were more accurate when specifying orientation relative to a CT angiogram compared to the standard CT volume (angular error 29 deg vs. 47 deg, $p<0.01$). The second experiment showed physicians correctly identified more landmarks when shown the imaging planes relative to a CT angiogram compared to standard laparoscopy (69% vs. 25%, $p=0.02$).

Plan: We are currently investigating what aspects of the visualization provided by our system are most helpful. By systematically removing certain components we hope to identify the key visualization concepts. With this new information, we'll be better able to generalize our results as well as potentially simplify the system by removing step which add complexity but provide only limited clinical value.

Specific Aim 2: Image-based registration

Progress: We have used our radiological phantom of the upper abdomen to generate four pairs of US-CT images. Using these pairs we have evaluated the potential of the image-based registration technique, mutual information, for automating the registration steps in our system. We found the with unprocessed images, we get poor convergence suggesting before we can use image-based registration techniques we'll need to develop algorithms that compensate for the differences in how the US and CT images are acquired.

Plan: We plan to generate 30 pairs of images in order investigate this issue. We have developed a new 3DUS system to generate these pairs (see below). In the past we attempted to manually align 2D US with CT slices to generate pairs. With the 3DUS volumes, we can automate the registration of the US and CT datasets and generate higher quality matching pairs. We have also investigated several image filters to provide the necessary processing step that comes after the image acquisition and but before the image registration. We plan is to compare the relative value of these filters by objectively assessing how they effect image convergence.

Specific Aim 3: Advanced tracking hardware design

Progress: The major design challenge to overcome before we can assess the clinical utility of our system is reducing the size of the tracked LapUS. Currently with a 5mm tracking receiver and the 10mm diameter LapUS probe, we have a laparoscopic instrument with an effective diameter of 15mm. Before we can consider clinical trials, we need to reduce this effective diameter to 12mm.

Plan: We are working with the laparoscopic ultrasound manufacturer (BK-Medical systems) and the tracking equipment manufacturer (Ascension Technology) to construct a second generation prototype that fits through a standard 12mm laparoscopic port. We expect to have a new prototype by the end of the next quarter.

Specific Aim 4: Processing 3D US volumes

Progress: We have set up the 3DUS software, Stradx (svr-www.eng.cam.ac.uk/~rwp/stradx) that was developed at Cambridge University (Cambridge UK). The software runs on the open source operating system, Linux (www.linux.org). It can read in the position and orientation information from our miniBIRD trackers as well the image data from our laparoscopic ultrasound and generate a 3DUS volume. We have developed routines that can read the output into our open source medical visualization software, 3D Slicer

Plan: We plan to use the 3DUS volumes for three purposes. The first is to generate high quality US-CT pairs to do the advanced image based registration work as mentioned above. The second is to evaluate whether 3DUS volumes can be used to simplify the manual registration techniques that we are currently using in our system. Lastly, we plan to formally compare our new visualization techniques with standard volume rendering techniques that are currently employed in many commercial 3DUS systems.

2.3 IMAGE-GUIDED THERAPY PROGRAM

Task 1: Cellular resolution endoscope and catheter -based optical imaging

Principal Investigator: Brett E. Bouma, Ph.D., MGH

Over the past three years, CIMIT investigators have developed a state-of-the-art optical imaging system and have led the world in pioneering clinical applications of this exciting new imaging technology. In related research, using non-DoD funds, human pilot studies have been conducted in six clinical fields demonstrating encouraging results such as near perfect sensitivity and specificity in the diagnosis of specialized intestinal metaplasia of the esophagus and detailed characterization of atherosclerotic coronary plaques.

The diagnostic capability of existing imaging technology is based solely on its ability to visualize tissue morphologic structure. While our results to date have been of great interest to the clinical community, established histopathologic methods are founded upon the visualization of subcellular tissue structure. We therefore anticipate that improvements in resolution will greatly expand diagnostic utility.

Our goal is to continue our international leadership in the field of OCT by demonstrating a 10-fold improvement in resolution for a clinically viable system and to establish that optical imaging of tissue with a resolution comparable to that of routine histopathology can be performed *in situ*. During the first year of this study, we will develop a high-resolution (1-2μm) OCT imaging system for clinical use and will evaluate the capabilities of this system using human tissue *in vitro*. During the second year we will conduct clinical pilot studies to evaluate the diagnostic utility of the technology. Although our immediate focus is on high-resolution OCT imaging, our overriding goal is to enable minimally invasive, non-excisional histopathology. Over the recent years, we have been developing three other technologies that we believe will be competitive with or superior to OCT for specific applications. The development of these and other new technologies will be highlighted in the later years of this program.

The first specific aim of this study is to develop a clinically viable light source that provides broad spectral coverage in a single-transverse spatial mode. During the first quarter, we have pursued two potential solutions. The first is to use a commercially available mode locked laser to seed self-phase modulation in novel optical fiber. We have demonstrated bright emission from the fibers spanning the spectral range from the ultraviolet through the near infrared to 1.6 μm. The second approach is to use dispersion compensating mirrors to enable broad spectrum generation directly from a laser oscillator. Both of these approaches have yielded viable sources for our continued work.

Key Results: The CIMIT team has developed a novel broadband light source based on dispersion compensating mirrors and nonlinear propagation in optical fiber. The source provides high-brightness light and enables high-resolution imaging over a large field of view. We have demonstrated that digital signal processing can be used to overcome image blurring that results from unbalanced dispersion and from non-Gaussian spectral distributions. These advancements have been combined with the development of a novel hand-held imaging probe that provides unprecedented resolution and field of view and have used this probe for imaging tissue *in vitro*.

Specific Aim 1: Develop a clinically viable, spatially coherent light source with a temporal coherence of 1-2 μm.

Progress: As intense light propagates within a transparent medium, it acquires a phase which is dependent upon the instantaneous power. For sufficiently intense light, this nonlinear phase can result in spectral broadening. Using focused light in bulk media yields only modest integrated nonlinear phase since diffraction results in a spatial reduction in the light intensity. In optical fiber, diffraction is controlled through a guided mode of propagation. A disadvantage to optical fiber, however, is that the dispersion of the glass results in a temporal broadening of the light pulse thus limiting the integrated nonlinearity. A novel solution to these problems is the use of a dispersion compensating fiber. We have investigated two different types of dispersion compensating fiber. The first, developed by Lucent, relies on multiple air holes within the fiber surrounding the optical core. The average index of refraction of the fiber cladding is therefore substantially less than that of the core and results in 1) strong mode guiding, and 2) waveguide dispersion that is anomalous, that is negative compared with that of glass. The resulting fiber allows a light pulse to propagate over large lengths while maintaining a short temporal duration as well as a narrow spatial extent. We have also developed a new method for making dispersion compensating fiber. In this case, we start with a standard telecommunications optical fiber and create a taper that adiabatically reduces the diameter of the guided mode. Within the tapered region, the air surrounding the fiber acts as the cladding. The result is similar to the microstructured fiber in that a short light pulse can propagate over a large distance without diffraction.

We have fabricated tapered fiber using several different telecommunications fibers including Corning SMF-28, SM800 and SM500. The SMF-28 fiber is the standard short-haul telecom fiber and is advantageous in that it permits simple coupling of light. However, the relatively long single-mode cutoff of this fiber results in significant spectral loss below a wavelength of 1100 nm. To address this limitation, we have experimented with narrower core fiber which has a shorter single-mode cutoff. These fibers have demonstrated greater power spectral densities in the visible portion of the spectrum but have also shown a greater polarization dependent loss. In the next quarter of research we will develop a polarization control mechanism to reduce this effect.

Dispersion compensating mirrors

An alternative to the light generation method described above is the generation of ultrashort light pulses directly from a laser resonator. Through the Fourier relationship between time and frequency, a short light pulse necessarily contains a broad spectrum. Typical mode locked lasers can provide pulses with a temporal duration of ~100 fs. In order to achieve high resolution OCT imaging, however, the pulse duration would need to be reduced to the order of 5 fs. The primary barrier to the generation of such short pulses is the control of dispersion within the laser cavity. Typical dispersion compensating approaches rely on geometric solutions such as the use of intracavity prisms. An alternative to this is to use special mirror coatings that directly compensate for dispersion. A laser mirror relies on multiple layers of dielectric coatings with alternating indices of refraction. By designing the precise thickness of the layers as a function of depth below the mirror surface, a mirror can be fabricated that allows longer wavelengths of light to penetrate more deeply before reflection. This varied reflection can then compensate for the normal dispersion contributed by the laser gain medium.

The combination of the chirped mirror laser with the nonlinear fiber has allowed the generation of light spanning the spectral range of 400 nm to over 1700 nm with an integrated power of 150 mW. This result vastly exceeds the capability of any other existing light source.

Specific Aim 2: Demonstrate dispersion compensated B-mode optical scanning.

Progress: The spectral shaping technique shapes the source spectrum by Fourier transforming the interferometric signal and then applying a correction to each Fourier component such that the spectrum becomes Gaussian. After an inverse transform, the ideal coherence function for a Gaussian source spectrum is obtained.

We calculated the spectrum from the average of the square root of the power spectrum of 500 A-lines (10,000 samples per A-line, zero padded to 16,384) by Fourier transforming the interferometric responses to a single surface. The resulting curve was then fit to a Gaussian spectrum determined by the zeroth, first, and second moments of the spectral density. The ratio of this ideal Gaussian source spectrum and the measured spectral density defines a spectral correction curve. We obtained the spectrally filtered response of each depth profile by multiplying the Fourier transform of each individual depth profile by the correction curve and performing an inverse transform. The coherence function envelope was obtained by digital quadrature demodulation with a spatial resolution of 1.6 μm.

Images acquired using this correction algorithm exhibited a superior axial point-spread-function. The spectrally shaped image showed a significant reduction of the structure associated with non-Gaussian spectral distributions. The improved image quality comes at a minor expense in increased noise, <0.9 dB.

Specific Aim 3: Demonstrate high transverse-resolution imaging using a single-mode optical fiber catheter.

The design of imaging probes appropriate for laparoscopic or endoscopic use is severely restricted by the limitations in size imposed by the instruments' narrow access ports. For diagnostic medical devices, the diameter is limited to the maximum bore available for the application (6 mm for large bore endoscopes, 12 mm for laparoscopes.) Currently, multiple-element, high-NA microscope objective lenses are required to perform adequate optical sectioning in tissue. Since the length of these objective lenses typically exceeds the diameter of the probe, the optical axis of the objective lens must coincide with the axis of the probe. As a result, all of the components must be designed to ensure beam propagation along one axis. This restriction is problematic as diffraction by a grating necessitates off-axis illumination and/or transmission.

To enable endoscopic imaging, we have developed a novel probe that enables on-axis spectral dispersion based on a dual prism grating combination (dual prism GRISM or DPGRISM). The DPGRISM allows on-axis illumination to be highly diffracted while maintaining on-axis propagation of the center wavelength. The characteristics of the DPGRISM are defined by tradeoffs in wavelength, spectral range, desired resolution, efficiency and complexity of design. Our first prototype was optimized for a large field of view (FOV) and sub-micron resolution. To achieve these goals, a high periodicity grating was required. The resulting large diffraction angle necessitated the use of high index of refraction prisms (silicon, $n = 3.51$) to maintain on-axis incident and output beams. For the current design, we used an 1100 line/mm holographic,

Dickson grating which had >95% efficiency for all polarization states when operated at Littrow's angle (47°). In order to avoid optical losses due to refractive index mismatches, the prisms were antireflection coated (AR) coated to match the air and glass interfaces. The theoretical resolution of this design was calculated to be 0.81 μm using a 0.9 NA objective lens and the transmission efficiency was calculated to be 73%. This design is flexible enough to allow further miniaturization without significant design changes.

Specific Aim 4: Correlate diagnostic information obtained with the high-resolution OCT system with histopathology using human cadaver tissue and surgical specimens.

Progress: Images of an electron microscopy grid (6 mm bars separated by 25 mm) were acquired to test the resolution of the imaging probe. Measurements of the cross-section of individual bars of the grid were used to determine lateral resolution. The combination of optics and light source used in this experiment resulted in images with a FOV of 658 μm and a lateral resolution of 1.1 μm. We attribute the degraded resolution (1.1 μm measured; 0.81 μm theoretical) to the use of 1.3 μm wavelength light in an objective which was optimized for use in the visible. The measured transmission efficiency on double pass of the DPGRISM was 63%. Images of human cadaveric tissue at various depths were acquired with the probe and are compared with histology. Microscopic features that were visible included cell walls and intracellular details including nuclei. The images have dimensions of 650 x 300 μm (1200 x 600 pixels), and are displayed using a gray scale look-up table.

Plan: To continue research to improve and enhance the capabilities of OCT. Specific goals will include the ability to identify goblet cells within intestinal epithelium, macrophages in atherosclerotic plaques, and nuclear features that are characteristic of dysplasia.

Task 2: Non-invasive image-guided opening of the blood-brain barrier
Principal Investigator: Kullervo Hynynen, Ph.D., BWH

The CIMIT team, lead by Dr. Hynynen, is awaiting animal use approval before initiating this project.

Task 3: Automated Segmentation of Anatomy from CT and MRI
Principal Investigator: Carl-Fredrik Westin, Ph.D. and Ron Kikinis, MD, BWH

The broad goal of this Enabling Technology project is to improve the way that information from medical image data is extracted. The project is a continuation of our ongoing effort to develop new technologies to improve efficiency and specificity in creating patient specific anatomical 3D models for surgery simulation, surgical planning, and image-guided intervention.

Key Results: This year, the team has been focused on developing a user-friendly software module, based on our optimized libraries developed last year, in the 3D Slicer. The 3D Slicer is a visualization tool developed as a joint effort between our laboratory and the AI laboratory at MIT (Cambridge, MA [http://slicer.org]). In addition, the team has focused on a novel method for extraction of vessel centerlines. Preliminary results were recently presented in [Krissian02]. The method has sub-voxel accuracy and is based on the gradient, and the eigenvalues of the Hessian matrix to interpolate the zero-crossing of the gradient vector in the cross-sectional

directions. The method is fast and efficient. It takes about 4 min on a standard workstation or PC to process a PCA-MRA data set of size 256x256x122. The method is currently tested on cardiac CTA data. The team has also developed a novel approach to correct flow data from phase contrast angiography (PCA) [Watanabe02a], [Watanabe02b]. The method is based on combining computational fluid dynamics (CFD) and segmentation in a level set framework.

Specific Aim 1: Extend our current implementation of adaptive filtering

Progress: See Quarterly Progress Report April 1, 2002 – June 30, 2002.

Plan: Project completed.

Specific Aim 2: To develop a segmentation model based on the team's experience on adaptive filtering and surface evolution.

Progress: See Quarterly Progress Report April 1, 2002 – June 30, 2002.

Plan: Project completed.

Specific Aim 3: To develop a symbolic description of vessel anatomy based on vessel mid-lines, vessel diameters and branching points.

Progress: This year the team has focused on developing a novel method for extraction of vessel centerlines. Preliminary results were recently presented [Krissian02]. The method has sub-voxel accuracy and is based on the gradient, and the eigenvalues of the Hessian matrix to interpolate the zero-crossing of the gradient vector in the cross-sectional directions. The derivatives are computed by convolving the image with the derivatives of a Gaussian kernel to minimize the artifacts introduced by the discrete sampling. The computational time for extracting the centerlines in a phase contrast MRA data set of size 256x256x122, is 4 minutes on a standard SunBlade 3000 sun workstation. Results are shown in Figure 1.

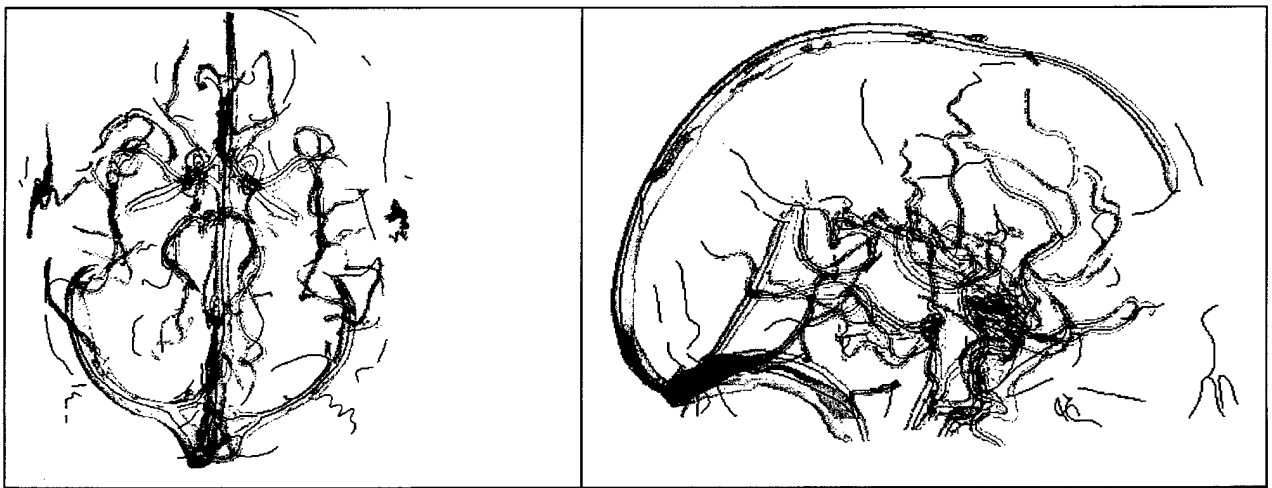


Figure 1: Axial (left) and sagittal view (right) of the result of sub-voxel vessel centerline extraction from library PC-MRA. The results are superimposed on an iso-surface. Notice that some centerlines are detected at lower intensity values than the displayed surface.

The team has also developed a novel approach to correct flow data from phase contrast angiography (PCA) [Watanabe02a], [Watanabe02b]. The method is based on combining computational fluid dynamics (CFD) and segmentation in a level set framework. The PCA-MRI velocity data is used in a partial differential equation (PDE) based level set method for vessel segmentation, and a second level set equation solving for a physically meaningful flow. Results from improving the flow are shown in Figure 2. The second level set is implemented using the ghost fluid method, where the MR library data defines initial and boundary conditions. The segmentation and CFD systems are simultaneously integrated to provide a robust method yielding a physically correct velocity and optimal vessel geometry.

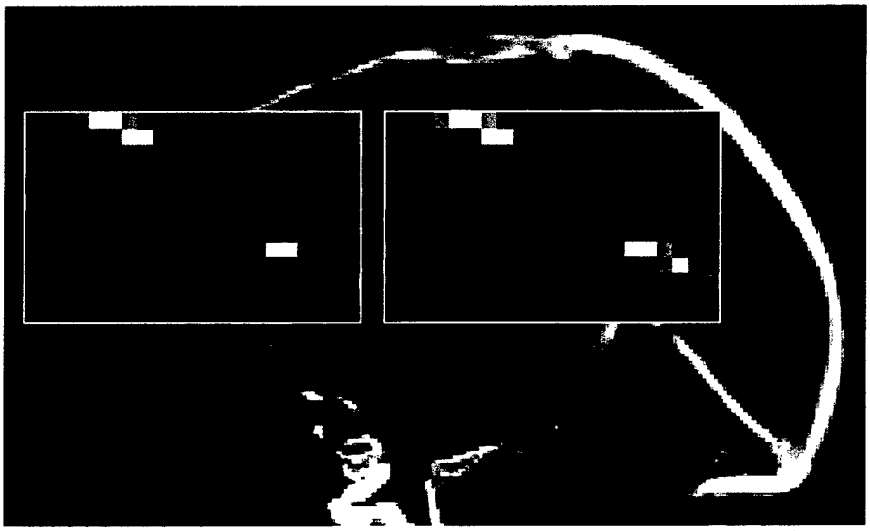


Figure 2. Maximum intensity projection (MIP) of a library phase contrast angiography data set. Results of flow correction of the original data set (left inset) using CFD methods greatly improves the continuity of the flow (right inset). Notice also that the level of background noise is reduced.

Plan: To compare three recent classes of algorithms leading to centerline representations of vessels. (1) Our recent sub-voxel method finding centerlines as ridges of the image intensity, (2) one method based on a pre-segmentation of the vessels, given by a binary image, to compute a topological invariant skeleton, and (3) a method based on integration of the gradient information along circles of different radii in the cross-sections, in order to find points located at equal distance from the contours.

Specific Aim 4: Optimization and Validation: to quantitatively validate and optimize the automated segmentation method results.

Progress: Preliminary results have been obtained comparing different centerline extraction methods. The outcome of this study is not straightforward to since different methods turned out to perform well at different aspects of describing centerlines. Whether robustness to noise is more important than for example subvoxel resolution, or connectivity of branching vessels is application dependent. The team is currently compiling a report detailing differences and performance between the implemented centerline extraction methods.

Plan: To validate the VTK vessel segmentation pipe line in the 3D Slicer.

Specific Aim 5: Extend our current implementation of adaptive filtering

Progress: This year has been focused on developing a user-friendly software module, based on our optimized libraries developed last year, in the 3D Slicer. The 3D Slicer is a visualization tool developed as a joint effort between our laboratory and the AI laboratory at MIT (Cambridge, MA [http://slicer.org]). The filter pipeline is now described in a VTK (freeware Visualization ToolKit by Kitware Inc., NY) software pipeline in order to be compliant with the 3D Slicer architecture. The new adaptive filtering module not only provides a user-friendly interface for the users, but also enables easy access to our collaborative developers, since VTK has become the de facto standard for software development in our laboratory. Figure 3 shows snapshots of the current implementation, with a sample module menu (left), a filtered MRI data set of the knee (middle), and visualization of a sample basis filter in the Fourier domain (right). The filter visualization capabilities are mainly for developers, but can be used for training and teaching of advanced users.

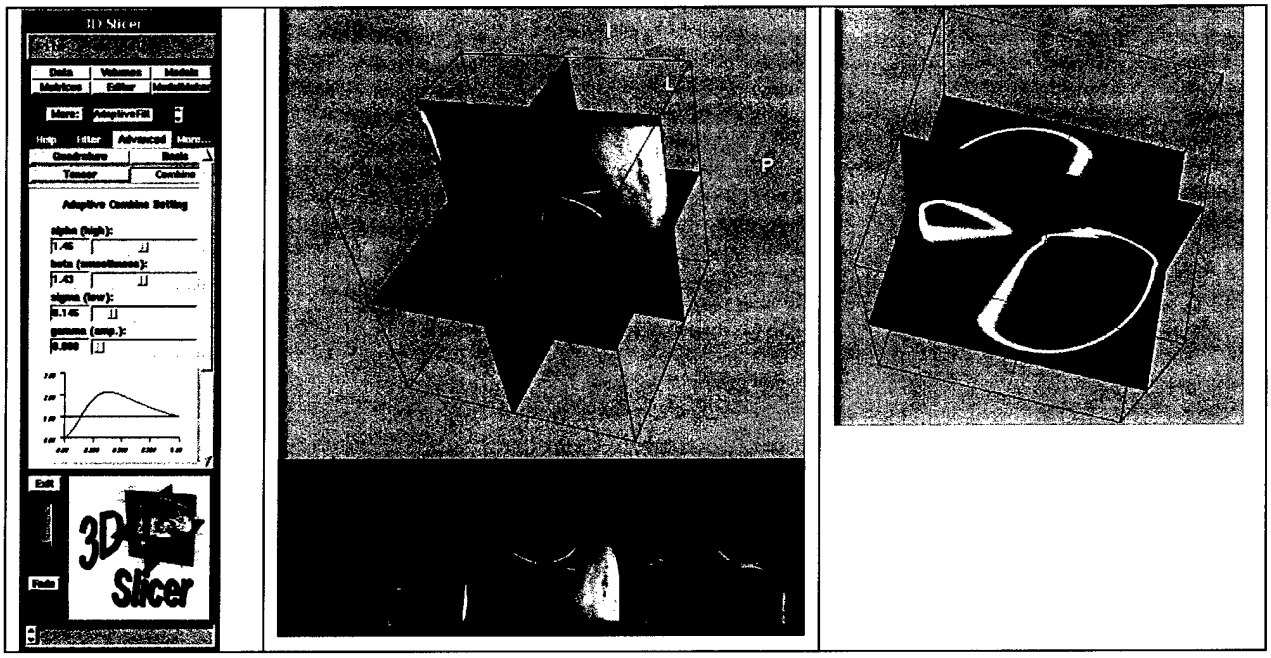


Figure 3. Sample images from the adaptive filtering module in the 3D Slicer. Parameters controlling the noise reduction are available to the user via sliders, and their effect is graphically represented in a contrast mapping function, which is in real time visualized in a dynamically updated plot (left). The result of the filtering can be visualized in both the traditional radiologic slice orientations (axial, sagittal, and coronal views), and in a 3D window (middle). In addition, adaptive filter functions can be studied using the same tool (right).

The team has also investigated a new class of filters for the local structure estimation. By using a Wiener filter in both the estimation and the synthesis step, it was predicted that fewer user control parameters will be necessary, which in turn will facilitate the use of the system. However, an experienced decrease in enhancement performance made the team decide not to incorporate this simplification. Further, the team has investigated the impact of optimization of the filter functions in the spatial domain and in the frequency domain simultaneously. The major

implication of using these filters is that filters can be made more local without sacrificing frequency properties, and thus greatly reducing spatial ringing artifacts.

Plan: Project completed.

Specific Aim 6: To develop a segmentation method based on the team's experience on adaptive filtering and surface evolution.

Progress: The team has recently developed the CURVES system, which segments vessels from MRA images by evolving an initial estimate toward the true structures in the image using the codimension-two regularization force. Last year the team focused on tuning a pipeline consisting of adaptive filtering of the vessel data followed segmentation by the CURVES system. Based on this system, this year the team has focused on creating a VTK to be integrated into the 3D slicer.

The team has during this year also revisited the basic implementation of the evolution algorithm in CURVES. Last year's implementation required approximately 40 min processing time for a standard size MRA data set. It turned out that most of the computational time was spent in the reinitialization of the levelset function. Theory of novel method has been developed and implemented, decreasing the computational time by a factor of about 10, making processing feasible in clinical time constraints.

Plan: To further interface the vessel segmentation module to the 3D Slicer.

2.4 TISSUE ENGINEERING PROGRAM

Task 1: Polymeric Nanoparticles for Localized High Efficiency Gene Transfer

Principal Investigator: Robert Langer, Sc.D., MIT

Safe and effective pharmaceutical delivery systems for DNA will need to be developed in order for the field of gene therapy to advance further into the clinic. For local therapeutic levels of protein to be generated, high levels of gene expression within a desired subset of cells is generally required. To this end, the local delivery of gene therapeutics via minimally invasive modalities, such as catheters or endoscopes could lead to important advances, because these techniques can be used to administer DNA (and thus therapeutic protein) at desired sites rather than administering them systemically.

The long-term goal of this project has been to create a safe synthetic polymeric gene delivery system with high transfection efficiency for local delivery of plasmid DNA. The work conducted toward Specific Aim 1 in the past year has been directed toward the continued development of new polymeric materials for gene delivery and the development of a mechanistic understanding through which these materials mediate transfection. We have synthesized a 140 member library of poly(β-amino ester)s for use as gene transfer agents, and we plan to extend this approach to create libraries containing thousands of polymer structures. The work conducted toward Specific Aim 2 in the past year has been directed toward the development of pH-responsive microspheres for use in DNA vaccine applications. We have recently overcome initial problems limiting loading efficiencies, and we plan to begin evaluating the transfection efficiency of this formulation in antigen presenting cells (APCs).

Key Results: The team has continued development on the first accelerated discovery approach for finding synthetic transfection vectors. Several new polymers discovered through this approach have higher transfection efficiencies than existing synthetic vectors in cell-based assays. We have also modified several factors in the synthetic procedure that will allow for much larger libraries, containing thousands of structures, to be synthesized using a semi-automated, high-throughput system.

Specific Aim 1: To synthesize a library of structurally-related poly(β-amino ester)s and apply the library to high-throughput screening assays to more rapidly identify degradable, DNA-complexing materials and efficient transfection vectors

Progress: This past year, the team used high-throughput screening assays to identify two polymers (B14 and G5) that yielded gene expression in model cell lines at levels surpassing those of both PEI and Lipofectamine 2000, two leading polymeric and liposomal transfection agents (Figures 1 and 2). The team investigated the library that yielded these polymers in order to understand the structure/property relationships for these polymers and other members of the polymer library. This team has characterized this library along the following dimensions: (1) relative uptake of complexes by 3T3 cells (Figure 3), (2) effective diameter of polymer-DNA complexes, (3) zeta potential of polymer-DNA complexes. The team has also validated the approach necessary to extend the library approach to thousands or unique polymer structures.

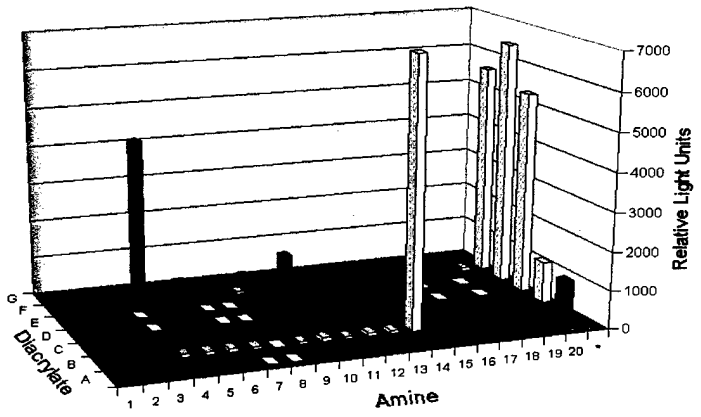


Figure 1: Transfection data as a function of structure for an assay employing pCMV-Luc (600 ng/well, DNA/polymer = 1:20). Light units are arbitrary and not normalized to total cell protein; experiments were performed in triplicate (error bars not shown). Black squares represent water-insoluble polymers, white squares represent water-soluble polymers that did not complex DNA. The right column (marked "*") displays values for the following control experiments: no polymer (green), PEI (red), and Lipofectamine (light blue).

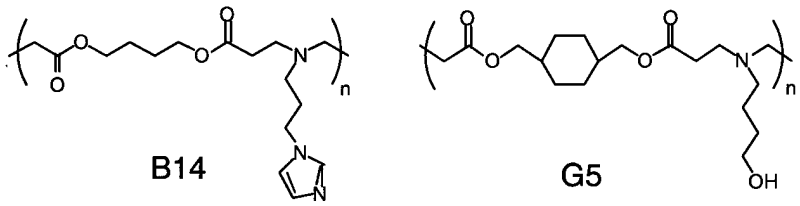


Figure 2: Structures of polymers B14 and G5 discovered using a parallel synthesis and screening approach (see Figure 1).

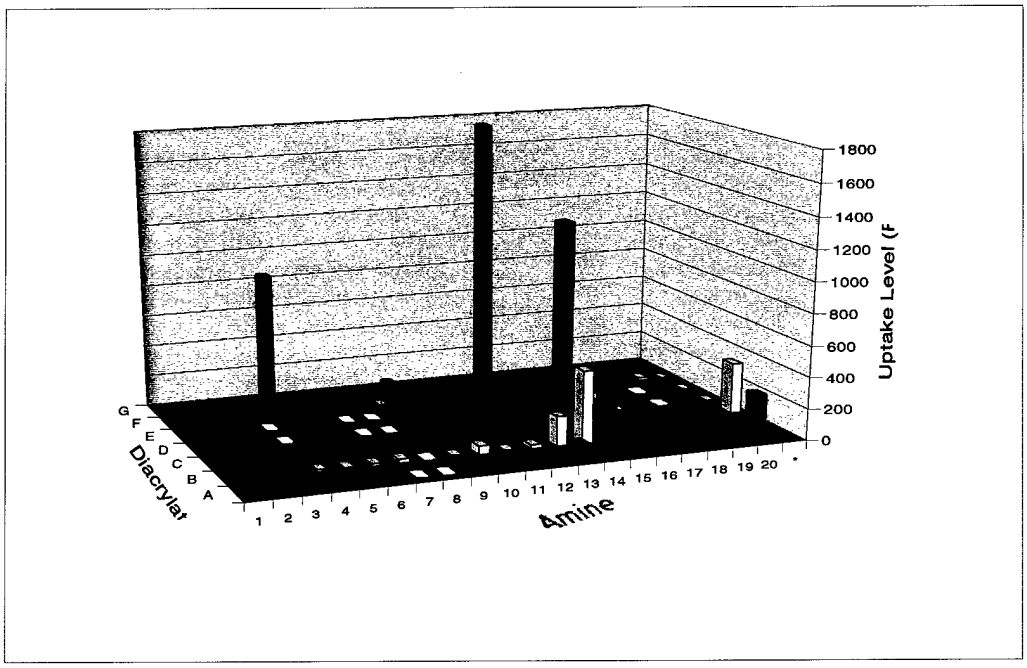


Figure 3: Relative uptake level of DNA-polymer complexes by NIH 3T3 cells as a function of polymer structure.

Table 1. Effective diameter (nm) of polymer-DNA complexes as a function of polymer structure. Complexes were formed at DNA/polymer ratios of 1:20, with DNA added dropwise to the polymer while gently vortexing the mixture. Table entries left blank represent water-insoluble polymers or polymers unable to complex DNA.

	Diacrylates						
Amines	A	B	C	D	E	F	G
1					1029		
2					175		
3							
4	350	561	150				
5	302	301	328	352	363		238
6		193			269		
7		271	205				276
8							
9	2471	1004	1583	1418	2033		
10	209	217	195	318	259		300
11	268	317	269	1308	351		185
12	237	298	278	510	425		271
13	176	130	134	168	164		159
14	159	223	111	224	255		114
15					550		
16							
17							
18							
19	458						
20						1484	

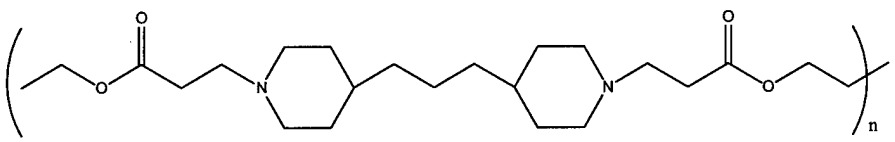
Table 2. Zeta potential (mV) of polymer-DNA complexes as a function of polymer structure

	Diacrylates						
Amines	A	B	C	D	E	F	G
1					-9.9		
2					-26.7		
3							
4	-17.0	-17.4	-41.6				
5	-11.5	-19.3	-8.5	-14.0	-12.5		-3.5
6		-15.9			-17.2		
7		-12.9	-20.6				-11.2
8							
9	-6.0	-8.1	-4.4	-5.7	-7.9		
10	6.9	6.0	6.6	2.2	0.1		2.9
11	-10.3	-17.8	-11.6	-12.5	-8.3		-11.5
12	-17.2	-11.8	-12.7	-10.7	-8.3		-8.2
13	19.0	23.6	19.5	15.6	16.5		15.8
14	5.0	1.8	24.8	-2.9	-13.3		22.8
15					-10.0		
16							
17							
18							
19	-4.5						
20						-20.5	

Plan: The team plans to synthesize and screen a library of nearly 4500 polymer structures in search of new polymers for gene delivery.

Specific Aim 2: To encapsulate DNA within pH-sensitive microspheres formed from poly(β-amino ester)s.

Progress: This past year the team used a pH sensitive poly(β-amino ester), poly-**1**, to encapsulate DNA for use in genetic vaccines. Microsphere integrity problems that had been limiting DNA loading efficiencies have been overcome (Figure 4), and the structural integrity of DNA encapsulated in microspheres was also verified (Figure 5).



poly-1

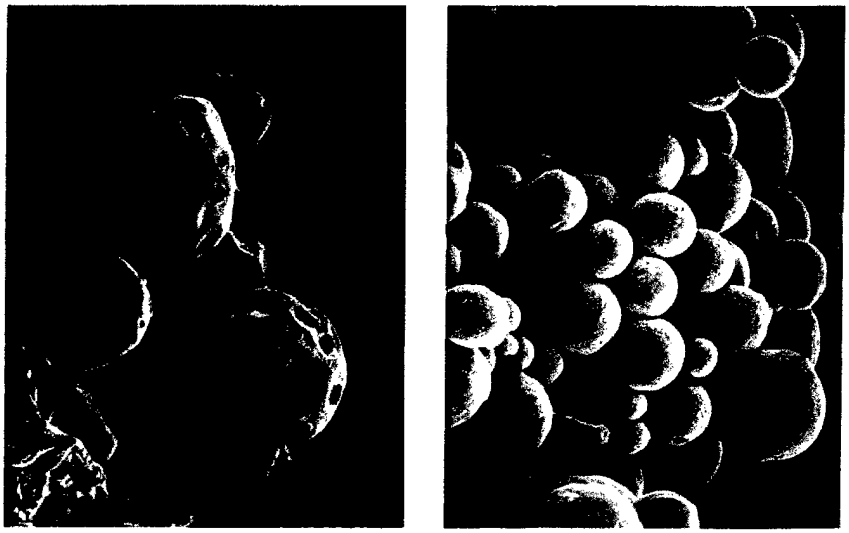


Figure 4: DNA Microspheres before (left) and after (right) adjustments were made to counter an osmotic gradient as viewed by SEM.

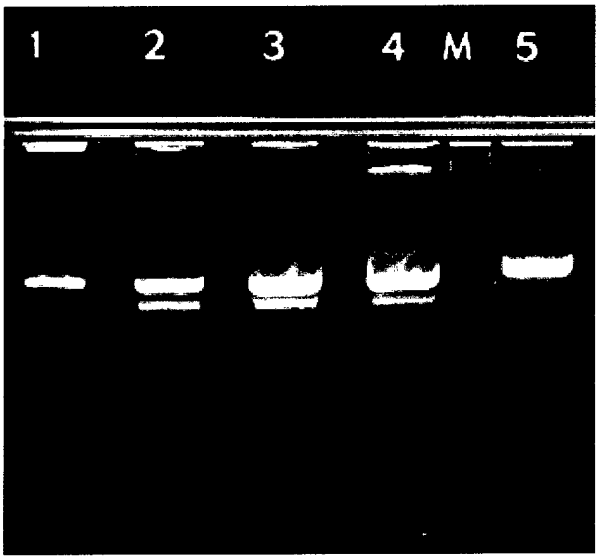


Figure 5: 0.8% agarose gel showing integrity of plasmid DNA encapsulated in polymer microspheres (Lanes 4 and 5) compared to unprocessed DNA controls (Lanes 1-3).

Plan: The next step in assessing the efficacy of the pH-sensitive microsphere system as a genetic vaccine is to assay the efficiency of gene transfer to antigen presenting cells (APCs).

Task 2: Mullerian Inhibiting Substance (MIS) for ovarian cancer
Principal Investigator: David MacLaughlin, Ph.D., MGH

The CIMIT team, lead by Dr. MacLaughlin, is awaiting animal use approval before initiating this project.

Task 3: Tissue engineering: vascular systems and angiogenesis
Principal Investigator: Joseph Vacanti, M.D., MGH

The CIMIT team, lead by Dr. Vacanti, is awaiting animal use approval before initiating this project.

Task 4: Tissue engineering: 3D tissue design
Principal Investigator: Joseph Vacanti, M.D., MGH

The CIMIT team, lead by Dr. Vacanti, is awaiting animal use approval before initiating this project.

Task 5: Tissue engineering vascularized tissue *in vitro* for implant
Principal Investigator: Jeffrey Borenstein, Ph.D., Draper

The shortage of replacement tissues and organs for patients suffering from organ failure due to trauma, congenital defects and disease is one of the most important clinical problems facing medicine today. Several approaches to this problem are being actively pursued, including xenografts, bioartificial devices, and tissue engineering. One of the central goals of the CIMIT Tissue Engineering Program is to develop a revolutionary technology for microfabrication-based engineering of replacement tissues and organs with a built-in vasculature.

The microfabrication technology being applied to this problem in part arises from a rapidly emerging new field known as MicroElectroMechanical Systems, or MEMS. Recently developed technologies such as Three-Dimensional Printing (3DP) and other forms of solid free-form fabrication have shown great promise in the development of scaffolds suitable for seeding cells and growing replacement tissues and organs. However, these technologies lack the required resolution necessary to form templates containing the microcirculation, in particular capillaries on the order of 10 microns in diameter, which comprise 85 percent of the blood vessel system of vital organs. Such limitations in resolution have led to the insertion of microfabrication as an enabling technology for tissue engineering. Micromachining technology, the core fabrication process used to build MEMS structures and devices, currently has a resolution limit of 0.1 microns, two orders of magnitude smaller than the dimension of the capillaries.

Transplant medicine has been limited by a worsening shortage of available donor organs for decades. In addition, the cost of treatment and morbidity associated with immunosuppressive drugs have led to a vigorous search for alternatives to traditional allogeneic transplantation. Among these alternatives is the emerging field of tissue engineering, which has shown early promise but has been hampered by the inability to grow thick complex tissues without an intrinsic vasculature. It is the express aim of this project, in concert with the CIMIT program in organ fabrication led by Dr. Joseph Vacanti, to provide microfabrication tools for use in generating complex tissues and organs with geometries as challenging as the capillaries. Early

results have shown that MEMS device fabrication technology can be applied towards fabrication of polymer scaffolds for cell seeding and tissue engineering.

Major milestones in the design and microfabrication of scaffolds for endothelial cell seeding and for full endothelialized devices seeded with parenchymal cells have been reached during the past year. In a major advance, a novel approach to three-dimensional designs with high capillary densities has been developed. This design is the first to demonstrate calculated values for pressure in the physiological range while simultaneously incorporating the high density of capillaries found in the circulatory system. In addition, the first known model, which describes the angiogenesis process in mathematic detail, was developed. In the area of microfabrication, new process technologies based on micromolding have been developed and brought into routine practice for scaffold generation. A porous intermediate membrane has been inserted between an endothelial channel layer and the parenchymal compartment in a biocompatible PDMS scaffold, the fundamental building block in an organ construct. Large numbers of biodegradable films have been joined in a single step, a major milestone in the fabrication of a fully degradable polymer scaffold. In addition, a revolutionary new biodegradable polymer developed at MIT has been microfabricated into channel networks, an advance which will ultimately lead to the creation of scaffolds with superior mechanical properties, more predictable degradation times and drastically reduced inflammatory response. Finally, a joint project with MIT has demonstrated that self-assembling peptides may be used to form liver sinusoids using microfluidic technology.

Key Results:

- Novel mathematical model for the angiogenesis process has produced physiologically viable capillary beds
- New, proprietary approach has been developed for the design of three-dimensional vascularized tissues with very high capillary densities
- High resolution features micromachined in industry-standard biodegradable polymer (PLGA), with minimum features 2 microns in size, and resolution of 0.02 microns.
- Multi-layer PLGA films (up to 6) integrated into a scaffold construct in a single step
- New biodegradable polymer from MIT (bio-rubber) micromachined at high resolution to form scaffolds which should have greatly reduced inflammatory response
- Formation of capillary wall membrane in microfluidic culture has been demonstrated using self-assembling peptides in a joint Draper-MIT-MGH project

Specific Aim 1: Develop micromachining technology suitable for the formation of scaffolds with full vascular networks, utilizing fluid dynamic models described in the Vacanti report.

Progress: Fluid dynamic modeling of organ vasculature, led by Dr. Mohammad Kaazempur-Mofrad of MIT, has provided a foundation for understanding the set of design criteria necessary to mimick the physiology of blood vessel and other microfluidic networks in vital organs. Early design efforts, culminating in the first design, TEP-0, were aimed at providing a preponderance of capillaries within the networks; fully 85% of the vessel cross-section (in toto) lies in the smallest capillaries. This feature leads to designs which develop a very high pressure head within the system, however, and later designs retreated considerably from this first approach in order to yield physiological pressure drops and uniform flows in the network. In the past few months, however, the Draper team has invented a novel approach for the design of three-dimensional networks which, for the first time, allows for simultaneous achievement of high

capillary density and physiological levels of pressure drop within the system. This breakthrough was enabled by the incorporation of a massively-parallel interconnected network in three-dimensions, as shown in Figure 1, below. Such networks are joined in the third dimension at many points, not just at a single inlet and outlet, as was done previously (Figure 2) Fabrication processes for these 3D systems are described following Specific Aim 3.

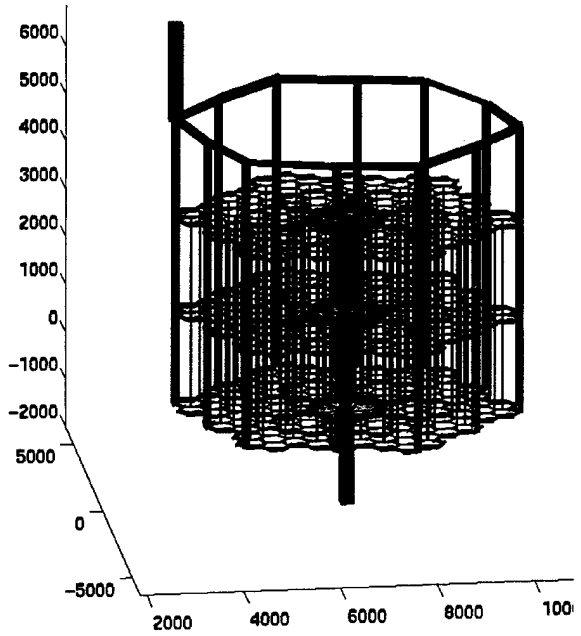


Figure 1. New 3D Design Concept

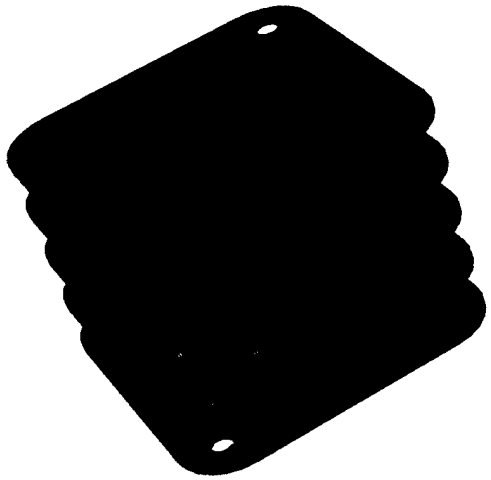


Figure 2. Former 3D integration method

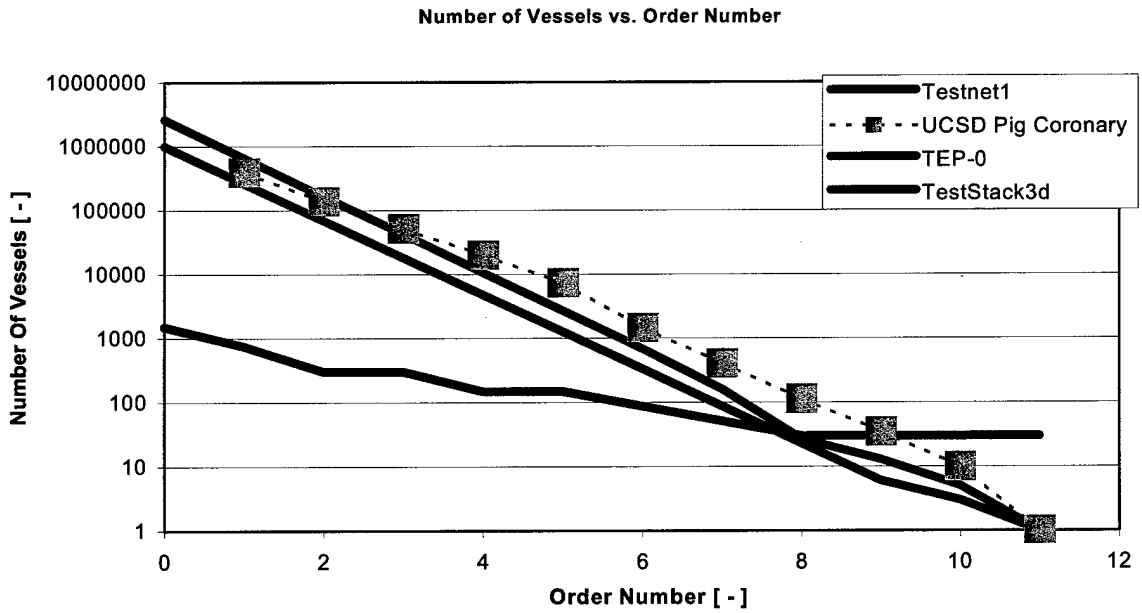


Figure 3. Vessel number vs. vessel "order" for generations of designs, vs. physiology.

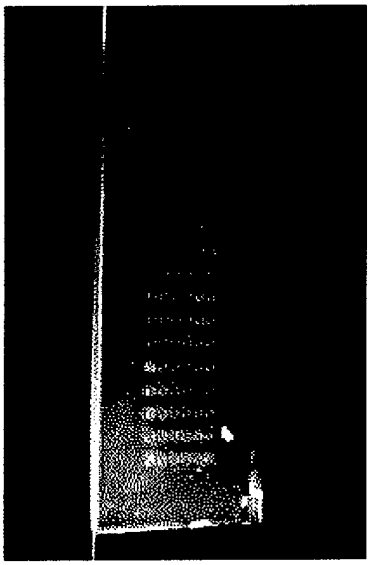
Figure 3 illustrates the advance in design enabled by the new 3D construct. Vessel number is plotted against the "order number", which corresponds to the vessel dimension. Here Order 1 refers to capillaries, while Order 11 refers to the largest inlet and outlet arteries and veins of a vital organ. Note that the physiological data, labeled USCD Pig Coronary, refers to published data previously discussed and referenced in an earlier annual report. The red TEP-0 line shows that the first CIMIT design provided a large number of capillaries and a good approximation to the vessel scaling law, but the pressure losses were extremely high. Newer designs such as TESTNET-1 rectified the pressure problem, but could not reproduce the vessel scaling, a fundamental problem for standard 3D integration techniques. With the new massively-interconnected approach, the novel design "TESTSTACK3D" provides physiological pressure losses but maintains very high capillary (and other low-order vessel) densities.

Plan: In the next year, efforts will be focused upon the development of micromachining process improvements to enable improvements in the geometry of channels and channel intersections in an effort to mimic the configuration of the microcirculation more closely. In addition, both the angiogenesis and three-dimensional stacking models developed this year will be translated into mask layouts and fabricated into scaffold constructs.

Specific Aim 2: Transfer the microfabrication processes developed for Specific Aim 1 to biocompatible and biodegradable materials through the use of micromachined masters, compression molding and other techniques.

Progress: In the Year 3 report, first results on micromachining of biodegradable polymers at high resolution were presented. In this past year, this effort was developed further, resulting in the demonstration of 2 micron channels machined into industry standard PLGA material at a resolution of 0.02 microns (standard deviation in channel width.) While PLGA has been used successfully in applications ranging from sutures to skin, bone, cartilage and muscle, it does engender an inflammatory response, and therefore, an MIT-Draper-MGH effort has been underway for several years to develop improved biodegradable materials. As a result of these efforts, a novel material known as biorubber has been developed, with greatly reduced inflammation, more predictable degradation times and superior mechanical properties. As part of the CIMIT program, micromachining experiments on the biorubber material have been conducted, in concert with Professor Robert Langer, Dr. Yadong Wang and Christine Willbert of MIT. Figure 4, below, shows a microfabricated biorubber film with one of the microvascular patterns; attempts to bond these materials into multiple layers are now underway.

A second effort in the area of biodegradable materials has been focused on the construction of multiple layers of material into a scaffold in a single step. In Figure 5, below, a 5-layer sandwich of PLGA is shown in cross-section; Kevin King bonded this sandwich together in a single thermal fusion step. This advance represents significant progress in the effort to develop a manufacturable, low-cost process for scaffold fabrication.



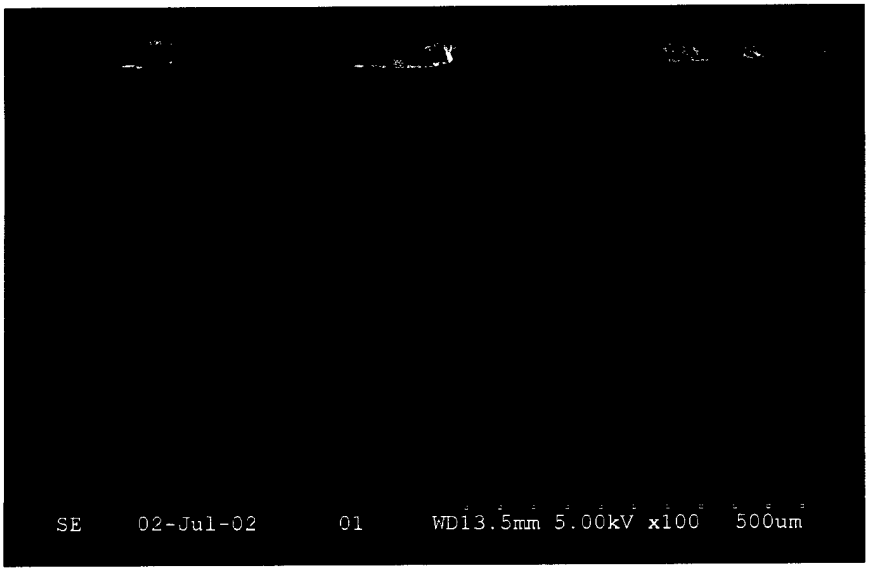


Figure 4. Biorubber scaffold. ***Figure 5. 5-layer PLGA sandwich bonded in one step.***

Plan: Biodegradable polymers, essential for the ultimate replacement organ, exhibit a vast range of biomaterials properties with regard to inflammatory response and fibrotic encapsulation. A major effort will be launched to incorporate the new MIT-developed biorubber technology into the CIMIT project, based on superior mechanical and biocompatibility properties.

Specific Aim 3: Scale microfabrication technology to enable manufacturable methods for producing three-dimensional constructs.

Progress: In the past year, several significant developments in the area of three-dimensional microfabrication have been achieved. For the first time, filtering of fluorescent microbeads (simulating red blood cells) was demonstrated within a biocompatible microfabricated polymer scaffold. A size-exclusion-based nanoporous filter was inserted between two layers of perpendicular microchannels by Kevin King, and the microbeads were confined to one layer while fluorescein dye traveled freely between the microchannel layers. Aggregation of the microbeads over the nanoporous filters is shown in Figure 6, below. Figure 7 shows the filling of successive layers of PDMS scaffolds in a three-dimensional stack with fluorescein dye.

Ernest Kim, a Draper Laboratory Fellow working jointly with Professor Roger Kamm of MIT, developed a novel technology for the formation of liver microarchitecture. Sinusoid formation in microfluidic channels was accomplished based upon the unique properties of a self-assembling peptide-based polymer. Figure 8, below, shows the formation of a capillary membrane in a MEMS-machined microfluidic channel. In Figure 9, a schematic of the unique peptide is illustrated.

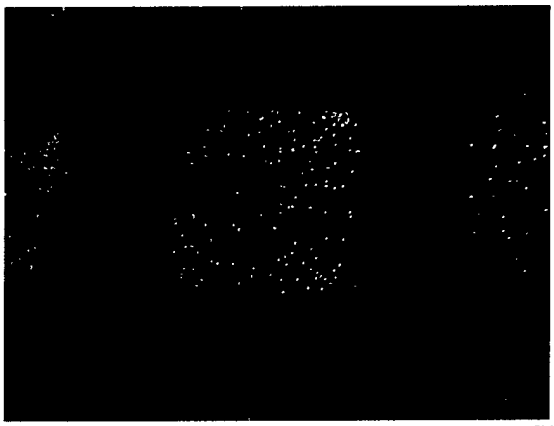


Figure 6. Demonstration of nanoporous filter.

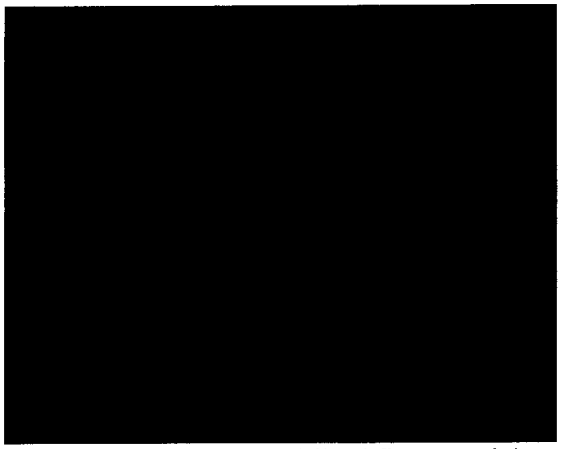


Figure 7. 3D microfluidics(fluorescein)

Figure 7. Sinusoid membrane formation.

Figure 8. Self-assembling peptide

Plan: In the coming year, three-dimensional microfabrication techniques for the integration of multiple vascular layers as well as capillary-parenchymal substructures will be further developed and perfected.

2.5 MEDICAL SIMULATION PROGRAM

The CIMIT Simulation Program has parallel primary thrusts: (1) developing the basic science required for realistic computer-based medical simulation and (2) validating state of the art simulations through the construction and testing of demonstration systems. The Program's principal activities involve measurement of tissue characteristics, integration of haptics into simulation, and realistic representation of medical procedures for training, device prototyping and procedural development.

Task 1: Enabling technologies for medical simulation

Principal Investigator: Steven Dawson, M.D., MGH

The Simulation Group had a successful and productive FY '02. We continue to pursue new answers for the fundamental enabling technologies of medical simulation, from tissue property measurements through validation, and we have also expanded our program in application-specific design.

In response to a request from RAD II/CCC to show practical applications of our long term research program, in September, 2001 we demonstrated the initial proof of concept VIRGIL Chest Trauma Training System to MG John S Parker, then Commanding Officer of USAMRMC, during the annual ATACCC meeting. Since that time, we have continued to modify the system and test its effectiveness as a learning system. We have begun validation studies of the VIRGIL system through a newly funded collaboration with the National Capital Area Simulation Center at USUHS. During the past year, we hosted Dr Daniel Kalanovic, a German surgeon who was awarded a visiting scholarship to study with our team and do comparative tissue property research. We developed new algorithms for flexible instrument collision detection and refined our earlier synthetic X-ray algorithms in order to produce finer resolution of images rendered using virtual fluoroscopic methods.

Key Results: Among the most notable accomplishments in the past year, we:

- Filed patents to protect the intellectual property in the VIRGIL Chest Trauma Training System;
- Secured trademark rights to the VIRGIL name for the training system;
- Began commercialization discussions for the VIRGIL system;
- Filed four new invention disclosures for existing research projects;
- Initiated a new collaboration with USUHS and the National Capital Area Simulation Center;
- Began validation studies comparing the VIRGIL system to existing accepted animal training models;
- Presented our vision of medical simulation in a keynote address to the leadership of the American College of Surgeons;
- Participated in drafting a white paper for a new thrust in simulation research by the American College of Surgeons;
- Submitted the Medical Simulation Training Initiative (MSTI) as a STO to the Defense Department, under the sponsorship of COL Robert Vandre;
- Demonstrated the VIRGIL system to GEN James Peake, Surgeon General of the Army, GEN Lester Martinez-Lopez, Commanding Officer of USAMRMC, and COL Jeffrey Roller, Commander of TATRC;

- Demonstrated the VIRGIL system to United States Representatives Murtha (D-PA), Capuano (D-MA) and Lynch (D-MA) during their visit to CIMIT;
- Added two new full time members to the group, emphasizing efficient management of individual projects and system design as key concepts in the conduct of our research;
- Hosted a visiting scholar, Dr Daniel Kalanovic, for a six month fellowship under a German government International Research Award; and
- Presented our research at peer-reviewed meetings of
    - Medical Image Computing and Computer Assisted Interventions (MICCAI)- Tokyo
    - Medicine Meets Virtual Reality- Newport Beach, CA
    - The Society for Medically Innovative Technologies- Oslo, Norway
    - The Society for Experimental Mechanics- Milwaukee, WI
    - Fifth IASTED International Conference, Computer Graphics And Imaging-Kauai, HI
    - International Workshop on Deformable Modeling and Soft Tissue Simulation, Bonn, Germany

In the coming year, we will transition from our previous research support model of matched funding from both TATRC and RAD II/Combat Casualty Care to sole support from RAD II/CCC, as part of a reorganization of program funding within CIMIT. We presented a proposal to the Defense Department for third year funding that emphasizes continued fundamental research in tissue property measurements, mathematical modeling, real-time visualization, system architecture design, validation and three new deliverables- an ATLS training system, a surgical skills training system and a new endoluminal haptics device as a generalized solution for medical simulations.

Specific Aim 1: VIRGIL™ Chest Trauma Training System

See Section 1.3: Annual Report Cover Project on page 15.

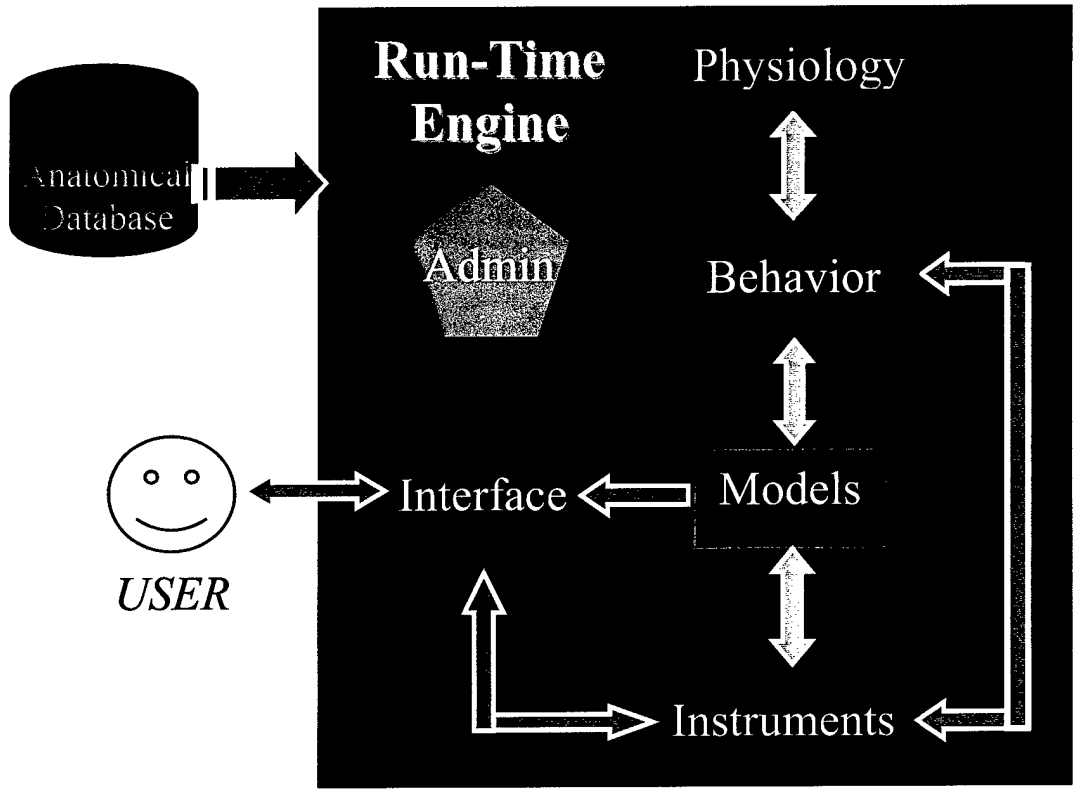
Specific Aim 2: CAML (OpenMedSim)

Progress: The CAML project has been renamed OpenMedSim to better reflect its objectives of developing a generic open-source software framework for the simulation community. During the last year, we have organized two committee meetings at the MICCAI conference in Utrecht, Netherlands in October, 2001 and at 'Medicine Meets Virtual Reality' conference in Newport Beach, CA in January, 2002. In February, 2002, Kevin Montgomery from the National Biocomputation Center at Stanford University donated the source code to their simulation system called SPRING to the OpenMedSim project. Over the summer 2002, two consultants (Paul Sherman and Cynthia Bruyns) were hired to reorganize SPRING's source code toward a more OpenMedSim architecture.

Although the OpenMedSim project is a long term initiative, we have been working on three primary components:

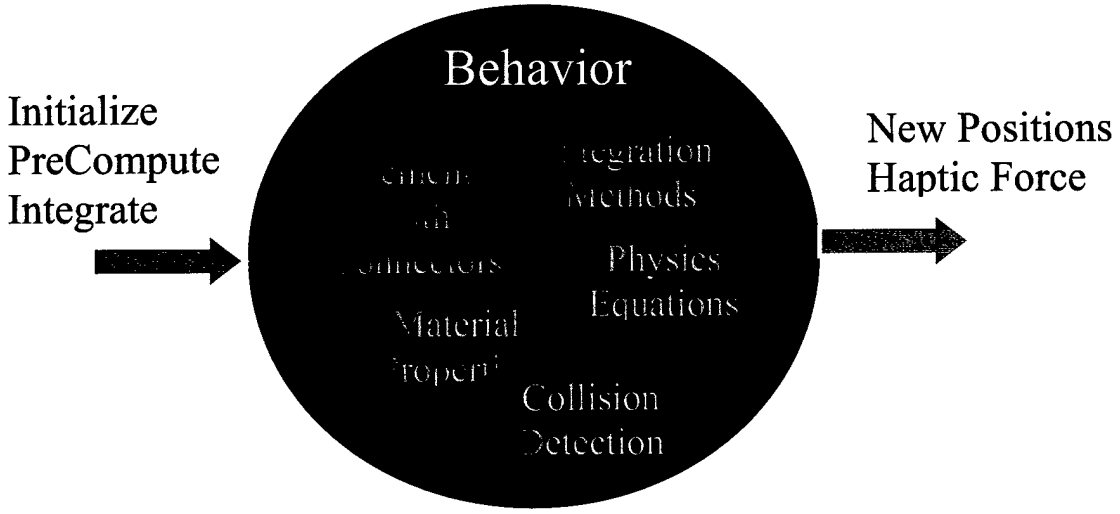
1) The Run-time Engine is a high level generic simulator engine template. It contains the general simulation control without knowing all of the internal details. The figure below illustrates a schematic diagram of the Run-Time Engine. From a high level point of view,

simulators all consists of interactions between a set of primary components such as models, behavior, instruments, etc. Although the Run-Time Engine does not know the exact implementation of these components, it does know that they conform to a fixed interface controlled by the Class API.



Schematic Diagram illustrating OpenMedSim's Run-Time Engine.

2) The Class API governs the intermediate programming interface between the primary components of a simulator. It defines the common functions and variables that a component must implement to be an accepted module into the OpenMedSim system. The development of such an API is challenging because it must clearly define the generic functionality of each component independent of any particular algorithms, as well as de-couple each component from any other as much as possible so that each is independent and can be loaded separately. Often simulators are overly dependent on a particular data structure or implementation which limits their upgradeability. One of the fundamental motivations of the OpenMedSim project is to provide a flexible environment so that simulators can be upgraded easily.



A diagram of the Behavior API.

3) Modules, the lowest level of the OpenMedSim's hierarchy, represent particular implementations or algorithms of a simulator component. Modules must conform and fulfill the Class API in order to be loaded by the Run-Time Engine. For example, a mass-spring system or Finite Element Method (FEM) would be two possible modules of the Behavior API. Eventually, modules should be available through a common WWW site.

Prototypes for the run-time engine, class API and modules have been developed but not tested. The Class API needs to be expanded to include a greater variety of simulators such as ones based on FEM and endovascular simulators. We are in discussion with the Swiss Federal Institute of Technology and the University of California at Berkeley to see if some FEM source code can be acquired. Also, the ability to develop a dynamic loading library for the modules has been a difficult issue. Such libraries exist under the UNIX operating system but are difficult to define on the PC Windows platform.

Plan: The immediate goal is to develop a functioning prototype system which demonstrates OpenMedSim objectives. Such a system would have the ability to combine different modules such as replacing a mass-spring system with a FEM module within the same simulator. The run-time engine and API must be expanded and be more thoroughly tested. If a dynamic library for the PC platform cannot be found, modules will be made static as an interim step. A web site is currently being developed to increase the awareness of the project. Legal issues surrounding shared source code files need to be investigated before OpenMedSim software can be released to the simulation community.

3.0 CLINICAL CHALLENGES

3.1 BIODETECTION

Task 1: Real-time blood assay

Principal Investigator: Christopher Dube, Ph.D., Draper and Stephen B. Calderwood, M.D., MGH

The goal of the project is development of a microarray sensor technology that is capable of measuring a detailed signature profile of blood (or other body fluid) components in near real-time. Components under investigation include both soluble proteins and microbial pathogens. The project is driven by several needs: 1) ICUs need more detailed, timely information on the metabolic, inflammatory, or infectious state of a patient, 2) Near real-time serum level of indicator proteins (e.g. Parathyroid hormone (PTH) level during parathyroid surgery), and 3) Faster detection and identification of blood-borne infectious disease. In particular, the impact of development of the later is significant in that it would revolutionize diagnostic microbiology from current culture-based methods to faster, more precise, more sensitive technology. Through our collaboration with Dr. Stephen B. Calderwood, Chief of the Division of Infectious Disease at MGH, we have identified specific clinical applications of our sensor technology. These focus largely on detection and identification of blood-borne infectious disease. If successful, a direct-read, near real-time detection and identification of human pathogens will revolutionize diagnostic microbiology from largely culture-based methods to a detection/identification approach that is highly specific in its ability to discriminate pathogens with a technology platform than can provide sensitive measurements in a short period of time. NB: This is the final year of this project. Hence, in the following report there is no discussion of future plans.

Key Results: The key milestones of the past year include: **1)** Detection of the microbial pathogen *E. coli* O157:H7 using individually functionalized μCANARY elements. This represents a major achievement in that it demonstrates rapid, sensitive detection of an important human microbial pathogen with flexural plate wave technology, **2)** Completion of assays of four different E. coli organisms to compare affinity ligand reagent specificity for E. coli. The organisms include DH5-α, O157 knockout, O55, and O157 knockout gene reinserted. The standard antibody for all assays was anti-O157H7. These results showed that our assay, based on the anti-O157:H7 antibody, is sufficiently selective to differentiate between these organisms. The O157 knockout (the gene that is responsible for expression of the O157 epitope, or outer surface feature of the bug, was deleted and as a result the O157 feature was not expressed) organism previously showed no binding to the anti-O157:H7 antibody. That result was tested again, as well as a version in which the O157 gene was reinserted, and the O157 feature should be expressed again. **3)** Correlation of the frequency shift of binding of *E. coli* with the optical density of the bound *E. coli*. This is significant in that it was an independent means of quantitation of the sensor frequency response to a biological target with an independent measure of binding (optical density) of the biological target to the sensor elements, **4)** The identification of bound *E. coli* to the antibody labeled sensors was confirmed with scanning electron microscopy (SEM), and the number of bound *E. coli* determined in the SEM correlated with the integration of the optical density of the bound particles and the frequency shift, **5)** Implementation of microfluidic sample handling for μCANARY sampling using a microfluidic flow cell for the μCANARY sensor that is not permanently bonded to the sensor. The microfluidic flow cell uses a PDMS molded flow distributor that seals against the μCANARY

sensor. World-to-device connection was achieved with a machined Lexan® plate. The ability to disconnect the flow cell enables us to use the BioDot to functionalize the sensor elements as well and gives us improved hydrodynamic performance needed for optimal sensor performance. This type of flow cell is also key to incorporation of the μCANARY sensor into a sensor system since this system requires that the sensor be replaced periodically. The projects final accomplishment **(6)** relates to the significant progress made by Prof. David Kaplan at Tufts University in the development of alternative affinity ligand reagents (ALRs) for the detection of microorganisms, based on peptides expressed on the outer surface coat of phage. Six peptide sequences were identified by the phage technique that exhibit specific and selective binding for two variants of *E. coli*, O55 and O111. These ALRs will be used in conjunction with the μCANARY sensors for detection of microbial pathogens.

Specific Aim 1: Determination of analytes of interest and detection requirements. To accomplish this Specific Aim the following items will be addressed:

- Characterize receptor coating application for microbial pathogens
- Characterization of exposure to laboratory samples
- Determine level of accuracy provided by technique
- Exposure to fluid samples with unknown concentrations
- Development of hardware
- Development of software

Progress: During the past year the team demonstrated the biological detection of the human microbial pathogen *E. coli* O157:H7 using the 9-element μCANARY. A commercially available antibody was attached to the sensor surface using our standard aminothiol/glutaraldehyde surface chemistry. The blocking protein bovine serum albumin (BSA) was used as a control (Figure 1). Only the anti-*E. coli* antibody bound the *E. coli* bacteria, as evidenced by a frequency shift concurrent with exposure. The *E. coli* work was done in collaboration with our MGH partner Dr. Stephen Calderwood and his group.

A

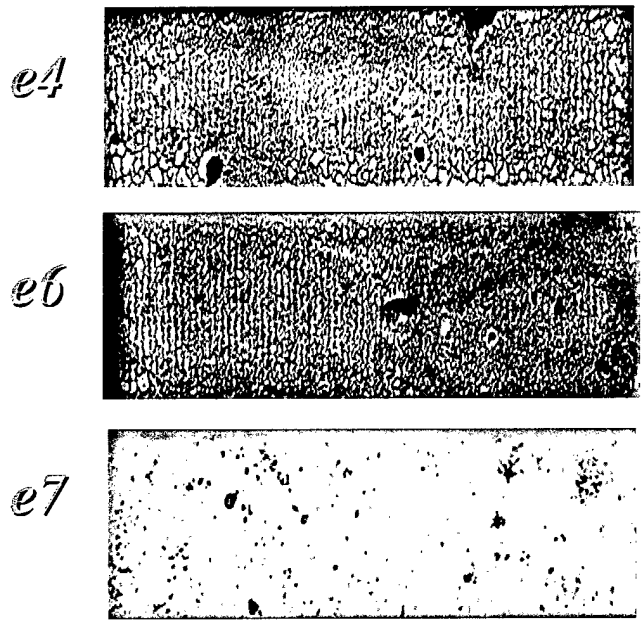


Figure 2. 8 elements of μCANARY used in bioassay. Four elements coated with commercially available anti-E. coli O157:H7 (e2,e4,e6,e8) and four elements coated with BSA blocking solution (e1,e3,e7,e9). Sensor exposed to sample of E. coli O157:H7 provided by MGH collaborator. Figure illustrates distinct pattern of E. coli binding on anti-E. coli coated elements and complete absence of binding to BSA blocked elements.

second major development within this subtask was the *visualization* of selective sensor element response using optical microscopy and scanning electron microscopy (SEM), with quantitation of the optical density, and hence the number of bound particles.

Characterize receptor coating application for microbial pathogens

Progress: Coating procedures to apply commercially available ALRs to the μCANARY sensor surface to detect *E. coli* were completed. Optimal performance of the antibodies are achieved with aminoethanethiol as the primary coating on the sensor, followed by covalent attachment of the antibody with a glutaraldehyde linker. Other surface attachment strategies (such as using protein G or MUA/PLL) gave similar performance in terms of protein attachment.

Development of peptidic ALRs with Prof. David Kaplan at Tufts is progressing well. This work is also being pursued for detection of E. coli, and the results will be directly comparable with our accomplishments using commercial antibodies. To date we have identified six peptide sequences that should be specific to the different E. coli targets and we are in the process of synthesizing the peptide sequences for attachment to the sensor surface.

A subtask within receptor coatings was sensor regeneration. We demonstrated excellent results for sensor regeneration using an oxygen plasma clean of the sensor and this task was completed.

Characterization of exposure to laboratory samples

Progress: Detection of *E. coli* O157:H7 suspended in buffer solution has been confirmed using BioDot addressing of the μCANARY 9-element sensor with commercial *E. coli* O157:H7 antibody (vide supra). In addition, we completed assays of four different E. coli organisms to compare affinity ligand reagent specificity for *E. coli*. The organisms included DH5-α, O157 knockout, O55, and O157 knockout gene reinserted. The standard antibody for all assays was anti-O157H7. These results showed that our assay, based on the anti-O157:H7 antibody, is sufficiently selective to differentiate between these organisms. The O157 knockout (the gene that is responsible for expression of the O157 epitope, or outer surface feature of the bug, was deleted and as a result the O157 feature was not expressed) organism previously showed no binding to the anti-O157:H7 antibody. That result was tested again, as well as a version in which the O157 gene was reinserted, and the O157 feature was expressed again.

The team has evaluated 9-element sensor performance in both air and under liquid-exposure conditions. Our best results (greatest sensitivity and reproducibility with analyte detection) are found with testing in air. To implement this mode routinely samples are exposed to the sensor in a liquid environment to enable reaction of the receptor coating and the analyte in solution, followed by flushing of unbound material with buffer. We then flush with air for 5-10 minutes to remove any liquid, and test the sensor for bound analyte in air ambient.

Plan: During the next quarter the team plans to:

- Continue to improve surface chemistry and bioassay technologies for better uniformity of protein binding. Includes modeling of surface loading of *E. coli* on sensor surface and gold chips, and verify limit of detection (LOD, also see below),
- Completion of a manuscript describing our work to date and submission of publications to key journals in the fields of biosensors and microbiology,
- Complete *E. coli* detection suite, including detection studies of the following microorganisms *using multiple antibodies*, to determine the selectivity and efficiency of

the ALRs to detect the *E. coli* whole organism; the wild type strain K12 (similar to DH5-α) that lacks F pili and the O antigen, the standard O157:H7 strain, and a O157:H7 knockout strain from MGH that does not express the O157 antigen, and the DH5-α strain, and

- Perform studies to address problems with DNA hybridization reaction. In addition, we will examine DNA hybridization on nitrocellulose that avoids the issues with avidin/biotin coupling since biotin will bind readily to nitrocellulose.

Determine level of accuracy provided by technique

Progress: The integrated optical density of the *E. coli* bound to the sensor elements, and hence the number of bound particles, agreed well with the frequency response of the elements, as shown in Figure 3. This provides an independent confirmation of the sensor response. Selected particle counts using the SEM samples (67,200 bacteria/sensor, 118,000 Hz frequency shift) also gave good agreement with both the observed shift and optical density of bound bacteria.

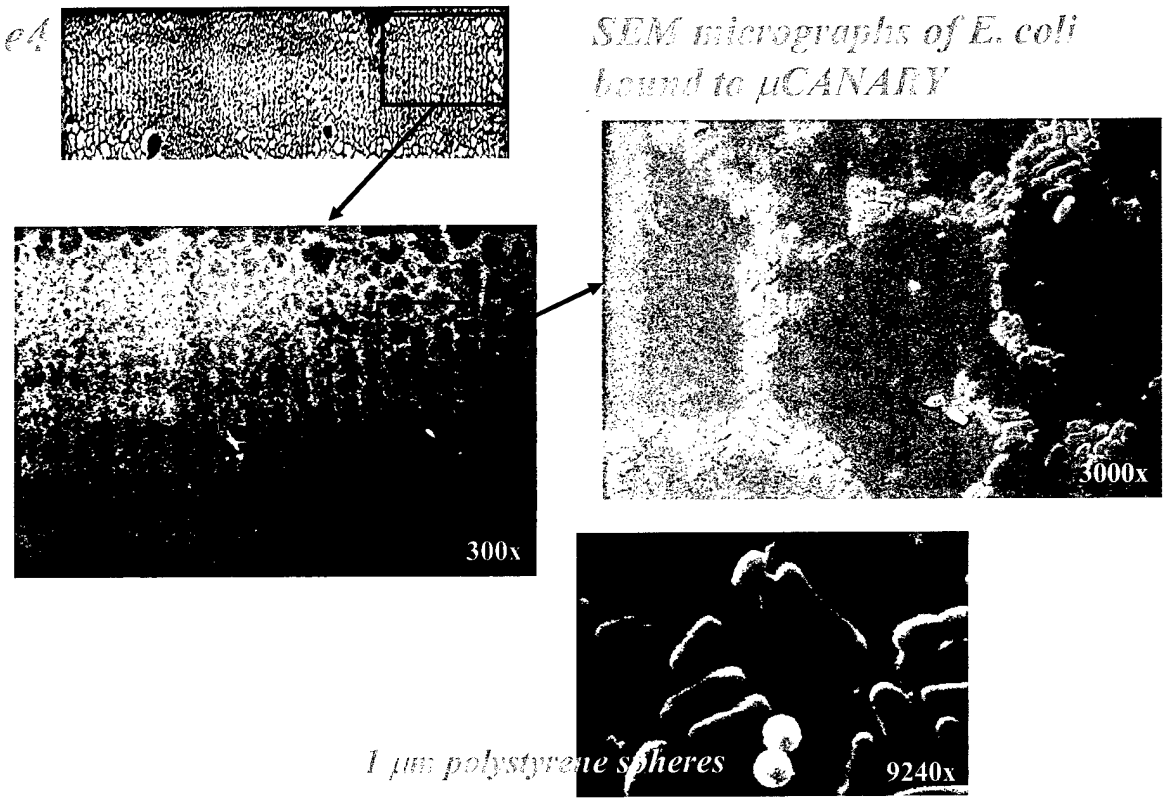


Figure 3. SEM images of E. coli bacteria bound to the μCANARY sensor surface.

Results of integration of the optical density of the bound *E. coli* bacteria correlate well with the sensor frequency shifts, as shown in Figure 3. Detection limit for this sensor is ~ 130 bacteria.

Improvement in sensor signal-to-noise should enable a detection limit of the order of 40 bacteria.

Plan: During the next quarter the team plans to:

- Implement a reference sensor algorithm to improve signal-to-noise by elimination of common mode effects,
- Improve detection of *E. coli* whole organisms detection using selective antibodies bound to μCANARY 9-element sensor and determine the reproducibility and LDR of the sensor to samples containing *E. coli* whole organism,
- To determine the selectivity of the sensor in detecting *E. coli* by using all three variants of *E. coli* to test for nonspecific binding of the *E. coli* antibodies,
- Demonstrate detection of *E. coli* in ground beef,
- Demonstrate detection of *E. coli* from a stool sample, if possible, and
- No work is expected on genomic typing until we are able to successfully run and verify the hybridization reaction on a glass slide.

Exposure to fluid samples with unknown concentrations
Progress: No activity this year.

Plan: During the next quarter the team plans to:

- Use the 9-element sensor array, to obtain the reproducibility, variance and linear dose-response curves of the sensor when exposed to *E. coli*, which enables the determination of the detection limit and the accuracy level of the sensor, and
- To compare ELISA response and μCANARY response for the *E. coli* samples.

Development of hardware
Progress: A total of 70 9-element μCANARY sensors designed for liquid exposure experiments have been fabricated around the open-loop testing electronics for this funding period. All devices were characterized in both liquid and air ambients prior to surface modifications of the sensor with the receptor coatings.

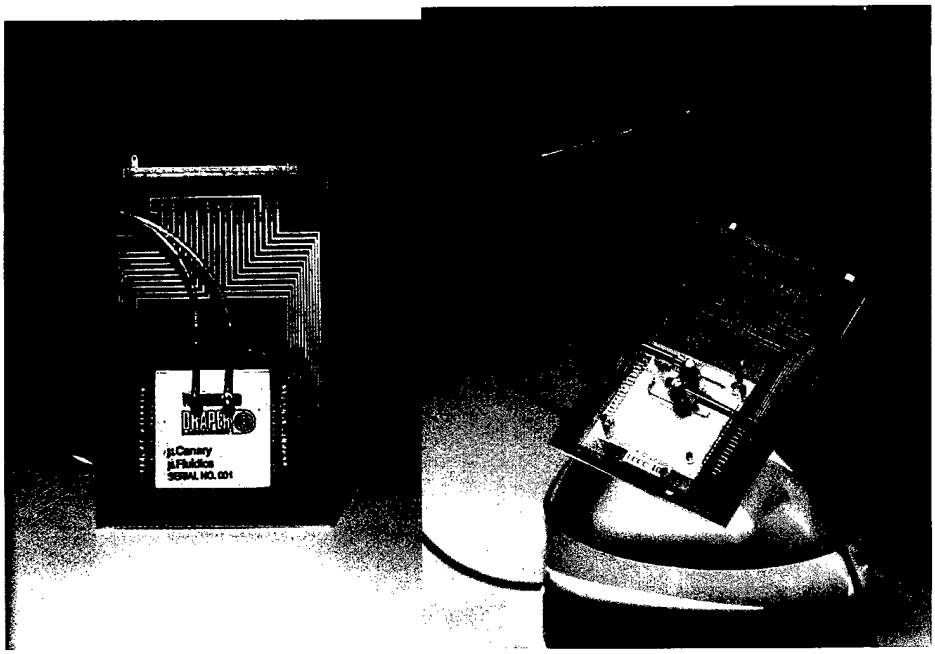


Figure 3. μCANARY sensor/package with Kapton integrated microfluidic device (left) and removable Lexan/PDMS microfluidic device (right).

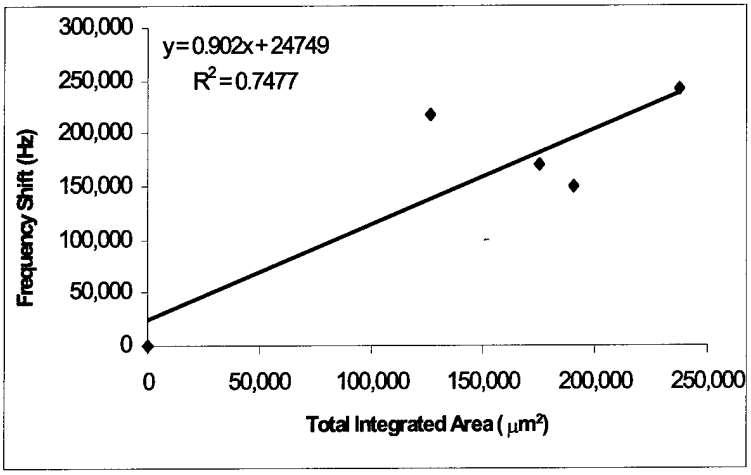


Figure 3. Sample correlation between observed frequency shift and element surface coverage (integrated area) for μCanary detection of E. coli bacteria (dead and alive).

In addition, we implemented two versions of microfluidic sample handling for μCANARY sampling. One version, using Kapton device interfaced directly to the μCANARY sensor is shown in Figure 4 (left photo). However, a more practical approach, using a microfluidic flow cell for the μCANARY sensor that is not permanently bonded to the sensor, is shown in Figure 4 (right photo). The microfluidic flow cell uses a PDMS molded flow distributor that seals against the μCANARY sensor. World-to-device connection was achieved with a machined Lexan® plate. The ability to disconnect the flow cell enables us to use the BioDot to functionalize the sensor elements as well and gives us improved hydrodynamic performance needed for optimal sensor performance. This type of flow cell is also key to incorporation of the μCANARY sensor into a sensor system since this system requires that the sensor be replaced periodically. We are completing design, fabrication and optimization of a microfluidic flow cell built with poly(dimethylsiloxane) (PDMS) using replica molding techniques. The microfluidic flow cell has demonstrated superior flow performance over the conventional flow cell and will become part of the SOP for sample testing.

Plan: To further develop hardware for μCANARY sensor/package.

Development of software

Progress: The team is working to develop data analysis algorithms for implementation of the closed-loop testing, and is expected to give a noise reduction for a typical device from about 3 ppm to 0.1 ppm. The team has completed the closed-loop algorithm for a dual-element sensor. and the same approach will be implemented with the μCANARY.

Plan: There is no plan at this time to implement completion of software for closed-loop μCANARY sensor interrogation since focus during the coming year does not include completion of closed-loop electronics hardware.

Task 2: Developing diagnostic and monitoring technology for circulatory shock states
Principal Investigator: Andrew Reisner, M.D., BWH and Harry Asada, Ph.D., MIT

Multi-channel blind system identification (MBSI) for central hemodynamic monitoring is a novel non-invasive technique intended to eliminate complicated catheterization that is often impractical or infeasible in military applications. Instead, the new method exploits a multitude of peripheral circulation-related measurements (blood pressure, blood flow, photoplethysmography,

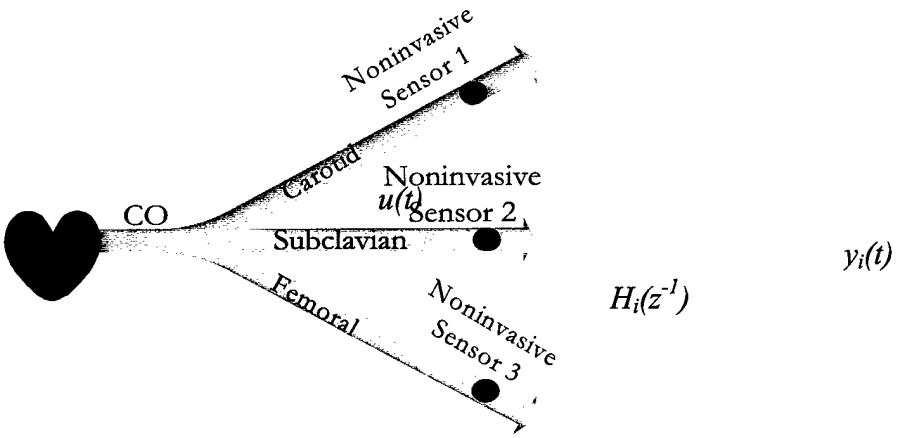
etc.) and examines the correlation among them for determination of the central hemodynamics as well as the state of individual arterial paths.

Key Results: Peripheral signals have been taken as arterial pressure waveforms because these waveforms, along with corresponding central hemodynamics data, are readily available in both pre-existing computational simulations (courtesy of MIT's Prof Roger Kamm) and pre-existing animal data.

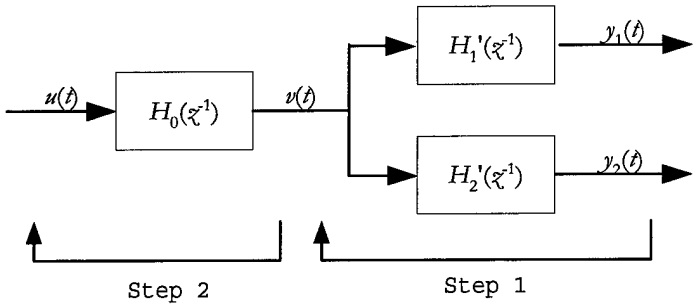
Specific Aim 1: To develop a technique to allow estimation of both unknown input and unknown channel dynamics from channel inputs only.

Progress: MBSI is a technique that allows the estimation of both unknown input and unknown channel dynamics from only channel outputs. In this application, the arterial system is modeled as a multi-channel system. The aortic flow, i.e., the source signal, is transmitted through different arterial paths and observed at multiple systemic locations, such as carotid, radial, brachial, femoral, etc. See Figure 1-a. Both the unknown channel dynamics, denoted $H_i(z^{-1})$, reflecting the mechanical properties of individual arteries, and the unknown source signal, denoted $u(t)$, representing cardiac and proximal aortic hemodynamics, are reconstructed by exploring the correlation among the output signals, denoted $y_i(t)$, simultaneously received at different locations. The authors were inspired by the application of MBSI to wireless communication systems, where a broadcast signal is transmitted through different paths and received simultaneously by multiple receivers. In developing this novel technique, it was realized that the conditions required by existing MBSI algorithms are not satisfied when being applied to cardiovascular monitoring due to the existence of common dynamics, denoted $H_0(z^{-1})$ involved in both channels, $H_i(z^{-1}) = H_0(z^{-1}) \times H_i'(z^{-1})$. A two-step approach, Intermediate Input IDentification (IIID), was developed to solve the problem. In IIID, the distinct part of the multiple channel dynamics, $H_i'(z^{-1})$, is first identified, followed by the construction of the intermediate input, $v(t) = H_i'(z^{-1}) \times y_i(t)$, and the single-channel identification of $H_0(z^{-1})$ from $v(t)$. See Figure 1-b.

Presently, the peripheral signals have been taken as arterial pressure waveforms because these waveforms, along with corresponding central hemodynamics data, are readily available in both pre-existing computational simulations (courtesy of MIT's Prof Roger Kamm) and pre-existing animal data. The technique is robust enough that it may be adapted for other peripheral measurements described above (doppler flow, PPG, etc.). In computer simulations, inputs were generated using the Kamm Cardiovascular Simulator (see Figure 2a). Results of the novel algorithm to estimate aortic flow, compared to the actual aortic flow, are offered in Figure 2b.

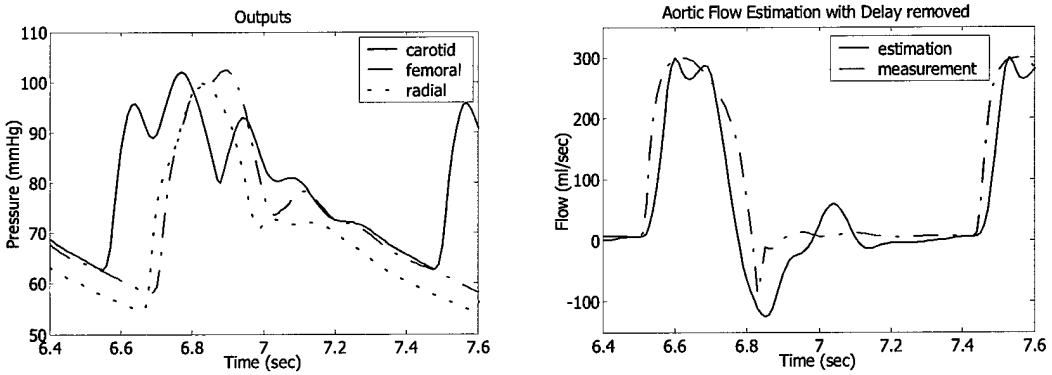


(a) The arterial network modeled as a multi channel dynamic system.



(b) The two step IIID approach

Figure 1. Multi-channel blind system identification for non-invasive central hemodynamic monitoring; Systemic non-invasive sensors alone are used to estimate both the cardiac output (CO) and arterial properties.



(a) (b)

Figure 2. Results of Novel MBSI Algorithm, Using Data from the Kamm Cardiovascular Simulator

Plan: To further develop and apply the MBSI system in our large animal model.

Task 3: Development and characterization of pyroly sis: FAIMS analyzer for the detection of Bacillus spores

Principal Investigator: Jeffrey Borenstein, Ph.D., Draper

Note: Dr. Zapata has left Draper Laboratory for a position in Industry. Dr. Borenstein has taken over as PI for this project as of August 1 , 2002.

Technologies capable of providing early warning of the presence of a biological warfare agent are a vitally important component of the United States Department of Defense, state and local emergency response agencies, and the nation's health care system. What is required is a detection technology that is fast and sensitive, robust and field-deployable, and inexpensive, in order to maximize its export to the civilian field responder or military soldier. Currently available field detectors lack many of the critical features necessary to insure accuracy, portability, reliability and overall viability under field conditions to meet pre-release operational needs of the modern military or civilian bioweapon defense team. Most of the technologies currently under development in the nation's universities and research laboratories, while providing promising bench-scale detection capabilities, are far too large, complex and expensive to be capable of providing a distributed network of early warning systems against a bioterrorist attack.

The goal of this project is to develop and characterize a Pyrolysis-Planar High Field Asymmetric Waveform Ion Mobility Spectrometer (Pyr-PFAIMS) to detect organic compounds released through pyrolysis from bacterial spores, with especial emphasis on realizing a low cost, hand-held analyzer for use as either a continuous, automated air monitor or as a single point analyzer. Figure 1 illustrates the currently available prototype FAIMS device being used for this investigation. This unit has been developed commercially by Sionex, Inc., an entrepreneurial venture started by Draper Laboratory in 2001. Detection of spore biomarkers can be used for "first-alarm" purposes, where the presence and/or change in bacterial spore count in sampled air is sensed, and as a trigger for a more specific biological agent detector. Specific detection of *B. anthracis* is envisioned by monitoring fingerprint patterns of additional biomarkers present in the spore cell walls. Specific aims to be addressed in this proposal are:

A. Aim 1. Assemble a Pyrolysis-PFAIMS system employing COTS components
B. Aim 2. Optimize operating conditions for pyrolytic detection of spore samples
C. Aim 3. Establish feasibility of PFAIMS detection of spore biomarkers
D. Aim 4. Evaluate system performance in regards to accuracy, reproducibility and effects of interferents

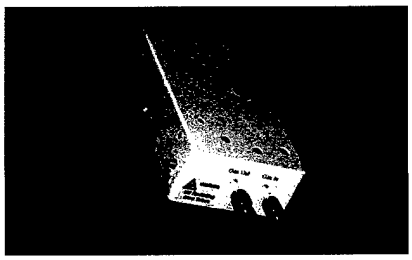


Figure 1. Sionex PFAIMS spectrometer development platform SDP-1

Key Results: During this first year of the project, a complete Pyr-PFAIMS system was assembled by coupling a commercial pyrolyzer with the PFAIMS prototype. A pyrolysis protocol was obtained from the manufacturer of the pyrolysis system; this protocol was evaluated and optimized using Ion Trap Mass Spectrometry. The protocols were tested with dipicolinic acid (DPA), picolinic acid (PA) and pyrolyzed *Bacillus subtilis* samples (as a simulant for *B. anthracis*.) Pyr-PFAIMS protocols have been developed, and test data has been obtained for pyridine, PA and DPA.

Specific Aim 1: Pyrolysis-PFAIMS System Assembly

Progress: A commercially available pyrolyzer was acquired from CDS Analytical with the necessary functions to handle the introduction of liquid and solid samples into the FAIMS detector. All of the ancillary hardware required for the full assembly was procured and the system assembled as shown in Figure 2. The pyrolyzer is capable of heating samples from room temperature to 1400 C at rates from 1 to 20 C/s. The controlled temperature ramping enables selective desorption of compounds from the probe (Figure 3), therefore enhancing resolution and signal-to-noise of the PFAIMS. A drying function evaporates and vents the solvent out a purge vent resulting in sample concentration and prevention of the solvent from entering the PFAIMS filter. A probe cleaning function, flash-heats and desorbs left-over sample between analyses. The pyrolate in transferred to the PFAIMS through a sealed and heated interface. During sample loading on the probe, the pyrolysis chamber is purged while a stream of clean N_2 is diverted into the PFAIMS. During pyrolysis, the flows are diverted through a 6-port valve into the PFAIMS for introduction of the pyrolate into the PFAIMS.

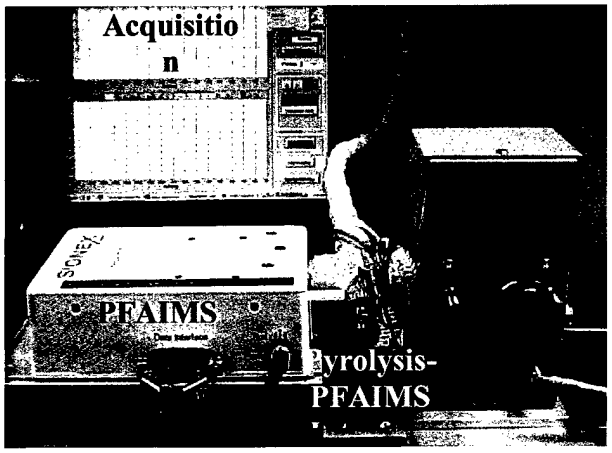


Figure 2. ***Pyrolysis-PFAIMS working prototype.***

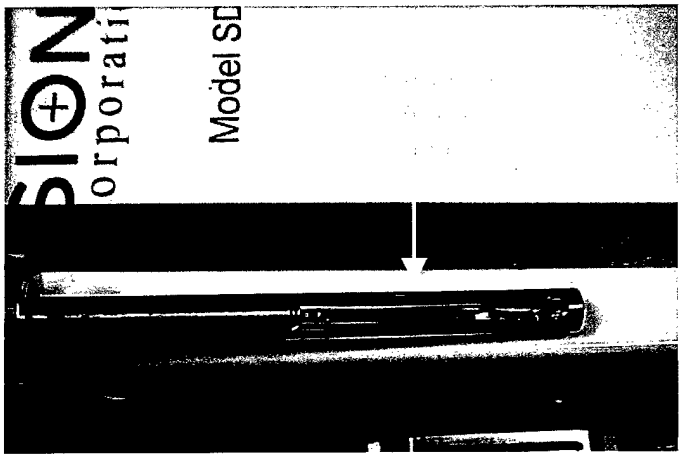


Figure 3. ***Pyrolysis probe.***

In order to provide a control result for comparison with data obtained using the PFAIMS unit at Draper Laboratory, a *B. subtilis* sample supplied by Dr. Sonenshein was sent to CDS Analytical for analysis. The results from pyrolysis-mass spectrometry showed that the expected biomarkers could indeed be detected using the pyrolyzer unit acquired.

Plan: During the second year of the program, the research team plans to investigate modifications to the pyrolysis instrumentation which will provide improved control over the

generation of biomarkers from samples of threat agent. In particular, the pyrolysis equipment is designed for heating samples more rapidly, and to higher temperatures, than are required to produce volatile biomarkers from a spore sample. A finer degree of control over the pyrolysis process is desired in order to optimize the overall performance of the system. Draper's expertise in MEMS technology will be leveraged in order to provide insight into methods for miniaturization and improved control over the pyrolysis system.

Specific Aim 2: Pyrolysis Optimization of Spore Biomarkers.

Progress: The pyrolysis method obtained from CDS Analytical was evaluated and optimized at Draper using Pyrolysis Ion Trap Mass Spectrometry. Both DPA and PA standard solutions and B. subtilis samples have been evaluated. Figures 4a and 4b provide spectra for PA and DPA in a standard solution, while Figure 5 represents the spectrum of a B. subtilis sample. The concentration of DPA and PA in the standard solutions was 100 ppm, the concentration of the B. subtilis sample was 10^9 organisms/ml. These concentrations are orders of magnitude above the ultimate detection limit of the system.

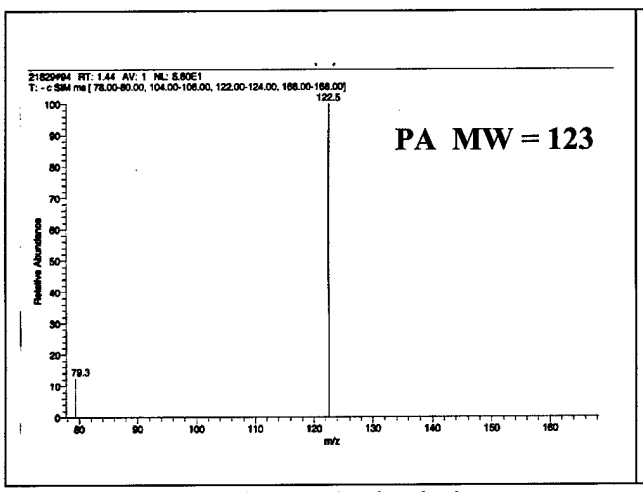


Figure 4a. DPA in standard solution.

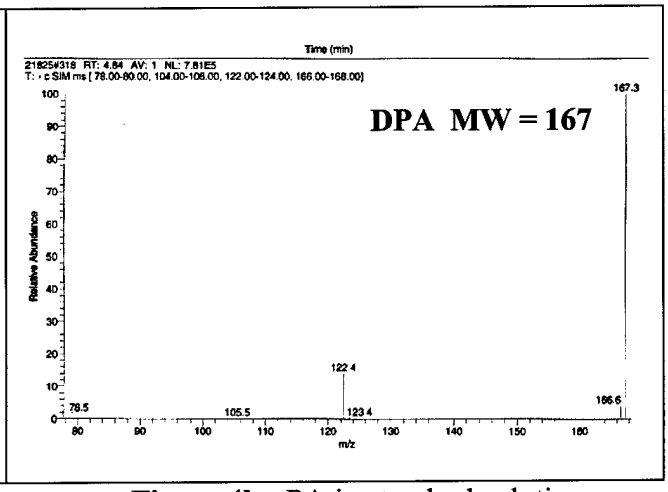


Figure 4b. PA in standard solution.

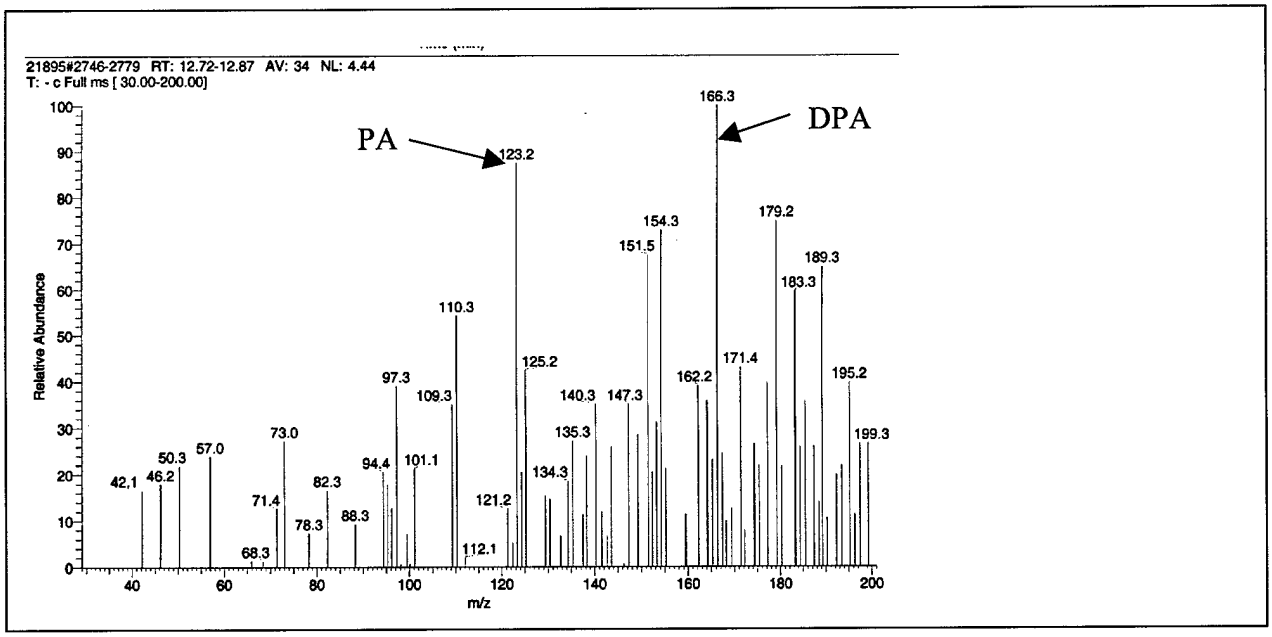


Figure 5: Pyrolysis Mass Spectrometry spectrum of B. subtilis. DPA and PA peaks at m/z 166 and 123, respectively

Plan: Mass spectrometric studies will be conducted as needed in order to provide independent characterization of additional biomarkers for construction of fingerprints for biothreat agents.

Specific Aim 3: PFAIMS Detection of Spore Biomarkers.

Progress: Pyr-PFAIMS spectra for PA and DPA are shown in Figures 6a and 6b. The spectra were obtained from solid samples pyrolyzed sequentially employing the same PFAIMS operating conditions. Picolinic acid was pyrolyzed through a temperature excursion of 130 to 300 °C at a rate of 20,000 °C/s, the interface temperature was held at 130 °C. Dipicolinic acid was pyrolyzed from 145 to 400 °C at 20,000 °C/s, the interface temperature was held at 145 °C. Both PA and DPA produce positive and negative ion peaks that can be used for identification. In addition DPA produces a secondary positive ion peak, further differentiating its fingerprint pattern. The peak width at half height averages 1.4 V. Even though compound identification is relatively straightforward under these controlled conditions, further optimization is desired to improve resolution of the peaks. It is known that pyrolysis is capable of fully decarboxylating DPA to pyridine. Ideally, controlled and more gradual pyrolysis conditions will lead to loss of only one carboxylic acid group to generate PA, enabling specific identification of the DPA source as bacterial spores.

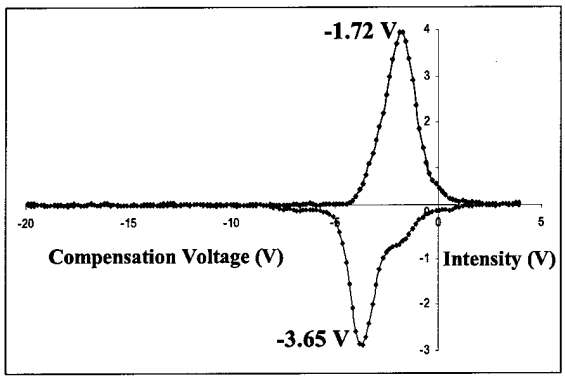


Figure 6a. Positive (blue) and negative (red) ion spectra for PA

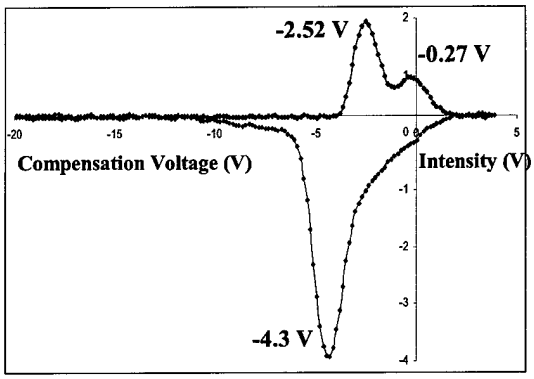


Figure 6b. Positive (blue) and negative (red) ion spectra for DPA

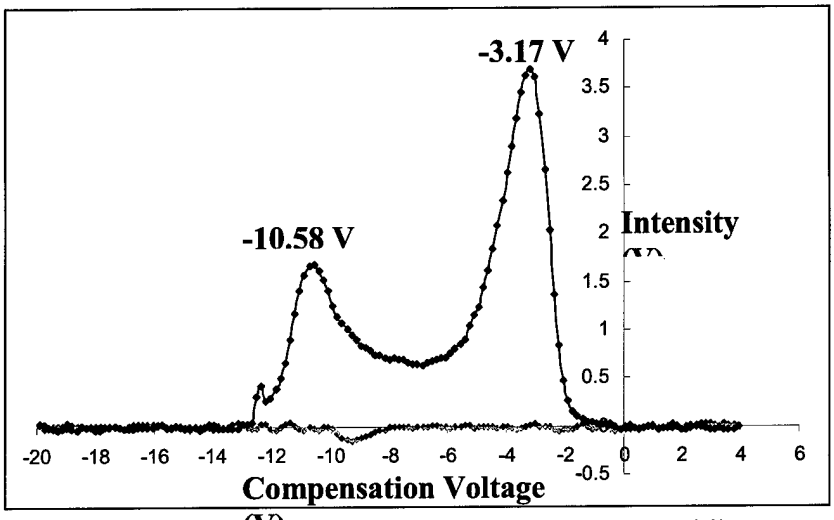


Figure 7. Positive (black) and negative (green) ion spectra for pyridine

To evaluate the pyrolysis conditions employed, PFAIMS spectra for pyridine were generated. Figure 7 is a positive and negative ion spectra obtained with the same PFAIMS conditions as those for DPA/PA analysis. Due to the volatility of pyridine, pyrolysis was not necessary for introduction. The interface temperature was held at 130 °C. As seen in the spectra, pyridine does not produce negative ions. The absence of a negative ion peak enables one to conclude that the pyrolysis conditions employed are mild enough to prevent full decarboxylation and that pyridine can be differentially detected.

Plan: Optimization of pyrolysis and PFAIMS protocols will continue to obtain the best possible resolution and sensitivity. Optimized protocols will be used to perform tests with *B. subtilis* samples. Pyr-PFAIMS detection of *B. subtilis* samples will be started during the first quarter of next year.

Specific Aim 4: Pyr-PFAIMS Performance Evaluation.

Progress: This specific aim was the focus of effort in the 4th Quarter of the project. Analysis of DPA, PA and pyridine samples in the concentration range of 50 ppm – 2500 ppm was carried out, using a wide variety of FAIMS setpoints. Effects of key parameters on FAIMS operation are summarized in the table below.

Independent Variable	RF Amplitude	Peak Width	Bias
Carrier Gas Flow Rate	Positive correlation	Positive correlation	Negative correlation
Drift Tube Temperature			Negative correlation (pyridine)
RF Voltage	Negative correlation		Positive correlation

Table 1. Experimental observations regarding PFAIMS operation and critical parameters.

Experiments aimed at PFAIMS system characterization and optimization of critical parameters are summarized below:

- Transient behavior related to RF cycling was traced to the PFAIMS unit itself, and replacement of the PFAIMS resulted in a substantial reduction in transients in peak heights.
- Headspace gas injection demonstrated the need for heating of the lines feeding the system, to prevent condensation of species on the walls of the tubing.
- Flowrate Optimization: Experiments were conducted using solid PA in the pyrolyzer at a controlled 110 C temperature, while the FAIMS and GC flowrates were varied independently, while using the ratio of peak height to peak width as a metric. Optimal performance was obtained using a low FAIMS flowrate and a high GC flowrate (19 mL/min.)
- Solvents including methanol, methylene chloride, acetone, chloroform, ethyl acetate and acetonitrile were all characterized using 1000 ppm samples of PA. Early results indicate that methanol and methylene chloride appear to be most suited for this application.

Plan: In the second year of the project, evaluation of the Pyr-PFAIMS will be completed using a full set of critical parameters varied using Design of Experiments (DOE) methodologies. Results obtained during the last quarter indicate that these critical parameters include carrier gas flow rate, drift tube temperature, RF frequency and amplitude, compensation voltage scan rate, and the solvent used as a carrier for the spore sample. In addition, pyrolysis conditions, primarily the thermal excursion recipe used to produce the biomarker, are critical to system performance. Results of these experiments will be used to modify the pyrolysis conditions to accommodate the optimal PFAIMS operating conditions.

A second avenue of investigation will pursue specific fingerprinting of target biomarkers using the flexibility and power of the PFAIMS System. PFAIMS can be operated to generate three-dimensional information by adding a time domain to the typical electric field vs. intensity spectra. These three dimensional patterns have been demonstrated to be unique to a given sample therefore expediting sample identification. Patterns are typically easily distinguishable from each other. Analysis selectivity from the patterns can be greatly enhanced using chemometric techniques (e.g. cluster analysis). Chemometrics has been developed to a high level of maturity and is widely used in conjunction with detection techniques such as mass spectrometry, electrophoresis and spectrophotometry.

3.2 COMBAT CASUALTY CARE PROGRAM

Task 1: RAFTS/Bioglove

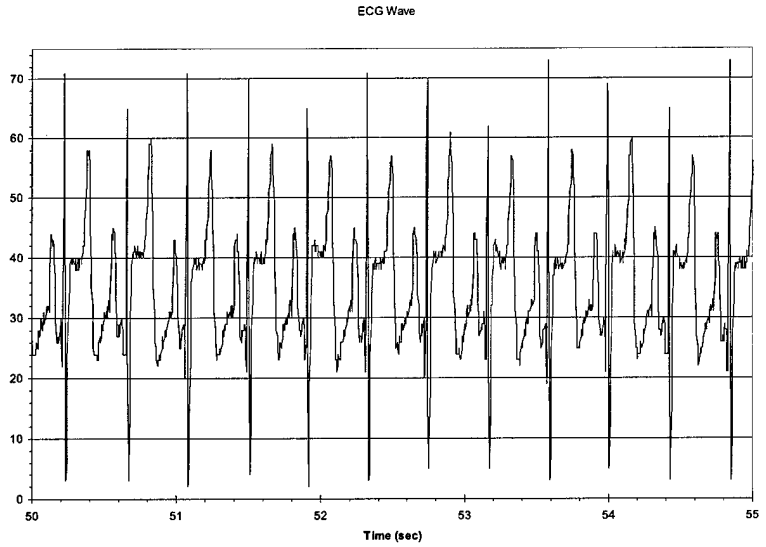
Principal Investigator: Geoffrey Ling, M.D., Ph.D., USUHS

Over the last year, work on the Bioglove and radio frequency (RF) triage system (RAFT) has continued. Over this past quarter, efforts continued on further refinement and modification of the prototype Bioglove system and analyzing the data collected from normal human subjects with RAFT. Data from initial Bioglove *in vivo* pig studies are being used to improve the Bioglove.

Key Results: For the Bioglove, a first prototype was constructed using the component parts previously identified. Animal testing was initiated over this reporting period. This device was used to EKG in 4 anesthetized pigs. The Bioglove was placed on the anterior chest over the heart. For RAFT, collection of normal baseline data of 15 normal human subject volunteers was completed. Data was obtained and processed of their chest, chest and leg using methods previously described. The collected information was obtained and processed as previously described. In brief, following informed consent, the RAFT antenna was held 6 cm away from each subject. Raw data was collected using a network analyzer. Data was processed using the MUSIC algorithm and the MATLAB computer program. The data was displayed as amplitude or phase as a function of radio frequency. Both real and imaginary data were used. Investigators analyzing the raw data were blinded to the treatment.

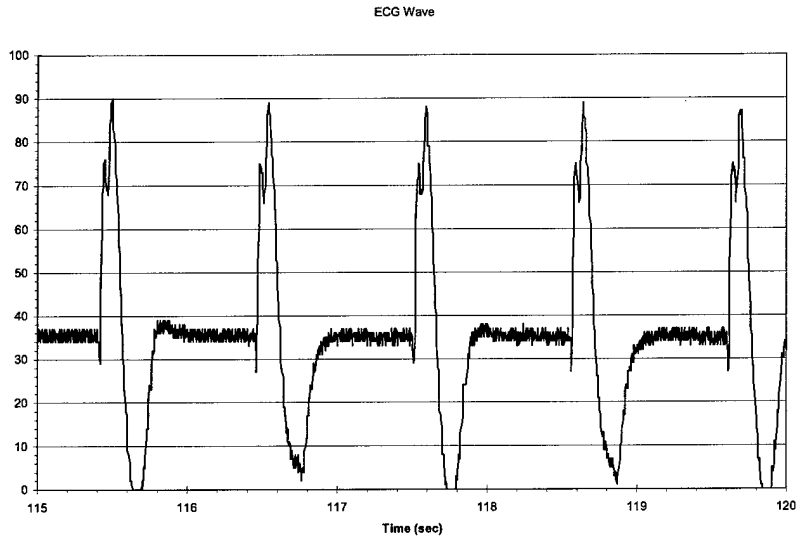
Specific Aim 1: Bioglove: EKG

Progress: Bioglove was used to measure EKG in 4 anesthetized pigs. This was done continuously. Resting heart rate was 120-140 beats per minute. Pigs were treated with esmolol, i.v. to slow the heart rate.



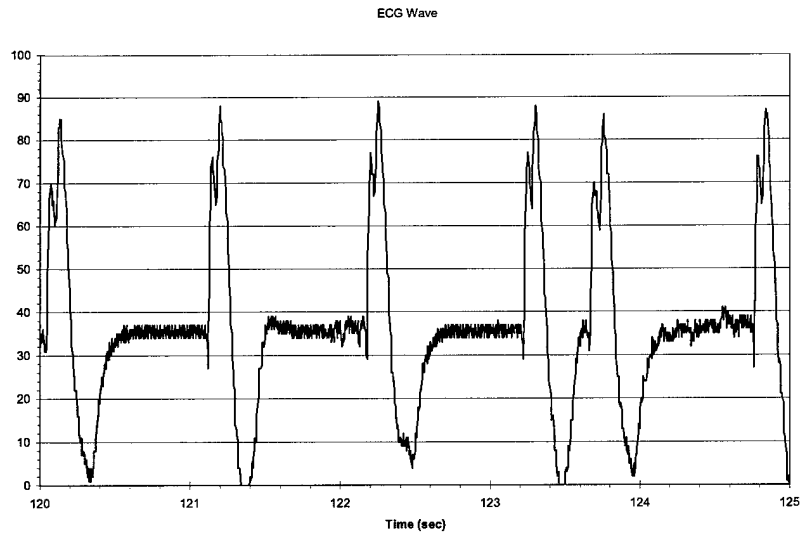
ECG 120-150 bpm

Figure 1. EKG at resting swine heart rate, which is tachycardic for humans.



ECG 80-100 bpm

Figure. 2. EKG of pigs slowed to a heart rate normal for humans.



ECG

Figure 3. EKG in pigs slowed to bradycardic range for humans.

Specific Aim 2: RAFT: Determine baseline signature of normal human chest

Progress: There is remarkable similarity among the 15 volunteers in their baseline chest curves for both magnitude (amplitude) vs frequency and phase vs frequency relationships. This is demonstrated in following figures. In the first 2 examples, the antenna is directed horizontally towards posterior aspect of each subject's chest. The graphs contain each subject's magnitude-frequency (Figure. 3) and magnitude-phase (Figure. 4) data. The mean plot is depicted in red dashed lines. When the antenna is directed horizontally toward the anterior chest, there is another unique signature (Figs 5,6). Similar graphs are shown for antenna orientation directed longitudinally toward the lateral aspect of the left chest (Figs. 7, 8). Similar graphs are shown for antenna orientation directed longitudinally toward the lateral aspect of the right chest (Figs. 9, 10). Further statistical analyses are underway to determine which antenna orientation provides the most consistent signature plot. From the data, the 0.5-2Ghz range may provide the optimal signature signal. However, all orientations are undergoing analyses. If baseline signatures can be determined for each antenna orientation, then clinical application will be vastly enhanced. The reasons are (1) the diagnosis will not be dependent on a specific antenna orientation and (2) data fusion from multiple antenna orientations might allow construction of an image.

Plan: Continued data analysis of the human leg data is also ongoing.

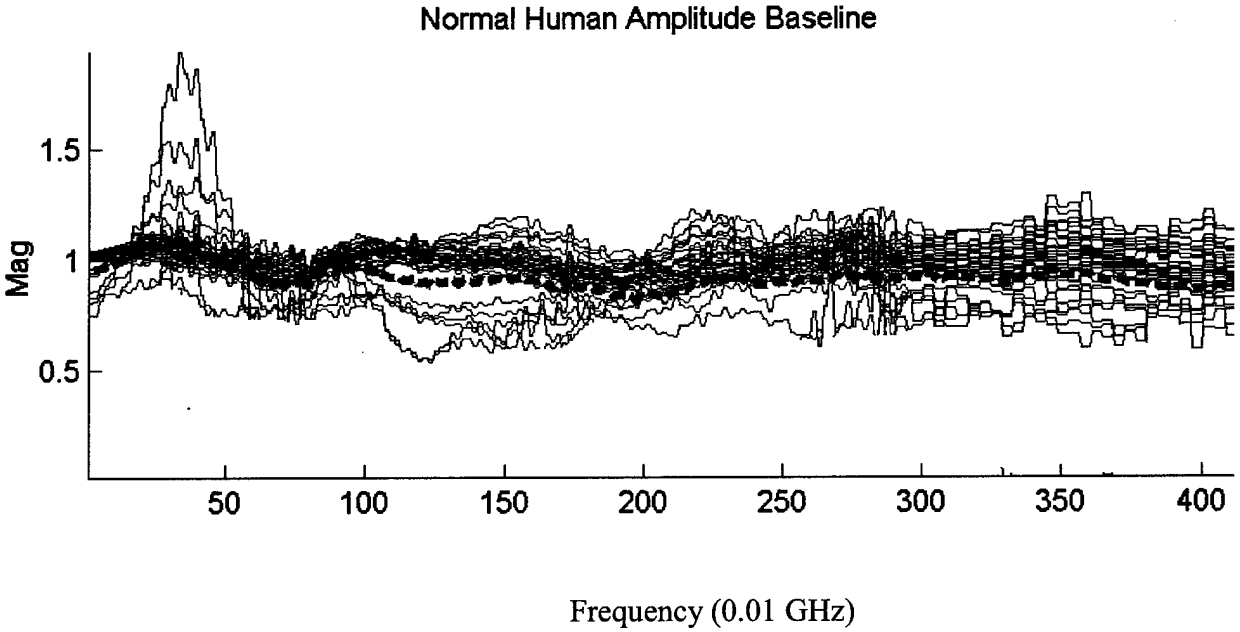


Figure 3. Baseline posterior chest amplitude signature RAFT signal. Magnitude (amplitude) vs. Frequency. Lines are the data of each subject (n=15). Red dashed is the mean.

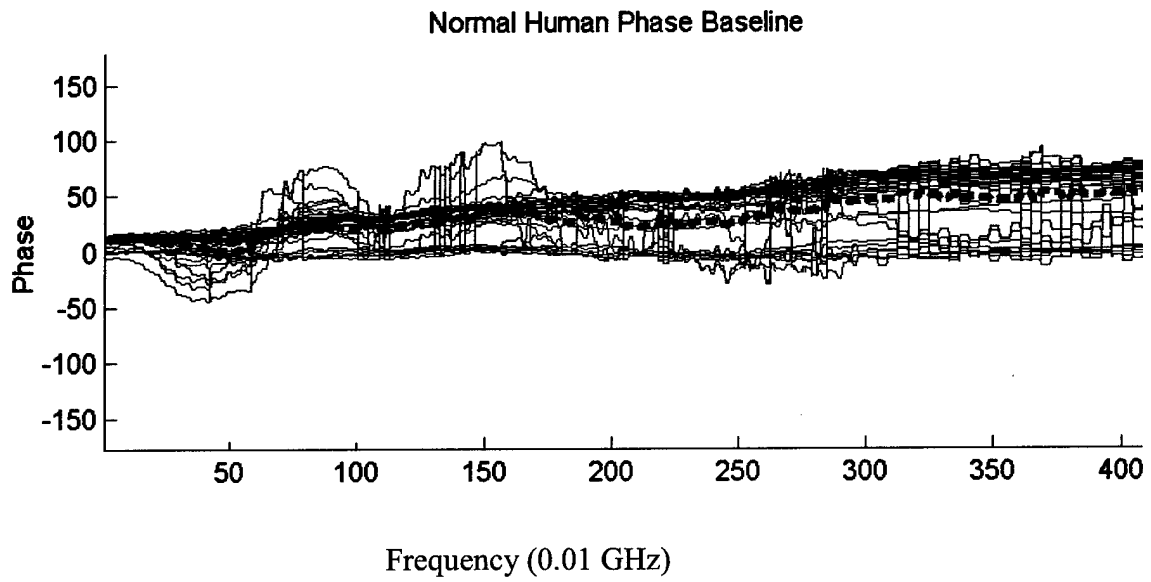


Figure 4. Baseline posterior chest signature RAFT phase signal. Phase vs Frequency. Lines are the data of each subject (n=15). Red dashed line is the mean.

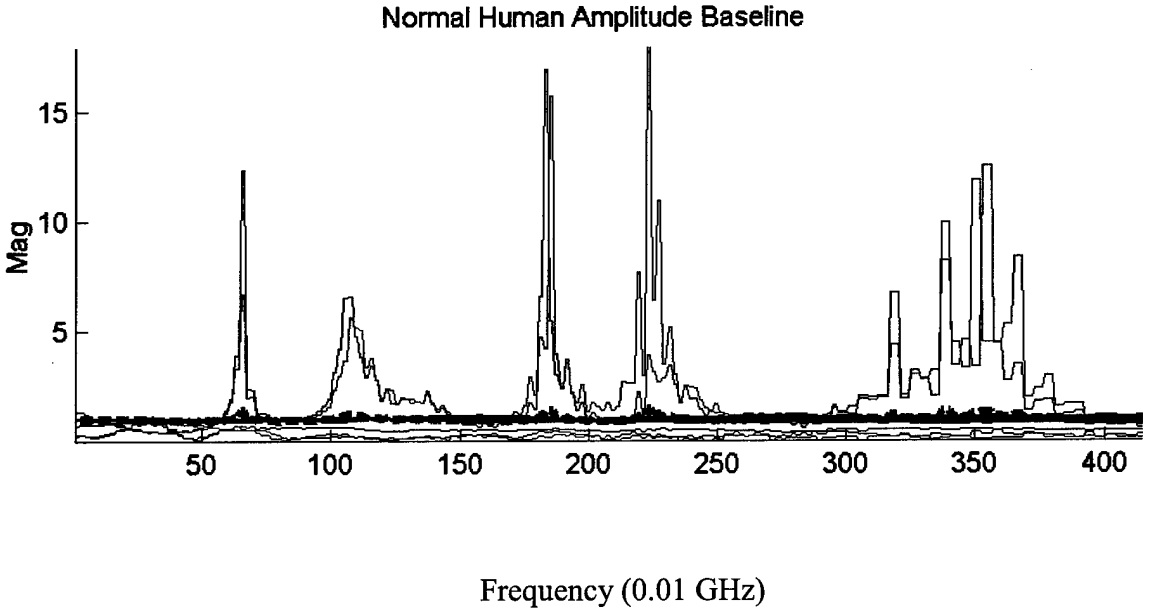


Figure. 5. Baseline anterior chest signature RAFT amplitude signal. Magnitude (amplitude) vs Frequency. Lines are the data of each subject (n=15). Red dashed line is the mean.

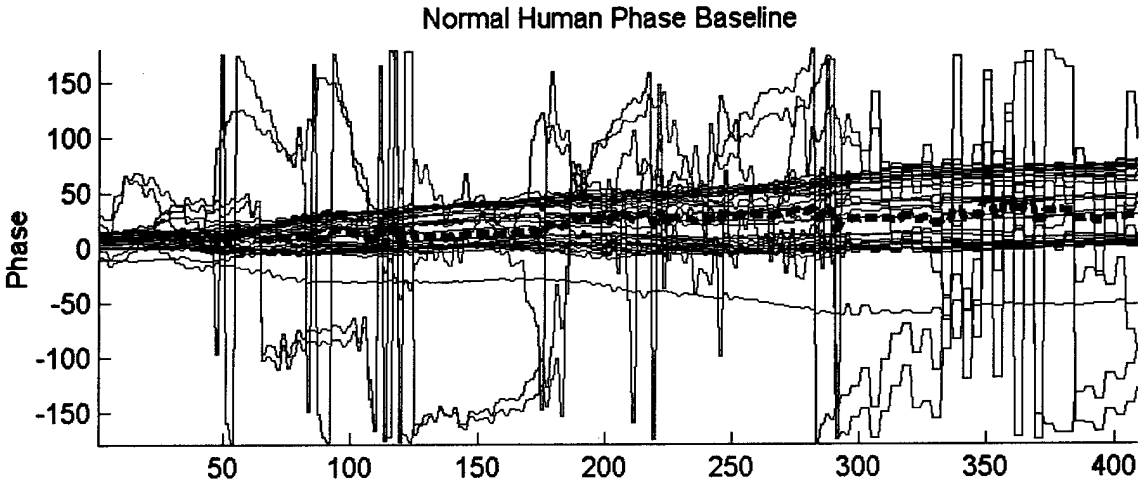


Figure. 6. Baseline anterior chest signature RAFT phase signal. Phase vs Frequency. Lines are the data of each subject (n=15). Red dashed line is the mean.

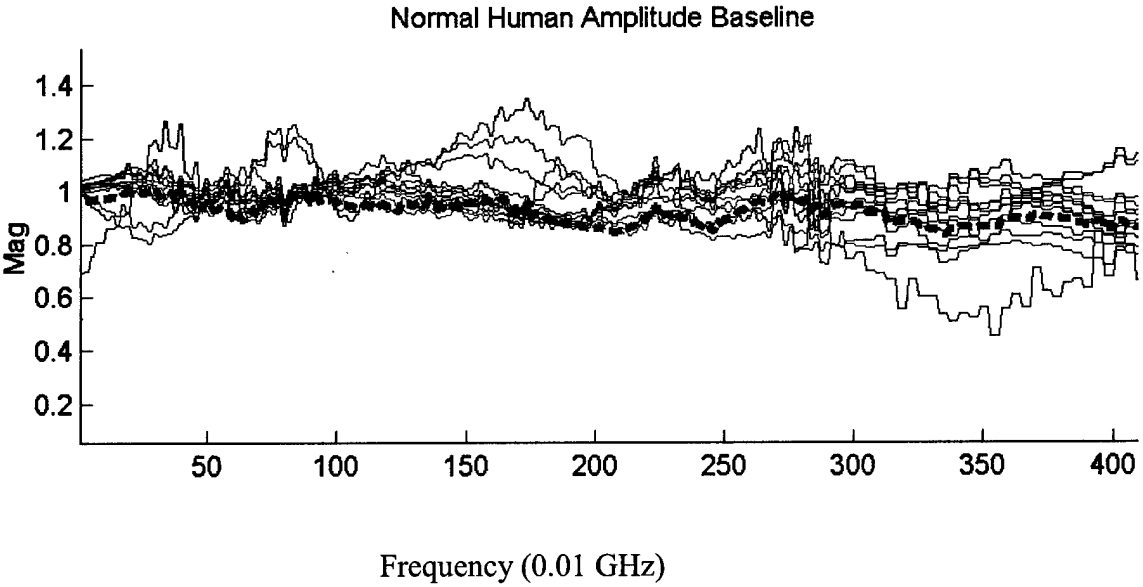


Figure. 7. Baseline left lateral chest signature RAFT amplitude signal. Magnitude (amplitude) vs Frequency. Lines are the data of each subject (n=15). Red dashed line is the mean.

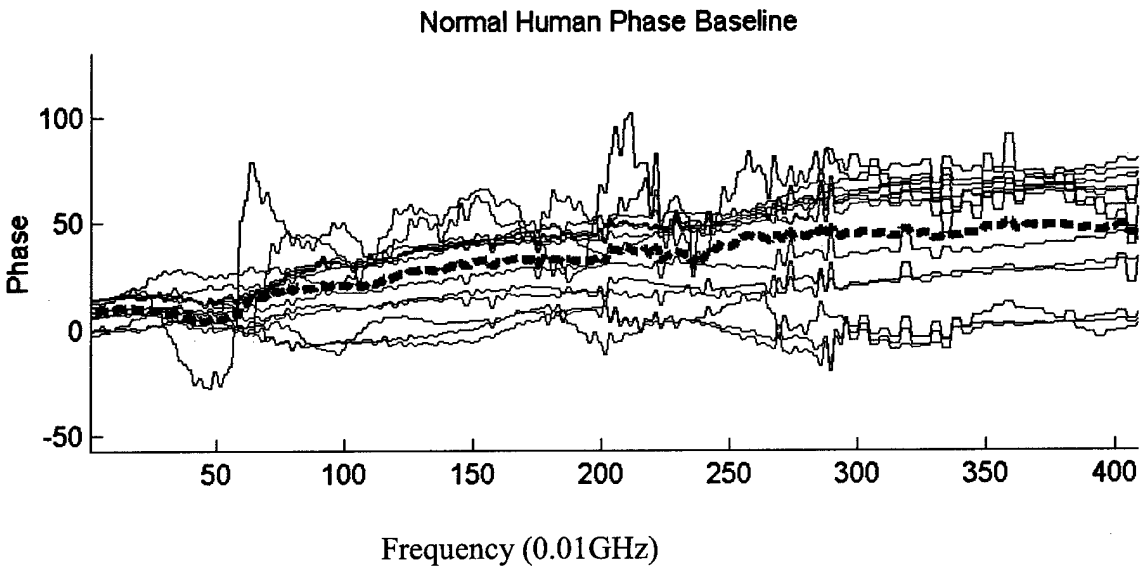


Figure. 8. Baseline left lateral chest signature RAFT phase signal. Phase vs Frequency. Lines are the data of each subject (n=15). Red dashed line is the mean.

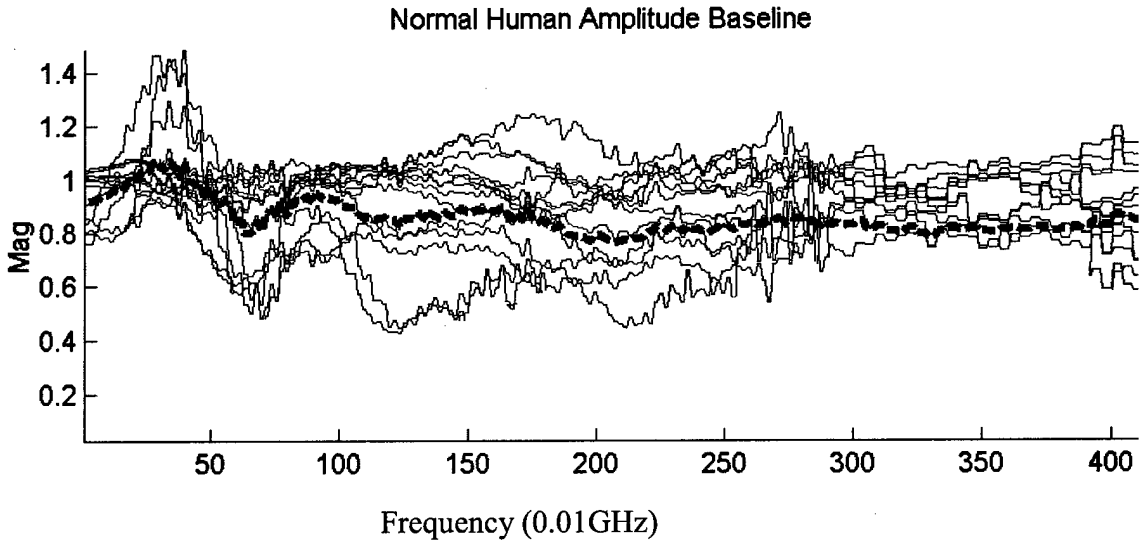


Figure. 9. Baseline right lateral chest signature RAFT phase signal. Phase vs Frequency. Lines are the data of each subject (n=15). Red dashed line is the mean.

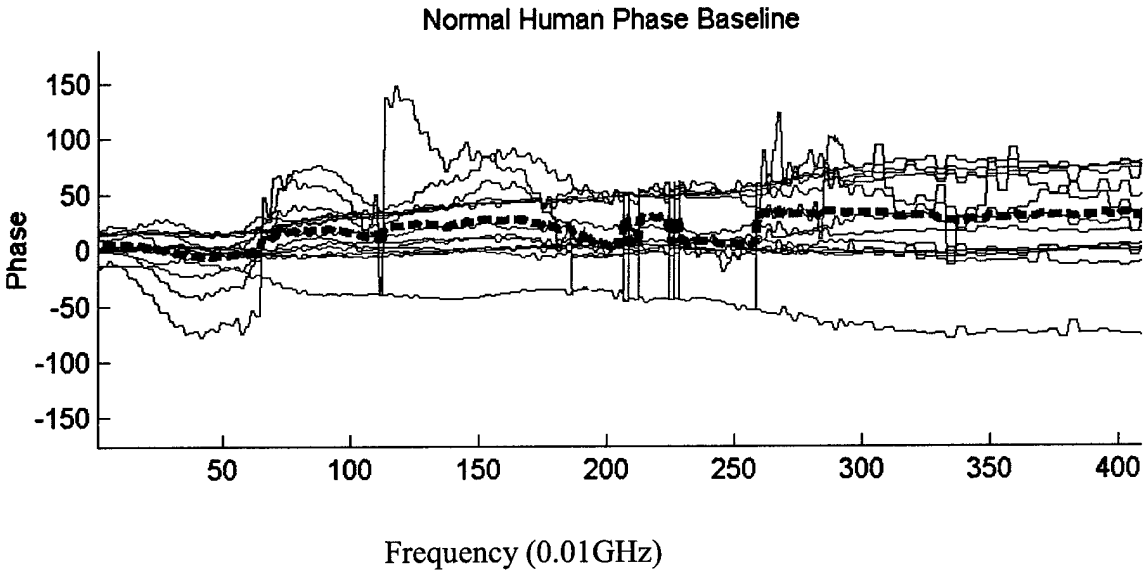


Figure. 10. Baseline right lateral chest signature RAFT phase signal. Phase vs Frequency. Lines are the data of each subject (n=15). Red dashed line is the mean.

Plan: Additional subjects are to be studied.

Specific Aim 3: RAFTS: Determine baseline signature of normal human head

Progress: There is remarkable similarity among the 15 volunteers in their baseline head curves for both magnitude (amplitude) vs frequency and phase vs frequency relationships. If baseline signatures can be determined for each antenna orientation, then clinical application will be vastly enhanced. The reasons are (1) the diagnosis will not be dependent on a specific antenna orientation and (2) data fusion from multiple antenna orientations might allow construction of an image.

Plan: Continued data analysis of the human chest and leg data is also ongoing.

Task 2: Parallel computer processing and modeling use in medical monitoring
Principal Investigator: William Wiesmann, M.D., Harvey Mudd College

Current patient medical monitoring techniques are used to identify sudden, unmistakable deleterious changes in patient status. Large volumes of data are generated both continuously and asynchronously, yet there is no standard protocol for transmitting and receiving patient data from medical monitors and data is generally not permanently archived, forfeiting the opportunity for correlate signal correlation and long-term trending and analysis. Without the ability to continuously analyze disjoint sets of patient data, it is difficult to detect slow-forming complications. As a result, the early onset of conditions such as pneumonia or sepsis may not be apparent until the advanced stages.

The primary goal of the Parallel Computer Processing and Modeling Use in Medical Monitoring project was to develop a distributed software architecture that provided a test bed for the

development of software medical models to analyze both asynchronous and continuous patient data in real time and report the results in a meaningful way. Hardware and software has been developed to support a multi-node distributed computer cluster capable of amassing data from multiple patient monitors.

Key Results: The 2001/2002 Harvey Mudd College CIMIT team designed and implemented a distributed computing architecture to serve as the foundation for a research tool to investigate the benefits of implementing a real-time patient monitoring system.

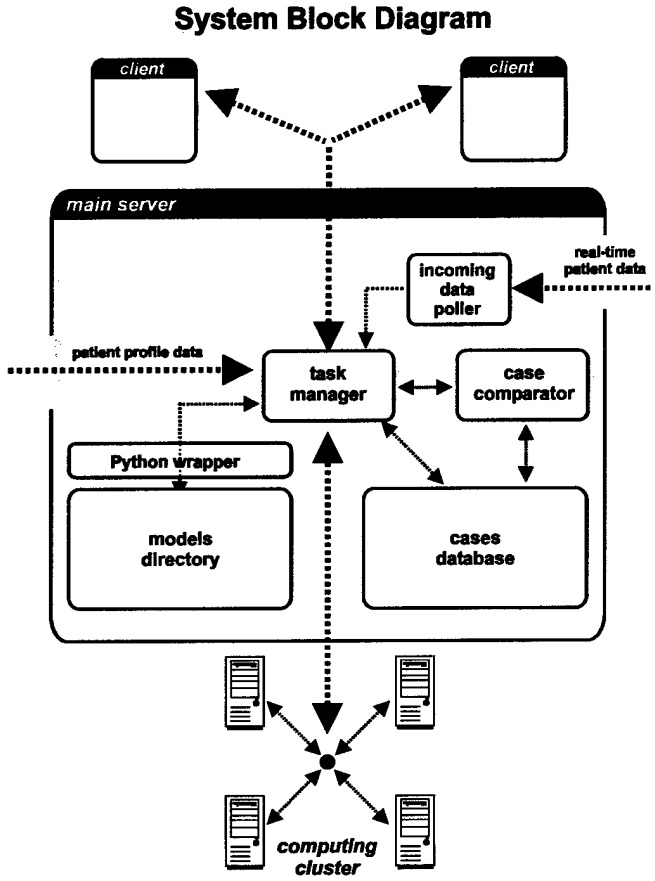
First semester accomplishments consisted of technology research, purchase and assembly of a small computing cluster, design of abstract software architecture, and the coding of a proof of concept iteration of the architecture. Second semester work involved the implementation, testing, and refinement of the system design. The multi-node distributed computer system was completed in June 2002. Project milestones included:

- Hardware and software was developed to support a multi-node distributed computer cluster.
- Infrastructure was developed to allow health care providers and researchers to use off-the-shelf computing components as a test bed for developing physiological software models.
- A generic computing architecture was designed and developed to serve as the foundation for a real-time patient monitoring system.
- One computer acts as a central coordinating node; additional computers can be added to the system to accommodate processing needs.
- Computer components were ordered individually and assembled on site to provide increased flexibility, incorporate superior components, and increase cost-effectiveness.
- A simple, non-clinical model for sepsis detection was implemented on the system for demonstration purposes.

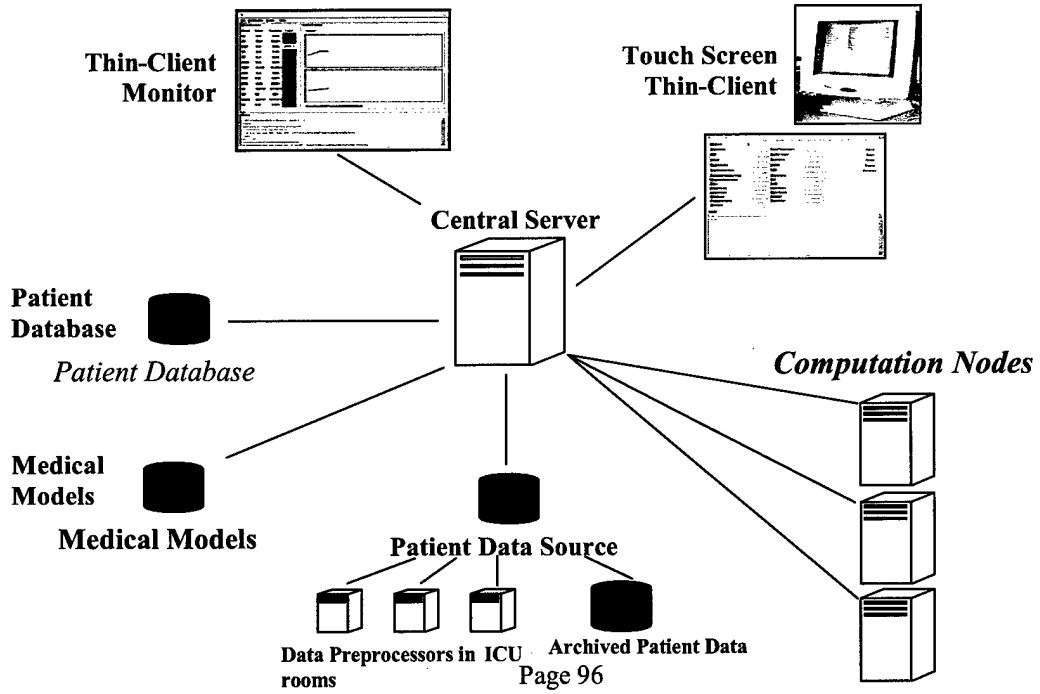
Specific Aim 1: Hardware for a Distributed Software Architecture.

Progress: Following initial consultations with the liaisons and preliminary research, an overall system design was created. To better suit the needs of the project, the system was redesigned to meet the essential requirements.

Initial Block Diagram:



Final System Block Diagram:



Specific Aim 2: Hardware for a Distributed Software Architecture

Progress: Five computers (or nodes) were built – one to be used as a server, and four to be used as computation nodes. Special care was taken to select high quality network interface cards for the computers. Care was also taken to build each computer in such a way that its own processing power was scalable, should the demand for the raw computing power of each node increase. In anticipation of the high demand placed on the networking components of the system due to the high volume of data being processed, the design of the nodes were structured to satisfy the computing resource demands that the models and our architecture would impose on the system.

The server node was designed to carry on multiple activities simultaneously, including serving files to computation nodes, communicating with both computation nodes and external computers via TCP/IP, providing access to at least one local database, and acting as web server. The server was fitted with a dual processor motherboard and two high-end processors, twice as much system memory as the computation nodes, a second hard drive for the databases, and a second network card to access an external network.

Plan: Develop an authentication system to limit access from the system's Graphical User Interface. Authentication will consist of a login name and password. Also, the team plans to stress test the system with a high processing load to expose possible bugs and incorporate methods to confirm if input data is formatted correctly and within defined bounds.

Specific Aim 2: Software Architecture Design.

One of the primary requirements of this software system is the ability to seamlessly incorporate models written in a variety of languages.

Progress: The Task Manager, Patient Database, and Node Client in Python were written in Python, a high-level object-oriented scripting language ideally suited to the task of wrapping models in a standard format. C++ is efficient and fast since it can be compiled down to machine code, therefore the simulated sepsis detection model was written in C++. The Thin Clients were written in Java because of its rich GUI building libraries and its ability to be embedded into web browsers. The Data Simulator was also written in Java.

Plan: Develop and incorporate a method by which the user can enter a timestamp for asynchronous data entered into the system via the GUI.

Specific Aim 3: Pneumonia Sepsis Model
To identify and evaluate the foundation for a system that will eventually accept robust models, a non-clinical, simulation model for detection of sepsis based on basic threshold checking was developed for testing purposes.

Condition Profiles for Sepsis, Pneumonia & Sepsis, and Pneumonia & Septic Shock			
Input Variables	**Sepsis**	**Pneumonia & Sepsis**	**Pneumonia & Septic Shock**
Pulse Rate (PR)	++	++	+++
Respiratory Rate (RR)	+	+++	+++
Mean Systolic Blood Pressure (mSP)	S/+	+	--
Core Temperature (CT)	+	++/+++	++
Skin Temperature (ST)	+	++	+
Oxygen Saturation (OSAT)	s	-	--
PEEP	s	+	++
PAO	s	s/-	--
PCO	-	+	--
BUN	S/+	+	++
Creatinine (CR)	+	+	++
Urine Output (UO)	s/-	-	--
Bicarbonate (BICAR)	+	+	--
Blood pH (PH)	s/-	s	--

Progress: The sepsis simulation model was written in C++ and takes 14 common ICU medical signals as input. The model calculates each signal's percent deviation from a defined baseline and compares these results to three signal deviation profiles that represent three distinct conditions in the patient. The levels are specified as follows:

Stable (s):	Signal value is within (+/-) 10% of baseline
Level 1 (+ or -):	Signal value is (+/-) 10-20% from baseline
Level 2 (++ or --):	Signal value is (+/-) 20-30% from baseline
Level 3 (+++ or ---):	Signal value is greater than (+/-) 30% from baseline

For each time step, the model calculates the level of each signal and compares these signals against three profiles: sepsis, pneumonia and sepsis, and pneumonia and septic shock. If any of these condition profiles match the current state of the data, the model throws a warning in its output.

The ultimate success of this project hinges on the development of physiological models capable of reducing the clinical time necessary to make accurate diagnoses and facilitate faster treatment. Before this system can be used in the clinical setting, robust physiological models capable of operating on streaming real-time data must be developed. Few facilities are equipped to capture streams of digitized patient data where the outcome of the patient is known, yet the development of such models is dependent on detailed long-term archived patient data.

Plan: This sepsis model will be used as a template for developing other models with critical care importance. These models will inclusively access relationships between signals in the data rather than intensely analyzing only a few signals.

3.3 VULNERABLE PLAQUE PROGRAM

Task 1: Vulnerable Plaque

Principal Investigator: James Muller, M.D., MGH and Thomas Brady, M.D., MGH

The CIMIT Vulnerable Plaque Program is now established in the former CIMIT Central Office space of approximately 2,200 sq. ft. at Charles River Plaza. The space houses 12 VPP investigators including cardiologists, radiologists, Ph.D. scientists, post-doctoral fellows and students. This stimulating environment has critically enhanced the success of the Vulnerable Plaque Program. In additional to scientific progress, the Vulnerable Plaque Program has initiated a strategic planning process under the leadership of Lynn R. Osborn, MBA.

The following is the list of Vulnerable Plaque and related projects funded for FY 02:

- Detection of Vulnerable Plaque using Optical Coherence Tomography in carotid and coronary arteries
- CT and MRI Imaging of Vulnerable Plaque
- MR Compatible Intravascular Coils
- Detection of Vulnerable Atherosclerotic Plaques with Radionuclide Technology
- MRI of Carotid Plaque
- Magnetic Resonance Imaging of Vulnerable Plaque, and
- Vulnerable Plaque Program Outcomes – Technology Assessment.

Task 1: Vulnerable Plaque Detection and Treatment

Principal Investigator: James E. Muller, MD and Thomas J. Brady, MD, MGH

The original programmatic aims of the Vulnerable Plaque program have been accomplished. The number of faculty, PhD fellows and students in the program increased significantly during the past year. The following represents the programmatic accomplishments.

Specific Aim 1: Establish a Vulnerable Plaque Lecture Series.

Progress: The Vulnerable Plaque Program completed year two of its weekly seminar series. The program consists of a weekly series of topics on various aspects of vulnerable plaque given by investigators within and outside the Boston community. The lecture-discussion format enables the transfer of ideas and generates provocative interaction. A written summary of each presentation is documented as well as a video of the presentations which are available to our corporate sponsors. The program topics and schedule are outlined below.

Plan: Re-evaluate the form and content of VPP Lecture Series. Develop a system to distribute presentation summaries to internal and external stakeholders.

Specific Aim 2: Establish an International Symposium on Vulnerable Plaque.

Progress: After a successful 2001 international symposium held in Cambridge, MA, the Vulnerable Plaque program is sponsoring two meetings in FY03. The first is a Cardiac Imaging postgraduate course to be held on October 20th and 21st at the Weston Copley Place in Boston. The program will have national and international speakers addressing many aspects of cardiac

imaging including the vulnerable plaque. The second international VP Symposium for the spring 2003 will be held in the Washington DC area. The meeting will be jointly by the NIH and the FDA. The program will deal with all aspect of the vulnerable plaque and is expected to generate several position papers.

Plan: To coordinate a post graduate course and second international VP Symposium for FY03

Specific Aim 3: Obtain Additional Funding for the Vulnerable Plaque Program.

Progress: Over the past year, the Vulnerable Plaque Program raised over $600,000 from industry to enhance the research activities beyond DoD-CIMIT support. In addition, successful pilot studies have been awarded external funding. The OCT project successfully competed for NIH funding and an industrial grant from Guidant to bring this technology into the catheterization laboratory for patient studies at the MGH. In addition, NIH grants were submitted to extend the research in non-invasive image detection and characterization of vulnerable plaque and the development of novel intravascular coils.

Plan: To continue to seek sponsorship and active collaboration with partners in industry whose companies have an interest in the detection and/or treatment of vulnerable plaque. 2) To continue to seek external support from NIH and industry for successful pilot projects.

Specific Aim 4: Initiate Strategic Planning process for the CIMIT Vulnerable Plaque Program

Progress: The Vulnerable Plaque senior management team has dedicated time and focus to developing a mission statement, SWOT analysis, a project and sources of funds portfolio, completing strategic stakeholder interviews and setting objectives for the short and long term. The process has been instructive and team building and has set the foundation for the future of the group.

Plan: To document and implement CIMIT VPP '02 strategic plan

CIMIT Vulnerable Plaque Detection & Treatment Program Lecture Series

October 29th Alan Daugherty, PhD
"Angiotensin II - Its Role in Atherogenesis and Aneurysms"
University of Kentucky
Division of Cardiovascular Medicine

November 5th Zahi Fayad, Ph.D.
"Atherothrombotic Plaque Imaging from Mice to Humans"
Mount Sinai School of Medicine, New York

November 19th Review of selected AHA Abstracts

December 3rd Farouc Jaffer, MD, PhD
"Molecular Imaging of Thrombosis: A New Tool for Vulnerable Plaque Detection?"
Massachusetts General Hospital

December 10th Andrew S, Greenberg, M.D
"Perilipin, Potential Marker of Plaque Rupture: What is Perilipin? Why is it Found in Plaques?"
Tufts University

January 28th Tayyaba Hasan, PhD
"Photodynamic Therapy"
Massachusetts General Hospital

February 4th K. McCully, MD
Homocysteine and Vascular Disease
West Roxbury Veterans Hospital

February 11th Morteza Naghavi, MD
"MRI for Detection of Inflammation- Insight into Structure and Activity of Plaque"
University of Texas

February 18th Holiday

February 25th Robert Weisskoff, PhD
"Targeted Molecular Imaging with MRI"
Epix Medical

March 4th George Abela, MD
"Angioscopy for Detection of Vulnerable Plaque"
Michigan State University

March 11th Chun Yuan, Ph.D.
"MR Imaging of Carotid Plaque"
University of Washington

March 18th American College of Cardiology Mtg - no lecture

March 25th Mizuno Kyoichi M.D., Ph.D.
"Angioscopy and Vulnerable Plaque"
Chiba Hokusoh Hospital and Nippon Medical School
Chiba, Japan

April lst Ahmed Tawakol, MD
"Macrophage-Targeted Detection and Therapy of Vulnerable Plaques"
Massachusetts General Hospital

April 8th Donald Baim, MD
"Stents and Other New Technology for Intracoronary Treatment of Vulnerable Plaque".
Brigham and Women's Hospital

April 29th Stephen Naylor, PhD
"Proteomic Methods of Possible Use for Vulnerable Plaque Research"
Beyond Genomics

May 6th James Liao, M.D.
"Non-Lipid Effects of Statins in Prevention ofThrombosis/CVD/Ischemic Disease"
Brigham & Women's Hospital

May 13th Steven Feinstein
"Effect of Aggressive Lipid Lowering on Conorary Calcium Score Using Electron Beam Computer Tomography" and "Contrast Enhancement with Optison Improves Carotid Wall Intimal Medial Ultrasound Determination".

June 3rd Brian Cunningham, Ph.D.
Homer Pien, Ph.D.
"A Direct Assay Optical Biosensor and Applications for Vulnerable Plaque Diagnosis"
SRU Biosystems

June 17th Jerry Ackerman, Ph.D.
"Novel Approaches for Intravascular Magnetic Resonance Imaging and Spectroscopy"
Massachusetts General Hospital

Jonathan Rosen, Ph.D.
"How to Protect Your Intellectual Property"
CIMIT

Task 2: Characterization of vulnerable plaque
Principal Investigator: Thomas Brady, M.D., MGH and Brett Bouma, Ph.D., MGH

The overall goal of this research is to demonstrate that OCT can be used to accurately characterize atherosclerotic plaques and to distinguish plaques that are vulnerable from those that are stable. In our previous research, using non-DoD funds, we have developed the necessary technology and have demonstrated the feasibility of performing intracoronary OCT imaging in swine and in human subjects. The evaluation of OCT's ability to characterize coronary plaques, however, is challenging. Since there is no established clinical method for characterizing plaques, it is not possible to compare OCT against a meaningful clinical gold-standard technology. Human studies are also complicated by the inability to obtain biopsy specimens for correlation. This is not to say that human studies are not important. Our ongoing clinical studies, funded through industrial sponsorship, will compare plaque features visible in OCT images obtained from disrupted plaque sites with images taken at locations of stable plaque and will also retrospectively evaluate images acquired at locations found to cause acute events in follow up.

Animal studies are also insufficient to rigorously evaluate OCT's ability to characterize plaques. With CIMIT funding, we are currently conducting an imaging study in a rabbit model for atherosclerosis. The aim of this work is to evaluate the ability of OCT to monitor plaque progression and regression in the aorta of rabbits. This study will provide valuable data for determining the ability of OCT to discriminate between lipid-rich, calcified, and fibrous plaques and to quantify lipid volume and fibrous cap thickness. The dissimilarities between the plaques developed in the model and those found in humans, however, limits the extrapolation of these results to a meaningful assessment of the clinical utility of OCT for identifying vulnerable plaques in human subjects.

The specific aims of this DoD funded study are complimentary to other non-DoD funded ongoing studies in human subjects and animals. They are also complimentary to the other projects within CIMIT's vulnerable plaque program. The immediate goal of the proposed work is to determine the accuracy with which OCT can be used to identify plaques exhibiting the accepted histopathologic features associated with vulnerability.

Key Results: Using cadaveric coronary, aorta and carotid specimens, we have developed criteria for plaque characterization and have tested these criteria against histopathology in a blinded study.

Specific Aim 1: Develop database of OCT images, IVUS images and histology of cadaver coronary vessels

Progress: A database of OCT images and correlating histology including 357 specimens was obtained. 50 pairs of OCT/histology were used as a training set with the remainder reserved as a test set.

Plan: Project completed.

Specific Aim 2: Develop and validate algorithms for characterization of atherosclerotic plaque with OCT.

Progress: Using coronary, aorta and carotid specimens, we have developed criteria for plaque characterization and have tested these criteria against histopathology in a blinded study. Three separate studies were performed to evaluate plaque-type criteria, macrophage content criteria, and cap thickness measurements. Results from two of these three studies have already been accepted for publication in the leading cardiovascular journal, Circulation, and are in press. A manuscript describing results from the third study has been submitted for review to Circulation.

Plaque type characterization
OCT images of 357 (diseased) atherosclerotic arterial segments obtained at autopsy were correlated with histology. OCT image criteria for three types of plaque were formulated by analyzing a subset (n=50) of arterial segments. OCT images of fibrous plaques were characterized by homogeneous, signal-rich regions, fibrocalcific plaques by well-delineated, signal-poor regions with sharp borders, and lipid-rich plaques by signal-poor regions with diffuse borders. Independent validation of these criteria by two OCT readers for the remaining segments (n=307) demonstrated a sensitivity and specificity ranging from 71-79% and 97-98% for fibrous plaques, 95-96% and 97% for fibrocalcific plaques, and 90-94% and 90-92% for lipid-rich

plaques, respectively (overall agreement, κ = 0.83-0.84). The interobserver and intraobserver reliabilities of OCT assessment were high (κ values of 0.88, and 0.91, respectively).

Macrophage content characterization
OCT images of 26 lipid-rich atherosclerotic arterial segments obtained at autopsy were correlated with histology. Cap macrophage density was quantified morphometrically by immunoperoxidase staining with CD68 and smooth muscle and compared to the standard deviation of the OCT signal intensity at corresponding locations. There was a high degree of positive correlation between OCT and histologic measurements of fibrous cap macrophage density ($r = 0.84$, $p < 0.0001$) and a negative correlation between OCT and histologic measurements of smooth muscle actin density ($r = -0.56$, $p < 0.05$). A range of OCT signal standard deviation thresholds (6.15% - 6.35%) yielded 100% sensitivity and specificity for identifying caps containing > 10% CD68+ staining. Additional features such as collections of macrophages at the cap-lipid pool border were also visualized by OCT.

Fibrous cap thickness measurements
OCT images of 30 lipid-rich atherosclerotic arterial plaques obtained at autopsy were correlated with histology. Fibrous cap thicknesses were measured by OCT and histology at the center of each lesion. There was an excellent degree of correlation between OCT and histologic measurements of fibrous cap thickness (range 30.8 - 496.3 μm) $y = 1.03x + 3.0$ ($r = 0.91$, $p < 0.0001$). In a Bland-Altman analysis, good agreement was found between OCT and histologic measurements of fibrous cap thickness (mean difference $= -8.0 \pm 48.0$ μm).

Plan: Project completed.

Task 3: Detection of vulnerable atherosclerotic plaques with radionuclide technology
Principal Investigator: Alan Fischman, M.D., MGH and Ahmed Tawakol, M.D., MGH

Cardiovascular disease remains the leading cause of morbidity and mortality in the United States, largely due to events caused by rupture of a vulnerable atherosclerotic plaque (VP). Currently the most reliable clinical tools used to diagnose coronary disease, (myocardial perfusion imaging and coronary angiography), are able to detect obstructive lesions, but can not detect VP. As such, a method to detect VP is needed.

This research proposal seeks to determine, in an animal model of atherosclerosis, whether noninvasive imaging with novel radionuclide technology can detect vulnerable plaque (VP). As such, we employed a radiolabeled bacterial chemotactic receptor agonist to successfully detect experimental atherosclerotic plaques by targeting the inflammatory cells that reside within them. In the course of this experiment, we found that the macrophage-targeted radiolabeled peptide accumulates in atherosclerotic aorta and can be imaged non-invasively using standard single photon emission computed tomography (SPECT).

Key Results: This past year, the CIMIT team employed an animal model of atherosclerosis, in which macrophage-rich atherosclerotic plaques were induced in New Zealand rabbits by balloon de-endothelialization of the infradiaphragmatic aorta followed by a high cholesterol diet. At 10 weeks, a technetium-radiolabeled derivative of bacterial chemotactic peptide (Tc-f-MLPK-HYNIC) was administered to seven control rabbits, and to 7 rabbits in which aortic

atherosclerotic lesions were induced. This peptide has been shown to avidly bind to leukocytes, with high specificity. At 12 hours after administration of the radiolabel, the live rabbits were imaged using SPECT. Two investigators that were blinded to the status of the rabbits examined the images. A semi-quantitative scoring system was employed, where a score of 0 (no uptake) to 3 (high uptake) was assigned to each rabbit's aortic image. At 16 hours, the animals were sacrificed and the aortas were examined for uptake of the radiolabeled ligand. Average radiotracer uptake within the atherosclerotic aortas was 72-fold higher than in the control aortas (297±187 vs. 4±1, P=<0.02)(figure 1). Moreover, with SPECT imaging of the live rabbits, the mean score for radiotracer uptake was significantly higher in the atherosclerotic aortas compared to healthy aortas (2.5±0.3 vs. 0.3±0.1, P=<0.03) (Figure 2). These data support the strategy of employing inflammation-targeted radionuclide technology to detect macrophage-rich atherosclerotic plaques.

Specific Aim 1: Test the hypothesis that experimental atherosclerotic lesions can be detected non-invasively, using radiolabeled bacterial chemotactic peptides that target inflammatory cells within the plaque:

- Determine site of localization of radiotracer within plaque in an animal model.
- Optimize the single photon emission CT (SPECT) technique used to detect target uptake of the radiotracer.
- To test the hypothesis that atherosclerotic aortas can be differentiated from normal aortas with non-invasive imaging (SPECT).

Progress:

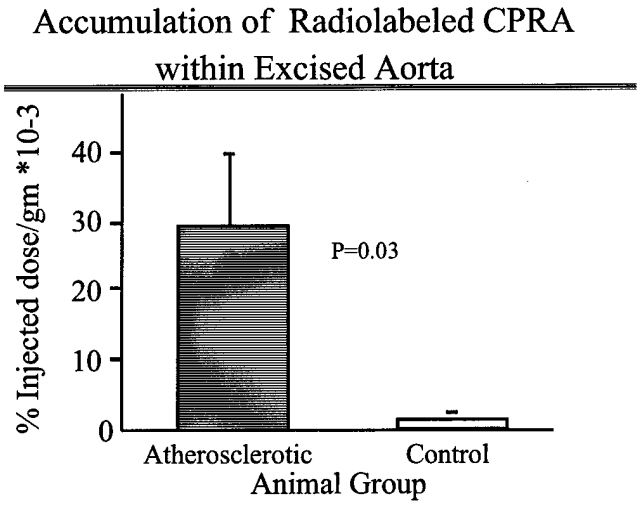
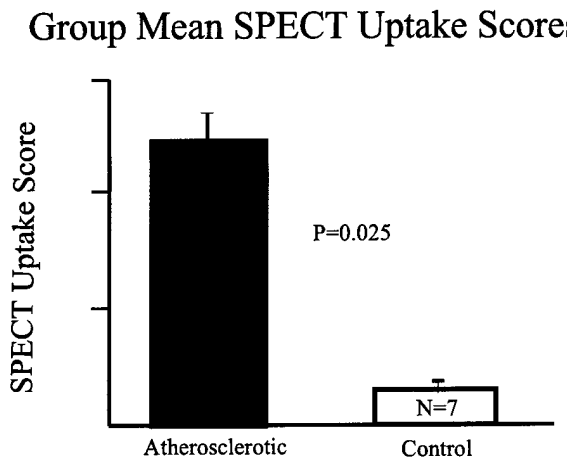


Figure 1.

Figure 2.

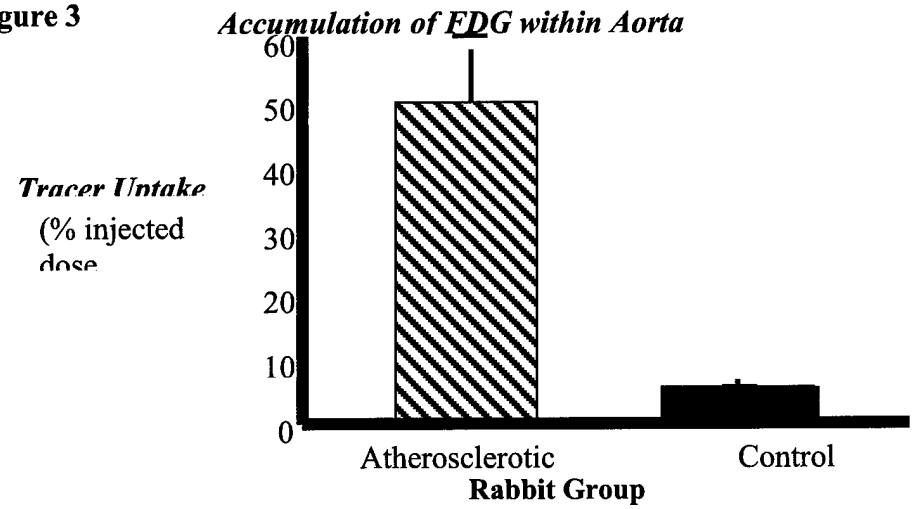


Plan: The next aim to be investigated (within specific aim 1) is to determine the site of localization of radiotracer within plaque. Specifically, we will test the hypothesis that the tracer accumulates within macrophages.

Specific Aim 2: Identify other nuclear imaging methods for detection of vulnerable plaques.

Progress: We again employed the same rabbit model of atherosclerosis used for the chemotactic peptide studies, (balloon injured, cholesterol-fed rabbits). FDG was administered to atherosclerotic and control rabbits. Three hours later, tissue localization of FDG was assessed. Radiotracer uptake was higher in the atherosclerotic aortas (52±4 vs. 3±2, %injected dose/gm $*10^{-3}$, P<0.001, **Figure 3**).

Figure 3



Plan: The next aim to be investigated (within specific aim 1) is to determine the site of localization of radiotracer within plaque. Specifically, we will test the hypothesis that the tracer accumulates within macrophages. Further, we will test the hypothesis that positron emission

tomography (PET) can be used to non-invasively characterize atherosclerotic plaques in this animal model.

Task 4: Magnetic resonance compatible devices
Principal Investigator: Jerome Ackerman, Ph.D., MGH

The majority of all deaths in the United States result from cardiovascular disease. The predominant precipitating event associated with acute coronary syndromes or stroke leading to sudden death is now generally recognized as the rupture of a so-called vulnerable atherosclerotic plaque. Vulnerable plaques are not necessarily the most conspicuous lesions visualized by angiography because vulnerability is not conferred by size, but rather by factors such as gene expression, enzymatic activity, inflammation, chemical composition, morphology, viscoelastic and biomechanical properties, and the local fluid dynamics of the impinging circulation. All of these factors impact the structural integrity of the plaque and its risk of catastrophic failure. Magnetic resonance (MR) imaging (MRI) is playing an increasing role in attempts to identity and characterize plaque, but often exhibits marginal spatial resolution and signal to noise ratio (SNR) in this role. Additionally, full advantage is not taken of the enormous power and the latest techniques of MR spectroscopy (MRS). An extremely effective route to improving the performance of MR imaging and spectroscopy of plaques is to place the RF receiver coil directly within the vessel adjacent to suspect plaques by means of a catheter: an intravascular coil.

The Specific Aims of this project were to: (1) Develop an infrastructure for the design of intravascular MR coils and associated tuning circuitry, and for simulation of electromagnetic fields and performance of coils; (2) Design, construct and characterize a series of catheter RF coils for intravascular and endocardiac applications based on novel inductive structures with sensitive volumes targeted precisely to the intravascular geometry; and (3) Develop pulse sequences as needed for basic MR guidance and tracking of coils.

Key Results: During the past year, the CIMIT team has largely accomplished Specific Aims 1 and 2. Special pulse sequence software that was installed on the cardiac MR scanner by the manufacturer is suitable for RF coil tracking, and has fulfilled the requirements of Specific Aim 3. We requested and were granted a no cost extension to March 1, 2003, in order to complete the building of several intravascular coils and to characterize their performance. Commercial software for numerical simulation of coil electromagnetic fields is up and running and producing results. We have written our own codes for analytic simulation of coil inductance and resistance. The software also produces masks for coil photolithography (Specific Aim 1). We have constructed a coil tuning box that works with a wide variety of interchangeable intravascular coils; produced and tested several coils; and compared their experimentally measured parameters with the numerical and analytic predictions, obtaining excellent agreement (Specific Aim 2). A means of external electronic coil tuning has been devised and tested. Both proton images and phosphorus-31 spectra have been obtained with the appropriately designed coils.

An NIH R01 grant application, "Atherosclerosis: Intravascular and High Field MRI/MRS," based in part on work accomplished with this CIMIT support, was submitted at the June 2002 deadline. Two invention disclosures related to the subject of this project were filed with the MGH CSRL.

Specific Aim 1: Creating an Intravascular Coil Development Infrastructure

We developed computer codes, using Fortran and Matlab, for calculating basic design parameters for intravascular MR coils from geometrical specifications of conductor locations, and have acquired, installed and used commercial software for detailed numerical simulations. The unique feature of this intravascular coil development effort is the ability to perform methodical, rigorous and accurate simulations of prototypical coil designs by computer, essentially allowing us to "test fly" many design variations without having to build them. We utilized a three pronged approach toward evaluating coil performance: 1) analytic simulation of the inductive structure of the coil—the antenna (which is quick and yields a first order approximation to the performance parameters); 2) numerical simulation of the antenna (which is accurate and detailed but computationally slow); and 3) experimental fabrication and testing.

First, coil parameters such as inductance L, resistance R, and $Q = \omega L/R$ are approximated with analytic expressions using the codes we developed in this project. This is a rapid calculation method that gives good results for these parameters, but does not take into account all electromagnetic effects such as radiation and proximity. The analytic calculation enables a wide variety of coils to be simulated quickly. The codes also output a PostScript rendering that can be used to generate a mask for fabricating the coil on copper clad polyimide substrate by photolithography. Second, numerical simulation using the Finite Difference Time Domain (FDTD) method implemented in the commercial software package XFDTD Bio-Pro 5.0 (Remcom, Inc.) performs what is effectively a complete solution of Maxwell's equations. The numerical simulation produces more realistic results than the calculation based on analytical formulae, but can take as long as 20 hours to complete on detailed coil geometry specified with a fine mesh. The analytical formulae evaluate in seconds.

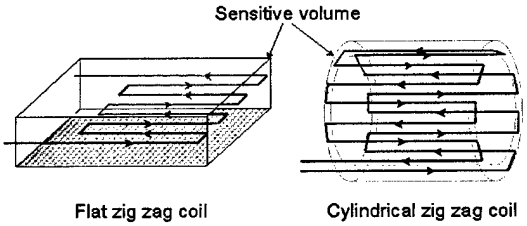


Figure 1. Comparison between the flat and cylindrical forms of zigzag or meanderline RF coil. In both cases the thickness of the sensitive volume is on the order of the wire spacing on either side of the coil surface.

Specific Aim 2: Designing, Fabricating and Evaluating Intravascular MR Coils

A wide variety of intravascular coil designs have been reported. Two general classes of coils are used: those which "illuminate" an extended length of vessel, and those which localize to a short stretch of vessel ("spot illumination"). Each class has its application, with the extended designs permitting the survey of a larger portion of the arterial tree at the expense of lower sensitivity; the more localized varieties yield better SNR over the smaller volumes. The prototypical extended design is the very simple and popular "loopless antenna", which is essentially a coaxial transmission line with a length of the shield removed. It has the distinct advantage of being the most easily miniaturizable.

Of course, it is the vessel wall that is the intended target when characterizing plaques, not the blood. Many localized catheter coils use various configurations of wires to force the sensitive region to the vessel wall, with varying degrees of success. For both the extended and localized coils, the blood is usually of no interest, and in fact contributes an interfering signal. However, despite attempts to localize the sensitive region to the arterial wall, most reported intravascular coil designs exhibit substantial (often their maximal) sensitivity within the lumen.

A solution to the problem of matching the sensitive region to the cylindrical geometry of vessels is found in an adaptation of a planar surface coil design known as a zig-zag or "meanderline" coil (Figure 1, left). In distributed approximation (valid in far-field), the meanderline has the unique feature of an RF field that rolls off exponentially with distance from the coil plane, thereby limiting the region of sensitivity to a thin slab of thickness comparable to the spacing of the wires. The meanderline is therefore ideally suited for imaging of the skin and other extended nearly flat surfaces.

As suggested by Dr. Van Wedeen of the MGH, one can wrap the meanderline into a cylinder (Figure 1, right) to achieve suitability for imaging or spectroscopy of the wall of the gut. Much later, it became apparent that this cylindrical meanderline configuration would be ideally suited for blood vessel walls. In the case where the desired thickness of the sensitive region (now an annulus) is smaller than the diameter of the blood vessel, the blood is to a reasonable extent excluded from the sensitive region. The excluded volume may be more sharply defined by inserting a solid cylindrical metal shield (effectively the ground plane of a cylindrical microstrip meanderline), essentially excluding the blood from the sensitive region. This both reduces interfering signal and largely eliminates the intrinsic Johnson noise arising from the highly conductive blood.

We computed the inductance and radiofrequency resistance (taking into account skin depth) of three simple meanderline coils using the analytical expressions (Table 1). We then built the coils and compared these computed parameters with the experimentally measured parameters. The inductance L of a meanderline coil is given by

$$L = \frac{\mu_0 \cdot \pi \cdot \lambda \cdot N}{4} \frac{1}{K^2[\sin(\pi \cdot w/2s)]} \sum_n \frac{1}{2n+1} (P_n[\cos(\pi \cdot w/s)])^2 \cdot (1 - e^{-(2n+1)\cdot 2\pi \cdot G/s})$$

where λ is the conductor length, N is the number of conductors, w is the width of the conductors, s is the spacing between the conductors, G is the distance between the plane of the conductors and the shield (i.e., ground plane), $P_n[x]$ is the n^{th} order Legendre polynomial, and $K[x]$ is the complete elliptical integral of the first kind. In the codes we wrote for computing the inductance we evaluate the elliptical integrals by a power series expansion derived from the improved accuracy Cephes Math Library release 2.0 polynomial approximation (11 pairs of polynomial coefficients). An approximation for the resistance R of the coil is given by

$$R = \frac{\rho \cdot \sqrt{\nu} \cdot \lambda_{total}}{2(w+t)},$$

where ρ is the resistivity of the coil material, ν is the frequency, λ_{total} is the total length of the conducting elements of the coil, w is the conductor width, and t is the conductor thickness. From the coil inductance and resistance the quality factor, or Q, can the be calculated from

$$Q = \frac{X_L}{R} = \frac{\omega L}{R}.$$

The excellent agreement between calculated and measured inductance and resistance gave confidence in our ability to predict coil performance.

FDTD simulations of the electric and magnetic fields were performed for a meanderline coil consisting of 18 conductors (9 loops or zig-zags), each 14 mm in length and spaced 1 mm apart. The diameter of the coil was 6 mm. The grid size used for the FDTD simulations was 100 x 100 x 200 with 0.1 mm grid spacing. The coil was excited with a simulated sinusoidal CW source operating at a frequency of 64 MHz and generating 1 A of current. 250,000 time steps were taken in the simulation. Calculation times for this model were typically 20 hours. Figure 2 shows transverse (left) and axial (right) views of the magnitude of the magnetic field. The simulation clearly demonstrates a cylindrical field profile, where maximum B-field is observed in thin cylindrical shells above and below the coil surface. In Figure 3, we demonstrate the use of a cylindrical shield (or ground plane) placed just within the RF coil, to restrict the magnetic field to a cylindrical shell above the surface of the coil. Note the excellent degree of suppression of field in the "lumen" of the coil.

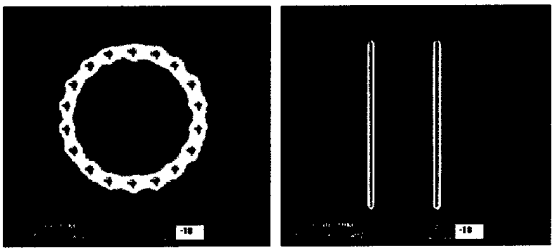


Figure 2. Magnitude of magnetic field in the transverse (left) and axial (right) planes for the simulated meanderline coil.

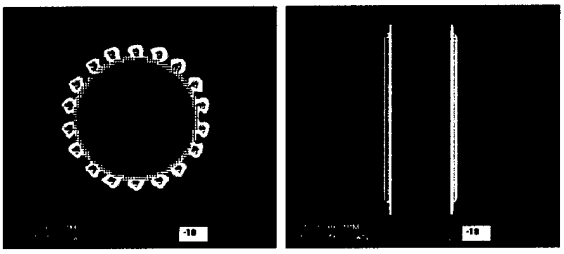


Figure 3. Magnitude of magnetic field in the transverse (left) and axial (right) planes for an internally shielded meanderline coil. The white cells represent the shield.

MR measurements were performed with a rectangular loop coil (68 mm long, 3 mm wide), made from 1.0 mm copper wire, attached to the end of a long (1.46 m), semi-rigid, thin (2.5 mm o.d.) 50 ohm coaxial cable. The measured inductance of the coil was 30 nH. Such a small inductive reactance requires a small tuning capacitive reactance and hence very large capacitance (X_C =

$1/\omega C$). The coil was tuned and matched with no fixed capacitors at the coil but with variable parallel tuning (C_t), series matching (C_m) capacitors at the end of the thin coax cable. In order to allow for the tuning and matching of a wide variety of different coils (with different inductances) at different frequencies, variable capacitors were employed with tuning ranges of $25 < C_t < 140$ pF and $1450 < C_m < 1870$ pF. The large parallel plate air variable capacitors used in tube radio sets of earlier generations are ideal for this purpose, and enable quick tuning of a wide variety of intravascular coils.

Table 1. Specifications for three test meanderline coils.

Coil #	1	2	3
Type of meanderline	planar	planar	cylindrical
Number of conductors	12	6	6
Length, mm	109	62	30
Spacing, mm	12	19	11
Width, mm	6	1.0	1.0
Thickness, mm	0.1	1.0	1.0
L_{exp}	510	270	120
L_{calc}	549	242	111
R_{exp}	0.20	0.20	0.11
R_{calc}	0.235	0.230	0.114

Magnetic resonance images were acquired on a General Electric 1.5 T Signa LX CNVi MR scanner using the loop coil in receive only mode, immersed in Gd-DTPA doped saline. Shown in Figure 4 (left) is a transverse slice that demonstrates the dipole field generated by the two lengths of wire that make up the loop. While the sensitivity achieved with this coil is relatively good the field profile is clearly dipolar in nature and not homogeneous over a cylindrical shell volume as would be desirable for imaging of an artery wall. This loop test coil is not decoupled during the transmit pulse. It therefore generates an inhomogeneous local B_1 field by inductive coupling with the body coil, which is the origin of the bands of signal intensity.

Measurements were also performed at 4.7 T on a GE/Bruker Omega CSI MR scanner on a 29 mm diameter meanderline coil consisting of 6 conductors, each with a length of 89 mm and a width of 6 mm and a spacing between conductors of 15 mm (Figure 4 (center)). The coil was connected to the circuit tuning and matching elements by a 1 m BNC cable. The conductors were attached to the outside of a plastic tube. The inside of the tube was filled with 0.1 mM

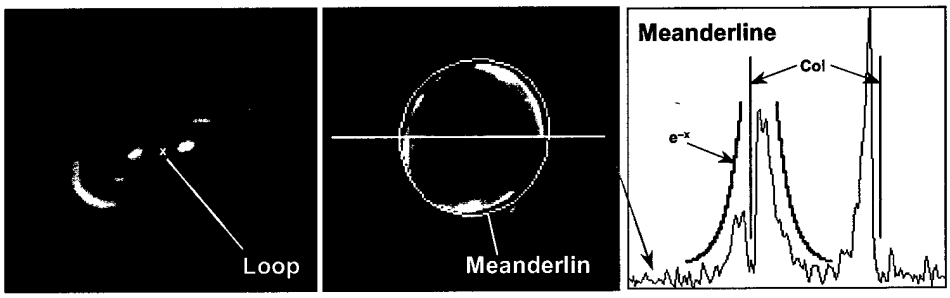


Figure 4. *Left:* Transverse image slice perpendicular to the loop coil's long axis at 1.5 T; coil is immersed in Gd-DTPA doped saline. *Center:* Cylindrical meanderline coil transverse image slice at 4.7 T. Coil contains a tube of water and is surrounded with bags of saline. *Right:* Profile of signal along the line shown in the center image. Note the dramatic restriction of signal to a thin annulus with exponential profile as predicted.

$MnSO_4$ doped water. The tube/coil was then sandwiched between two saline solution bags. As demonstrated in Figure 4 (right), a cylindrical field profile is observed, with an exponential dropoff. (Note that the image represents signal intensity resulting from a spin echo pulse sequence, and is not strictly an RF field map.) Despite this very crude test set-up, fairly uniform cylindrical shells of spins, just on either side of the RF coil shell, are excited.

The best performance is obtained when the tuning and impedance matching capacitors are as close to the RF coil as possible (Figure 5 top). These capacitors must be finely adjusted to achieve the optimum settings. However, because of the extremely restricted space at the coil, the capacitors must be very small, and cannot be adjusted with knobs or screws. In common practice, tiny chip capacitors with fixed values would be placed at the coil. The capacitance values must be chosen when the coil is constructed, and are not likely to be the optimum values under all conditions. Alternatively, robust variable capacitors may be used at the end of the cable to obtain fine adjustment, but this is a poor tuning arrangement because of the extended length of unterminated cable (Figure 5 middle). We therefore designed a tuning system employing varactor diodes, which function as electrically variable capacitors when reverse biased; the capacitance values are a function of the applied voltage (Figure 5 bottom). This provides an optimum tuning arrangement which can be adjusted for a variety of conditions.

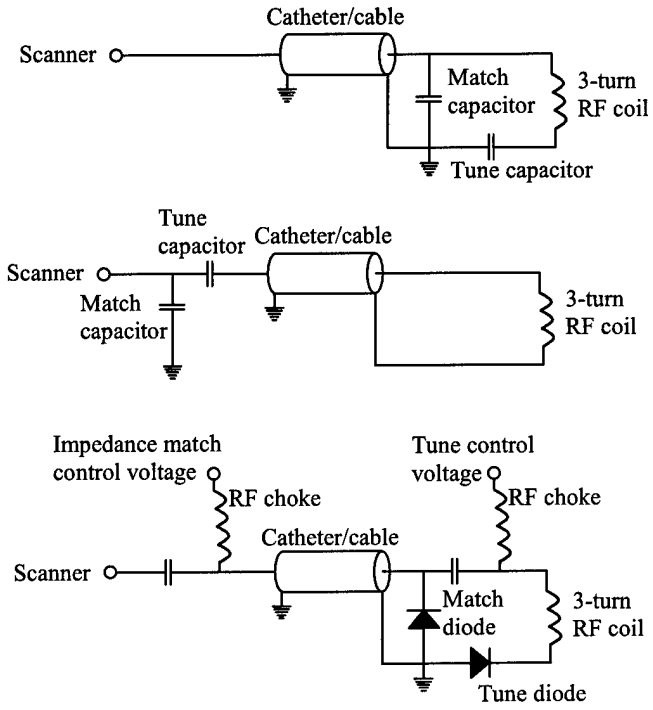


Figure 5. *Top:* Optimum placement of tuning capacitors for minimum signal loss, maximum transmitter power utilization, and maximum signal to noise ratio. *Middle:* External placement of capacitor to enable adjustable tuning, but poor performance. *Bottom:* Optimally placed electrical variable capacitors (varactor diodes).

^{31}P spectra were obtained on the 4.7 T scanner to obtain preliminary data to assess the possibility of *in vivo* localized spectroscopy with intravascular coils. The first coil we constructed used a pair of external mechanically variable capacitors and a single loop at the end of the cable. Figure 6 top shows the spectrum of a calcified human plaque specimen obtained with this coil. Although extensive signal averaging was necessary, the coil quite remarkably detects not only the solution phosphate metabolites (primarily inorganic phosphate because of the time elapsed between harvest and scanning), seen as a sharp line, but also the solid calcium phosphate of the calcification (the broader feature). A second coil system, utilizing a three loop pickup and a single varactor for approximate tuning adjustment, was used to obtain a spectrum of 85% phosphoric acid, achieving a signal to noise ratio of 522:1. Since the concentration of ^{31}P in phosphoric acid is about 16 M, the solution metabolites are at least three orders of magnitude lower in concentration. With the expected improvements afforded by the second varactor diode and other factors, we anticipate being able to acquire *in vivo* ^{31}P spectra in reasonable times.

Specific Aim 3: Develop pulse sequences as needed for basic MR guidance and tracking of coils.

Progress: Special pulse sequence software that was installed on the cardiac MR scanner by the manufacturer is suitable for RF coil tracking.

Plan: Project completed.

3.4 STROKE PROGRAM

Task 1: Continuous monitoring of stroke using diffuse optical tomography
Principal Investigator: David Boas, Ph.D., MGH

The CIMIT team, led by Dr. Boas, is awaiting animal use approval before initiating this project.

Task 2: MGH XMR suite
Principal Investigator: R. Gilberto Gonzalez, M.D., Ph.D., MGH

Stroke is the third leading cause of death and the leading cause of severe disability in adults. Over 80% of strokes are ischemic and the great majority of these are due to thromboembolism. This is a treatable disease if the patients are diagnosed rapidly and the cause of the stroke is removed. Approximately 27% of all strokes are a result of an embolus to a major artery, such as the middle cerebral artery or its branches. These strokes are typically catastrophic and intravenous administration of thrombolytic agents is ineffectual, but they are treatable using direct, transarterial catheter-based thrombolysis. Unfortunately, results to date are disappointing due to the long time required for artery recanalization by chemical thrombolysis. A second important impediment is the relatively high rate of hemorrhage induced by reperfusion injury and by the thrombolytic agent. We propose to significantly improve the safety and efficacy of major artery recanalization in acute stroke by guiding revascularization with advanced MRI techniques. Our hypothesis is that endovascular recanalization in acute ischemic stroke can be made safer and more efficacious through the provision of real-time data on the physiological state of the brain during the procedure.

Key Results: Work is continuing on the xMRpm software package to develop models for physiological probability maps within the xMR environment. The XMR suite at MGH is scheduled to be open for acute stroke diagnosis and treatment in December 2002.

Specific Aim 1: To create a real time physiologic state-of-the-brain monitoring system in the CIMIT/MGH xMR Stroke Treatment Suite.

Progress: Work is continuing on the xMRpm software package to develop models for physiological probability maps (Prediction Metric) within the xMR environment.

Plan: The Prediction Metric will be used to assess the results of the improved model on the training set, and an optimization technique will be developed to determine the best set of hypothetical parameters to predict ultimate outcome.

Specific Aim 2: To implement real time physiologic state-of-the-brain monitoring system in the CIMIT/MGH xMR Stroke Treatment Suite.

Progress: In prior periods we developed the techniques for interfacing the Signa LX MR system to xMRpm package database. In this quarter we determined that a Microsoft Windows based workstation can be integrated in the xMR suite for display and interaction.

Plan: We are currently researching workstation platforms and plan to purchase and install the workstation during the coming quarter.

4.0 TECHNOLOGY ASSESSMENT AND OUTCOMES ANALYSIS PROGRAM

The Technology Assessment and Outcomes Analysis Program is divided into a Core and two major Outcomes Projects. The Program Core functions to: 1) assist the Operations Group with resource allocation decisions by performing preliminary analysis of technologies identified in requests for funding; 2) provide scientific direction, project coordination and administrative support to two major Outcomes Research Projects; and 3) provide consultation and guidance to CIMIT investigators and collaborators regarding issues such as project feasibility, study design, optimal endpoint determination and data analytic or statistical methods. Work is progressing in all three areas.

The two major Outcomes Projects are related to two major CIMIT focus areas: Operating Room of the Future and Vulnerable Plaque.

Task 1: Technology Assessment Program Core
Principal Investigator: Scott Gazelle, M.D., Ph.D.

The Technology Assessment and Outcomes Analysis Program Core supports CIMIT research, administrative and clinical activities using a variety of analytic techniques to investigate specific technology related questions as well as broader national health policy issues. Projects may range from examining the potential cost-effectiveness of a new technology under consideration for CIMIT funding, to determining the optimal point of intervention in any one of a number of broad disease areas.

The Program Core is fully integrated with the entire spectrum of CIMIT research, clinical, educational and administrative activities. Its primary activities are the development and application of rigorous analytic methodologies including clinical epidemiology, cost-effectiveness analysis, decision analysis, economic analysis and risk analysis. The Program provides the infrastructure and expertise to properly evaluate new medical technologies at all stages of development, and in so doing, to promote the optimal use of increasingly limited health care resources.

Key Results: With CIMIT support and guidance, we have succeeded in establishing a large and capable group of investigators. These investigators have developed a rich network of collaborations throughout CIMIT. We have collaborated and/or consulted with other CIMIT investigators on issues such as project feasibility, study design, endpoint determination, and approaches to data analysis. We have also assisted with primary data collection and analysis. This work complements other more traditional laboratory and/or clinical research being carried out by individual CIMIT investigators or within the context of major CIMIT Programs.

In the coming year, the Program Core will continue to support the entire CIMIT scientific and administrative community, as well as the two Technology Assessment and Outcomes Analysis Program Research Projects (see below). The Program Core will help CIMIT focus resource allocation for the development of innovative medical technologies that can result in improved patient care; provide advice on and perform studies to assess the effectiveness, cost and cost-effectiveness of new technologies under development; and demonstrate the value of these new technologies to the public, physicians, payers, industry, and legislators so as to facilitate their appropriate dissemination and implementation.

Specific Aim 1: Assist the CIMIT Operations Group with resource allocation decisions via preliminary analysis of technologies identified in requests for funding.

Progress: CIMIT has been fortunate to have access to a tremendous wealth of ideas, talented investigators, and interested physicians. We have also been fortunate to receive and sustain funding that can support the development and application of new medical technologies. However, resources are not unlimited, and each dollar allocated toward one project is in effect a dollar not available to support another. It is therefore critically important that the Operations Group is able to guide the allocation of research funds to competing technologies on the basis of their potential future impact. The Technology Assessment Program Core is available to work with the Operations Group in order to review specific proposals under consideration, collect and provide relevant data to the Operations Group concerning costs, disease burden, etc., and perform economic and/or outcomes analyses of the technologies or programs under consideration. The results of these analyses will help to focus resource allocation for the development of innovative medical technologies that are most likely to result in improved patient care and healthcare outcomes.

Specific Aim 2: Provide scientific direction, project coordination and administrative support to major Technology Assessment Program Research Projects.

Progress: As part the larger Technology Assessment and Outcomes Analysis Program, we are conducting two specific research projects: 1) the Vulnerable Plaque Outcomes Project, and 2) the Operating Room of the Future Outcomes Project. These are the continuation of ongoing research efforts which involve collaboration with leaders of the corresponding major CIMIT research focus areas. The Technology Assessment Program Core provides scientific direction, project coordination, and administrative support to these individual projects. The specific Outcomes Projects are described elsewhere in this report, but are summarized briefly in the following paragraphs.

In the Vulnerable Plaque Outcomes Project, we are developing a comprehensive model of cardiovascular disease and therapy. The model will be used to evaluate the clinical effectiveness and economic impact of new diagnostic and therapeutic technologies for coronary artery disease. The model will be comprehensive in nature, in order to allow us to evaluate the full spectrum of potential diagnostic and therapeutic interventions, from the identification of high-risk individuals, through non-invasive and invasive diagnostic testing, to the delivery of local and/or systemic therapy. Work to date has been limited to model development and preliminary analysis. Our initial analysis, focusing on catheter-based diagnostic tests, is nearly complete. In the upcoming months and years we will use the model to determine the relative benefits and cost-effectiveness of specific diagnostic or therapeutic technologies not included in the initial analysis, such as optical coherence tomography (OCT), spectroscopy, ultrafast CT, and statin therapy, among others. The model will also be used to determine the relative effectiveness and/or cost thresholds that any new technology must meet in order to be a viable alternative to currently available technologies. The model will thus serve as a useful tool for physicians, scientists, industry, payers and policy makers, all of whom must make difficult decisions concerning the development and implementation of these new technologies.

In the Operating Room of the Future Outcomes Project, we have developed, verified, and begun to and utilize a discrete event simulation model in order to evaluate the OR of the Future as it is developed and utilized. The model is a comprehensive, robust and expandable model of the

entire surgical suite, and will be used in order to better understand the optimal approach to integrating ORF activities. We have also worked with the ORF Project team to plan and begin to execute additional studies related the the actual ORF, as it is being readied for operation.

Specific Aim 3: Provide consultation and guidance to CIMIT investigators and collaborators regarding issues such as project feasibility, study design, optimal endpoint determination and data analytic or statistical methods.

Progress: The original mission of the CIMIT Technology Assessment and Outcomes Analysis Program was to develop a world class program in technology assessment and outcomes analysis that would support all research, education, and clinical activities of the CIMIT Consortium. The specific goals of the Program were to focus the allocation of resources for the development of new diagnostic and therapeutic medical technologies, to facilitate rapid and accurate assessment of their efficacy, and to more clearly demonstrate their value to physicians, payers, legislators, and the public. The Program now provides an infrastructure to assist in the evaluation of new diagnostic and therapeutic procedures at all stages of development, particularly during the early stages from discovery to preliminary clinical testing, when extensive data regarding clinical effectiveness may not yet be available.

In the current funding cycle, we refocused the overall Program goals. These changes were necessary in order to respond to the evolution and maturation of CIMIT as an organization, and due to changes in the individual research projects. Our major research efforts are now directed primarily towards two specific Outcomes Projects (Vulnerable Plaque, Operating Room of the Future). However, we continue to be available to collaborate with CIMIT investigators on issues such as project feasibility, study design, endpoint determination, and approaches to data analysis. These collaborations over the past three years shaped the major research focus of the Program, and laid the groundwork for the Vulnerable Plaque and Operating Room of the Future Outcomes Projects.

Plan: As projects are funded and move from the conceptual stage through the various stages of development, we will work with investigators to accurately and expeditiously evaluate the capabilities and potential impact of the new technologies on health outcomes and costs, particularly as the magnitude of the expenditures required for widespread clinical implementation increases. Specifically, we will develop plans for and carry out rapid and accurate analyses of effectiveness, cost and cost-effectiveness. The results of these analyses can then be used to demonstrate the value of specific technologies to the public, physicians, payers, industry, and legislators, in order to facilitate appropriate dissemination and implementation.

Task 2: Operating Room of the Future outcomes
Principal Investigator: G. Scott Gazelle, M.D., Ph.D., MGH

The overall aim of the Operating Room of the Future (ORF) project is to develop new surgical equipment, procedures and processes that will result in improved patient outcomes, operating room efficiency, or both. The ORF project has sought to establish links to both industry partners and academic researchers who are developing these new technologies, in order to make the ORF surgical suite a comprehensive test platform for product and process development. Substantial progress has already been made towards creating a prototype operating room which incorporates modular equipment, new surgical information systems, and new approaches to process flow. Testing the effects of each of these components on system efficiency, cost, or cost-effectiveness

is complex and time-consuming and expensive. Since it impossible to perform a truly randomized controlled trial in the surgical environment, we have developed a factorial study design to introduce and evaluate new technologies in a staged process. To help understand how individual technologies and innovations contribute to changes in outcomes and to identify new opportunities for new technologies and innovations, we developed a discrete event computer simulation model. This allows us to simulate both the current surgical system and proposed changes. In the OR of the Future Outcomes Project, we will continually develop and utilize this model in order to evaluate this complex and changing system. These models and stage trials will focus on identifying the most effective new technologies and techniques as they are developed, and thus help to guide resource allocation for further development and clinical implementation.

It is important to note that the CIMIT Operations Committee requested that work on this project be limited entirely to the OR efficiency studies originally described in relation to the PinPoint tracking system in our initial proposal. We therefore agreed to limit our research activities accordingly (focusing, however on a similar system made by Sentinel Technology), and have scaled back on the effort committed to the project. Work on other components of the original proposal which is requested by program leaders in this area will require additional funding, commensurate with the magnitude to the work to be done.

Specific Aim 1: Develop a discrete event simulation model for the ORF Surgical Suite.

Progress: The preliminary simulation model was expanded to incorporate multiple operating rooms using either standard anesthesia procedures, the proposed two anesthesiologist handoff model, or a combination of both. This model has been populated and verified with process data from the MGH department of surgery's dynamic scheduling system and the hospital cost accounting database (TSI).

Using the model, analyses are ongoing, and this work is carried out in collaboration with the ORF Project team.

Plan:

- Validate data using Sentinel wireless technology
    - Sentinel Wireless provides a technology to locate tagged objects in both space and time with up to 10 second resolution. Timing data currently used in the model was recorded by hand in the course of routine care. We intend to validate these data using the Sentinel Wireless technology.
    - Mobile sensor tags are in production and will be attached to all relevant staff and resources. Fixed sensor locations have been identified and dataports are currently in the process of being installed in the operating rooms, surgical corridors and other locations.
- Test model performance in same day surgery unit
    - The current model uses data derived from the inpatient OR. The same day surgery unit has a somewhat different patient population and process times. We will collect data regarding these process times to model the performance of the same day unit and subsequently the effect of new technologies in this environment.
- Test anesthesia carousel model
    - Once the above models are validated, the model will be used to test and predict the effect of alternative approaches to delivering care before they are implemented. One possibility is an anesthesia carousel model where a single

anesthesiologist is responsible for the anesthesia induction of patients going to multiple operating rooms. In this model, care would be handed off to an anesthesiologist in each receiving OR following induction.

Specific Aim 2: Evaluate surgical technologies and processes as they are integrated into the ORF.

Progress: No progress has been made on specific aim 2 at this point.

Plan: Our work on this project will be limited to an evaluation of the Sentinel tracking system and its potential effect on ORF efficiency.

Specific Aim 3: Identify opportunities for further technology/process development in order to guide resource allocation and optimize the development process.

Progress: No activity this quarter.

Plan: To identify opportunities for further technology/process development

Task 3: Vulnerable Plaque Program outcomes
Principal Investigator: G. Scott Gazelle, M.D., Ph.D., MGH

Traditionally, the detection of coronary artery disease has focused on finding atherosclerotic blockage of blood flow in the coronary arteries (i.e., stenosis). However, it appears that many acute coronary syndromes such as myocardial infarction, unstable angina, and sudden death are instead caused by the rupture of so called "vulnerable plaques" which have thin fibrous caps, lipid-rich cores, and inflammatory properties. These insights have begun to reshape the development of new technologies for the detection and therapy of coronary artery disease. Currently, several new diagnostic and therapeutic technologies are under development. These technologies have the potential to improve patient outcomes, however, many clinical and policy questions remain unanswered.

In the Vulnerable Plaque Outcomes Project, we are developing a comprehensive model of cardiovascular disease and therapy. The development of the model will proceed in several steps, that correspond decisions of management of cardiac disease. We have continued to make progress on the development of a model with which we are now using to analyze the effect of vulnerable plaque detection using new catheter-based technologies. The model also includes treatment of the plaque with percutaneous coronary interventions. We are finalizing the initial analysis using this model. In next steps, the model will be expanded in order to allow us to evaluate the full spectrum of potential diagnostic and therapeutic interventions, from the identification of high-risk individuals, through non-invasive diagnostic testing, to the delivery of local and/or systemic therapy. We will determine the relative benefits and cost-effectiveness of specific diagnostic or therapeutic technologies such as optical coherence tomography (OCT), spectroscopy, ultrafast CT, and statin therapy, among others. Furthermore, the model will also be used to determine the relative effectiveness and/or cost thresholds that any new technology must meet in order to be a viable alternative to currently available technologies. The model will thus serve as a useful tool for physicians, scientists, industry, payers and policy makers, all of whom must make difficult decisions concerning the development and implementation of these new technologies.

It is important to note that the funding for this project was reduced significantly from our initial request to the CIMIT Operations Committee. Our work for the year one of this project was therefore limited almost exclusively to model development and verification (Aim 1 of the original proposal). However, we were able to initiate a preliminary analyses of candidate technologies over the past few months of this first year of funding..

Specific Aim 1: Develop, refine and verify a comprehensive model of cardiovascular disease and therapy, focusing on the role of "vulnerable plaque".

A primary aim of the Vulnerable Plaque Outcomes Project is to develop a comprehensive model of cardiovascular disease and therapy which can be used to evaluate the full spectrum of potential diagnostic and therapeutic interventions, from the identification of high-risk individuals, through non-invasive and catheter-based diagnostic testing, to the delivery of local and/or systemic therapy.

Progress: The development of the model has proceeded in steps that correspond with management decisions in cardiac disease. We have continued to make progress on the development of a model with which to analyze the effect of vulnerable plaque detection with a new catheter-based technology, including treatment of the plaque with percutaneous coronary interventions.

More specifically, we have developed a state-transition (Markov) decision model, a mathematical construct which can be used to estimate the outcomes of care in a predefined population. The initial investigation included patients eligible for percutaneous coronary interventions (PCI). In the model, we compare a new invasive diagnostic test with coronary angiography. Several possible courses of action can be followed. Once a diagnostic test is performed, we consider PCI treatment. If PCI fails within the hospital stay, patients will undergo coronary bypass surgery. After treatment, a patient might experience no cardiac event, an acute coronary event such as a myocardial infarction, die suddenly, or die of natural causes. This model can be used to estimate life expectancy, (acute) coronary event-free life expectancy, quality-adjusted life expectancy, lifetime costs and/or cost-effectiveness for patient eligible for PCI who undergo a new diagnostic catheter-based invasive test and are being treated with PCI.

Plan: In the next quarter, we hope to complete the analysis using the model developed in year 1. We have begun to address questions regarding the clinical effectiveness, costs and cost-effectiveness of a variety of new catheter-based diagnostic tests for the detection of vulnerable plaque. In addition to evaluating specific tests, the model can be used to investigate questions such as: what must a new test add (in terms of sensitivity and specificity for the detection of vulnerable plaque) in order to be a viable alternative, given reasonable assumptions concerning its costs. The model will also be used to determine the cost threshold that a new catheter-based test must meet at a given level of performance, or to determine the appropriate target population for a test with specific performance characteristics and costs.

Next steps in model development will include expanding the model to include a broader patient group. More specifically, in addition to the patient group eligible for PCI, we will in the next step include all patients who are eligible for catheter-based diagnostic tests. In the next two years, we will develop the full vulnerable plaque policy model incorporating the all potential management options for cardiac disease. This model will be used to examine the potential role of technologies currently under development, from catheter-based technologies to blood markers,

and to determine the critical performance thresholds that any new technology must reach in order to be an attractive alternative to other established technologies. The completed model can be used to help focus resource allocation for technology development and to answer policy-related questions regarding the benefits of specific technologies for individual patients and the population at large.

Specific Aim 2: Evaluate the relative clinical benefits and cost-effectiveness of specific technologies for the detection (either invasive or non-invasive) and treatment (either systemic or local) of vulnerable plaques in the coronary arteries.

Progress: Due to budgetary limitations, we were forced to limit our work during the first year almost entirely to that described in our initial Aim 1.

Plan: No progress is anticipated on Aim 2 in the next several months.

Specific Aim 3: Determine the conditions that a new technology must meet to be a viable alternative to currently available diagnostic and therapeutic technologies.

Progress: Due to budgetary limitations, we have been forced to limit our work during the first year almost entirely to that described in our initial Aim 1.

Plan: No progress is anticipated on Aim 2 in the next several months.

5.0 REFERENCES

Alexander N, Zelikin NA, Izumrudov VA, **Langer R**. Aliphatic ionenes as gene delivery agents: elucidation of structure-function relationship through modification of charge density and polymer length. *Bioconjugate Chemistry*, 2002, in press.

Borenstein JT, Terai H, King KR, Weinberg EJ, Kaazempur-Mofrad mR, Vacanti JP. Microfabrication Technology for Vascularized Tissue Engineering. Biomedical Microdevices, in press, 2002.

Bouma BE, Tearney GJ, Yabushita H, Shishkov M, Kauffman CR, Houser SL, Aretz HT, Halpern EF, Jang I-K. Intravascular optical coherence tomography evaluation of intracoronary stenting. Submitted to Heart.

Henderson JA, **Smith JJ**. Financial Conflict of Interest in Medical Research: Overview and Analysis of Federal and State Controls Submitted to the *Food and Drug Law Journal*, 2002.

Kim ES, Kaazempur-Mofrad MR, **Borenstein JT**, Vacanti JP. Design of a Single Capillary-Parenchymal Co-culture Bioreactor. Submitted for publication, 2002.

King KR, Wang CC, Shin M, **Vacanti JP**, Borenstein JT. Biodegradable Polymer Microfluidics for Tissue Engineering Microvasculature. MRS Symp Proc. Vol. 729, Paper U1.3, in press, 2002.

Smith JJ, Henderson, JA, Baim DS. The FDA and Reprocessing of Single-Use Medical Devices: A Revised Policy and New Questions Submitted to the *Journal of Vascular and Interventional Radiology*, 2002.

Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Halpern EF, Bouma BE. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. Circulation 2002, in press.

Tearney, GJ, Jang, IK, Bouma, BE. Evidence of Cholesterol Crystals in Atherosclerotic Plaque by Optical Coherence Tomography. Submitted to Circulation.

King KJ, Borenstein J. Biodegradable Polymer Microfluidics For Tissue Engineering Microvasculature. Spring 2002 MRS Meeting, San Francisco CA, MEMS and BioMEMS Symposium Proceedings, in press.

"Nanoparticle Adjuvancy of a HIV-envGP120 Epitope DNA Vaccine." Putnam D, Locher C, Langer R. Submitted for publication, 2002.

Putnam D, Zelikin NA, Izumrudov VA, Langer R. Poly-histidine-PEG:DNA Nanocomposites for gene Delivery. Submitted for publication, 2002.

Wang S, **Smith JJ**, Tunis S. Potential Legal Barriers to Increasing CMS/FDA Collaboration: The Law of Trade Secrets and Related Considerations Submitted to the *Food and Drug Law Journal*, 2002.

Yabushita H, **Bouma BE,** Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Halpern EF, Tearney GJ. Measurement of Atherosclerotic Plaque Fibrous Cap Thickness by Optical Coherence Tomography. Submitted to Circulation, 2002.

6.0 APPENDICIES

APPENDIX A: Industry Liaison Program (ILP)
Program Director: Janice E. Crosby, RN, MBA

CIMIT's Communication Program is designed to address its diverse communication needs, audiences and resources. Key objectives include: educating researchers and clinicians about the potential of new technology to meet the medical needs, catalyzing collaborations and establishing CIMIT as a preeminent resource on the development and integration of technology into Medicine.

Key Results: This past year, CIMIT's Communication Program made some significant progress. The www.cimit.org site was enhanced to improve the content, navigation, and graphic appeal. The MyCIMIT section, which provides remote access to over 100 CIMIT Forums via web-enabled video streaming, now is being accessed regularly by over 300 members. CIMIT's Annual Stakeholder Briefing provided an overview of the magnitude of CIMIT's projects and programs--highlighting the many collaboration with MIT and Draper Lab. In addition, CIMIT held a major multidisciplinary symposium on the detection and treatment of Vulnerable Plaque and produced a CD-ROM that captures all the presentations and discussion. CIMIT also began to gain visibility in the media with a number of events and investigators being covered.

Specific Aim 1: To utilize the Internet and web-based intranet applications to help promote the CIMIT mission and communicate its goals and objectives.

Progress: The Internet & the subscribing web technologies are breaking down the barriers of location, time, money, and most importantly, individual computer hardware and software preferences. The web is the universal tool that exemplifies and can help execute CIMIT's mission of creating those unlikely collaborations. Because of these attributes, the webs can truly "accelerate the process" for CIMIT.

- Web Hosting This year web hosting needs became more complex due to the implementation of the online ILP and FORUM secure databases. Negotiated by Partners Telemedicine, CIMIT entered a contract with IIS (Integrated Information Systems), an Arizona-based hosting company that provides 24/7 support. This level of support provides immediate customer service, proper firewall technology to access the secure databases, ample data storage and streaming capacity, and excellent redundancy protocols. Firewalls are essential to protecting sensitive data from unauthorized users and hackers. Storage became an important factor when we implemented databases—especially the Forum videos. We upgraded our service to IIS because of the need to store many large media and data files associated with all our websites. In addition to the secured database sites, IIS hosts all of CIMIT's sites, including CIMIT.ORG (the public site), the OR of the Future site, and the CIMIT International site. All sites are receiving increased traffic and our level of service with IIS enables users to enjoy fast data transfer regardless of the level of activity.

- Web Development for Public Site Receiving an average of 650 hits per day, the public CIMIT site is often the first experience potential collaborators have with CIMIT. Beyond the first experience, CIMIT wanted members of the CIMIT community to continue obtaining updated information about the organization's current activities, ongoing major

research programs, and news & events. Phase I of an updated CIMIT web site was implemented this year with afresh homepage, improved navigation and revised content.

- The MyCIMIT site was enhanced this year to allow members to access Forum archives, Apply for a Research Award, or members of the OR of the Future Team to view project plan. Implementing a portal to these secure sites with the appropriate security protocols was a major task in FY02. Over 300 members of the CIMIT Community are routinely accessing access FORUM archives, and in the case of industry, a specific site about their interactions with CIMIT.

Plan:

- Implement Phase 2 of website enhancements to www.cimit.org to improved visual appeal, navigation flexibility and automation of the site.
- Enhancements to ILP and Forum databases with improved user interfaces. Add Regulatory Affairs Newsletter to database for archives.
- Develop database on CIMIT Investigator Community—integrates bios, research interests etc. that can be used to catalyze collaborations.

Specific Aim 2: Position CIMIT as the catalyst and knowledge center for technology in medicine through various educational conferences and communications media

Progress:

- *CD-ROM from the CIMIT Vulnerable Plaque Symposium*—This milestone educational event held October 5, 2001 provided a unique, multidisciplinary forum to world-renowned experts for the sharing of current information and future needs regarding Vulnerable Plaque. This CD-ROM reflects the 2 1/2 day symposium, slides synchronized to original speaker audio and full screen video of the spirited discussion surrounding this critical but often controversial topic.

- ***Annual Stakeholder Briefing October 17th***--This event provided CIMIT's Stakeholders with an overview of the multitude of CIMIT projects and programs and an opportunity to interact with CIMIT investigators. The morning presentations highlighted the technology development done in collaboration with MIT and Draper. The afternoon session was held in CIMIT's new home at Landsdowne Street. A CD-ROM of the day's events was provided to all stakeholders.

- ***Newsletters***—Monthly newsletters continued to be provided to CIMIT stakeholders by the Regulatory Affairs Program. In FY02, Technology Assessment and Industry Liaison programs initiated newsletters.

- ***Presentation Support*** –CIMIT central has provided graphic and Power Point slide support for management and program leaders' multiple presentations to stakeholders and various potential collaborators, donors, and other sponsors.

Plan:

- CIMIT will continue to convene educational events around topics of interest to the medical community: Conflict of Interest; OR of the Future, "Dual Use" Technologies to meet the needs of military and civilian first responders; Annual Stakeholder Briefings etc.

- Develop a new CIMIT Brochure to highlight how CIMIT facilitates the translation of innovative concepts in to measurable improvements in the standards of patient care.
- To provide the "CIMIT Story" on a business card CD.

Specific Aim 3: To capitalize on media opportunities that can help build the CIMIT "brand" and further catalyze collaborations and support.

Progress: This past year saw the beginning of a number of CIMIT activities and investigators being highlighted in the media:

- 10/21/01 Boston Herald reports on new Partners Facility in Cambridge—home to CIMIT
- 10/22/01 Boston Herald story on CIMIT Annual Briefing—featuring APRIL projects and OR of the Future
- 10/24/01 Boston Business Forward article highlights work of CIMIT Simulation Group
- 11/01 Simulation Program Leader, Steve Dawson MD is featured in The Interventionalist
- 6/20/02 CIMIT's Dr. James Muller was featured in June issue of Fortune Magazine
- 6/20/02 Boston Globe story on Growing Organs highlights CIMIT Joseph Vacanti, MD and Tissue Engineering team
- 8/26/02 David Rattner, MD featured in Business Week on "Minimal Medicine".
- 8/28/02 CIMIT's work on Biosensors highlighted as part of Sensor Expo

Plan:

- To hire a CIMIT Communication Manager to develop and manage a comprehensive communications program for CIMIT including a media relations component, a publications and graphics component, an institutional and government relations component, a public affairs component and a development/fundraising component.
- To capitalize on CIMIT events such as opening of the OR of the Future and Annual Briefing to get national coverage for CIMIT activities.

B. EDUCATION PROGRAM

Program Director: Lynn Osborn, M.B.A., MGH

CIMIT Forum Presentations: October 1, 2001 – September 30, 2002

Status of Laparoscopic Colon Surgery in 2002
Dennis L. Fowler, MD, New York-Presbyterian, The University Hospitals of Columbia and Cornell

Endoscopic Approaches in Cardiovascular Surgery: Present and Future Applications
Albert K. Chin, MD, Vice President of Research
Guidant Corporation, Cardiac Surgery and Compass

Microfabricated Nanoporous Platforms for Cell-based Delivery and Sensing
Tejal Ashwin Desai, PhD, Associate Professor, Department of Bioengineering, College of Engineering, Boston University

The Retina Project at Rensselaer: Image Analysis Algorithms for Assisting in the Diagnosis and Treatment of Retinal Diseases
Charles V. Stewart, PhD, Professor, Department of Computer Science, Rensselaer Polytechnic Institute

Disruptive Technology
John Abele, Founder and Chairman, Boston Scientific Corporation, Boston, MA

Panel on Disruptive Technology in Health Care
John Abele, Founder Chairman, Boston Scientific Corporation
Richard Bohmer, MD, Assistant Professor, Harvard Business School
Scott Donnelly, Senior Vice President Global research, General Electric
Paul Citron, Vice President Science and Technology, Medtronic
Chris Little, Director Franchise Development, Johnson & Johnson Ethicon EndoSyrgery

The BioIntelligence Age: Science after the Information Age
Richard Satava, MD, FACS, Professor of Surgery, Yale University School of Medicine

Optical Methods for Minimally Invasive Diagnosis and Visualization of Tissue
Brett Bouma, PhD, Assistant Professor, Harvard Medical School, Wellman Laboratories of Photomedicine, Massachusetts General Hospital

A Distributed Medical Monitoring System for Real-Time Patient Diagnosis
Harvey Mudd College
Grant Baxter, Engineering Senior, Harvey Mudd College
Steve Yan, Computer Science Senior, Harvey Mudd College
Daniel Lee, Engineering Senior, Harvey Mudd College
Adam Fischer, Computer Science Senior, Harvey Mudd College

MR Imaging Approaches to Articular Cartilage Research
Carl S. Wilanski, MD
Brigham and Women's Hospital

Technology Developments in Minimally Invasive Procedures: Stereota ctic Radiosurgery, Image-Guided Surgery and Medical Robotics
Kevin Cleary, PhD, Research Associate Professor, Imaging Science and Information Systems Center (ISIS), Radiology Department, Georgetown University Medical Center

Fluid Jets - The next energy based surgical tool
Kevin P. Staid, Vice President of Engineering
HydroCision, Inc.

Looking at the Brain Optically
Lester Wolfe Workshop in conjunction with Wellman and MIT Spectroscopy Lab

From Single Neurons to Brains: In the Big Picture Do the Details Matter?
Mathew Wilson, PhD
Associate Professor, Brain and Cognitive Science, Massachusetts General Hospital

Optical Tomography and Functional Measurements
Britton Chance, PhD, Department of Biochemistry and Biophysics, University of Pennsylvania

***In vivo* Optical Imaging of Neocortical Epilepsy**
Theodore H. Schwartz, MD, Director, Epilepsy Research, Director, Center for Epilepsy Surgery
Weill Medical College, Cornell University, Ithaca, NY

Advances and Remaining Challenges in Technology -Guided Therapy
Bob Galloway, PhD, Associate Professor of Biomedical Engineering, Associate Professor of Neurological Surgery, Director, Center for Technology Guided Therapy, Vanderbilt University

3D Ultrasound: New Methods and Applications
Jason C. Birnholz, MD

Clinical Photodynamic Therapy: Are We There Yet?
A symposium sponsored by Wellman Laboratories of Photomedicine, Massachusetts General Hospital, and CIMIT

Introduaction to PDT
Tayyaba Hassan, PhD, Wellman Laboratories of Photomedicine
Massachusetts General Hospital

Brain Tumor PDT: Theory and Practice
Paul Muller, MD, St. Margaret's Hospital, Toronto

PDT- a Gentle but Effective Technique for Controlling Diseased Tissue Stephen
Stephen Bown, MBBS, MRCP, University Hospital, London

Potential Role for PDT in the Management of Cardiovascular Diseases
Campbell Rogers, MD, Brigham and Women's Hospital

Is there a Role for PDT in the treatment of Intraperitoneal Disease
Steve Hahn, MD, University of Pennsylvania

PDT in the Management of Airway Compromise and Lung Ca ncer
Raphael Bueno, MD, Brigham and Women's Hospital

SWOT Analysis
Brian Wilson, PhD, Ontario Cancer Institute, Toronto

PDT Panel Discussion
Moderated by Rox R. Anderson, MD, Associate Professor of Dermatology, Wellman Laboratories of Photomedicine, Massachusetts General Hospital

From Mendel to Microarrays: the Basic Concepts & Tools of Molecular Genetics
Andrew Webb, PhD, Professor of Biological Sciences, Wellesley College

Pharmacogenomics
Richard M. Weinshilboum, MD, Professor of Medicine and Pharmacology, Mayo Medical School, Rochester

The Interface of Information, Imaging, and Genetics
Brian Athey, PhD, the University of Michigan

Genomics/ the Genome Project
David Altshuler, MD, PhD, Professor, Massachusetts General Hospital/Harvard Medical School

Genetic Testing
Lewis B. Holmes, MD, Professor of Pediatrics, Genetics and Teratology Unit, Massachusetts General Hospital

Quantitative Proteomics: Past, Present, and Future
Steven Gygi, PhD, Assistant Professor, Department of Cell Biology, Harvard Medical School

Proteomics – a Clinical Perspective
Bruce Korf, MD, PhD, Director, Harvard-Partners Center for Genetics and Genomics

Cardiac Imaging Symposium
Carl Jaffe, MD, FACC, Medical Director, Yale Center for Advanced Instructional Media, Yale Medical School

Innovations in Medical Imaging
Thomas Brady, MD, CIMIT Co-Program Leader: Vulnerable Plaque; Director of Radiology Research, Massachusetts General Hospital

Biomarkers in Imaging for Drug (and Device) Development
Greg A. Sorensen, MD, Associate Director, MGH-NMR Center

Imaging in Oncology: Unsolved Problems
Daniel Sullivan, MD, Associate Director, Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI); Head of NCI's Biomedical Imaging Program

Tissue Engineering Program Review
Joseph Vacanti, MD, CIMIT Program Leader: Tissue Engineering; Massachusetts General Hospital: Visiting Surgeon, Director of Pediatric Transplantation, Director of the Laboratory of Tissue Engineering and Organ Fabrication
Mohammad Kaazempur-Mofrad, PhD, Department of Mechanical Engineering, Massachusetts Institute of Technology
Eli Weinberg, Department of Mechanical Engineering, Massachusetts Institute of Technology
Jeff Borenstein, PhD, Draper Laboratories
Michael Shin, PhD, Department of Surgery, Massachusetts General Hospital
Craig Neville, PhD, Department of Surgery, Massachusetts General Hospital
Osamu Ishii, MD, Department of Surgery, Massachusetts General Hospital
Lauren Hartman, MS, Department of Surgery, Massachusetts General Hospital

APPENDIX C: Regulatory Affairs Program

Program Director: John J. Smith, M.D., J.D., MGH

Maximum clinical impact of safe and effective new medical technologies is highly dependent on timely Food and Drug Administration (FDA) marketing approval and third-party payer coverage and payment decisions. The Regulatory Affairs Program at CIMIT provides a unique, nationally-recognized resource to address regulatory and coverage/payment challenges throughout the product development lifecycle.

During fiscal year 2002, the Regulatory Affairs Program continued to work with stakeholders to make the existing regulatory and coverage/payment system more efficient, transparent and predictable. A major focus on conflict of interest in medical research will culminate in a CIMIT forum that will gather thought leaders to discuss this crucial issue in late October 2002. Three CIMIT white papers have either been released or are nearing completion to support this forum, with this research serving as a foundation for several related articles in the scholarly literature. A successful internship in conjunction with the Centers for Medicare and Medicaid Services (CMS) and the Harvard School of Public Health has laid the groundwork for an on-going CIMIT/CMS policy internship, to be filled by suitable individuals from industry and government. Also with regard to government, the Program continues to work with FDA and CMS to provide these agencies efficient, maximum access to the vast resources of the CIMIT consortium. Finally, the Program continues to provide regulatory tracking and project-specific regulatory support for the CIMIT community and beyond.

Key results during this period include:

- Establishing the foundation for an October 2002 CIMIT Conflict of Interest Forum in Boston, MA. In cooperation with project partners Harvard Medical School and Stanford University, the CIMIT Regulatory Affairs Program has taken the lead in planning this important event. Designed to bring together a select group of thought leaders to delineate workable solutions to the conflicts issue, planning activities have included extensive scholarly research, ultimate release of three CIMIT white papers, and design of meeting materials and format, as well as management of the administrative details for the meeting itself.

- CIMIT/CMS internship: Coordination of FDA marketing and CMS coverage decisions. This extremely successful initial project between CIMIT and CMS involved a Harvard School of Public Health intern, who performed high-quality research on the law of trade secrets and how it may impact FDA/CMS collaboration, work of substantial current importance to CMS and the federal government. The CIMIT/HSPH intern, Stanley Wang, M.D., J.D., presented his work to senior CMS officials, with this research forming the basis for several scholarly articles submitted for publication.

- Presentation to the Department of Health and Human Services Committee on Regulatory Reform. At the invitation of the Secretary of Health and Human Services, Director of Regulatory Affairs John J. Smith, M.D., J.D., presented the Program's work to the Committee on Regulatory Reform, a prestigious invitation made to only a few academics. The focus of this presentation was research conducted during the CIMIT/CMS internship, detailing legal implications of closer collaboration between FDA and CMS.

- Work towards institution of a formal, ongoing CIMIT/CMS health policy internship. Following the success of the initial CIMIT/CMS and the realization that additional CMS research project could greatly benefit from objective, academic analysis, CMS has agreed in principle to an on-going CIMIT/CMS internship, which would include both graduate students and industry employees on loan to CIMIT.

- Providing FDA and CMS access to CIMIT consortium resources. The Regulatory Affairs Program assists these key government agencies in identifying and obtaining medical and scientific expertise within CIMIT to aid in specific government decisions.

- Regulatory tracking and education. The Program continues its publication of a well-regarded Regulatory Affairs Newsletter. To further education on regulatory matters, the Director of Regulatory Affairs has given several invited presentations to students, professional societies, and to the CIMIT community at our weekly forum.

- A complete appendix of Regulatory Affairs Program metrics is attached at the end of this document.

Specific Aim 1: Identify key systemic regulatory and coverage/payment issues facing the device development process across product lines.

Progress: An open dialogue with government, industry and academia to identify and define these issues has been established. These discussions have identified the following areas of concern: 1) conflict of interest in medical research; 2) providing government with objective, scholarly research on health policy issues of current interest; 3) building productive relationships between the stakeholders in the medical technology community, including government, industry and academia; 4) providing easy government access to the considerable resources of the CIMIT consortium.

Plan: The Program will continue to identify systemic regulatory and coverage/payment issues, so that CIMIT may be fully prepared to thoughtfully address them as they develop.

The Program's dialogue with Harvard Medical School and Stanford University will continue to sharpen efforts to address conflict of interest. Discussions with CMS, FDA, industry and the Harvard School of Public Health will further aid our understanding of government research needs, as well as industry's areas of regulatory concern.

Specific Aim 2: Develop and apply a process for developing workable solutions to identified regulatory and coverage/payment issues.

Progress: The Regulatory Affairs Program regulatory and coverage/payment problem-solving process continues its use of three coordinated mechanisms to realize positive change: (1) objective, scholarly white papers, serving as an informational resource and basis for further action; (2) innovative solutions crafted in collaboration with relevant stakeholders; (3) CIMIT-sponsored forums directed at specific issues.

Over the past year, this process has been applied to conflict of interest in medical research. A major research effort has been completed, with three white papers either released or to be released in the near future. This effort has provided the foundation for a conflict of interest forum in October 2002, where thought leaders will come together to offer practical insight on addressing real world conflicts issues, sharing this insight via a consensus document.

A similar process was applied to increasing collaboration between FDA and CMS, a project identified by senior CMS officials and conducted by a CIMIT/CMS/HSPH intern. This project produced high-quality research, which was presented to CMS and subsequently used in the formulation of agency policy. Articles based on this work were submitted for publication in the medical and legal literature.

Building on the needs of the stakeholder community and the unqualified success of the initial CIMIT/CMS internship, discussions were undertaken with government, industry and academia on how to formalize and continue this valuable program. This discussions have resulted in an agreement in principle to institute a continuing internship program, involving industry and student interns, funded by industry, and focusing on research projects of current concern to CMS. In addition to providing government with much-needed, high-quality research, this program will have the ancillary benefit of forming personals contacts between government, industry, and academia, building understanding and trust among stakeholders in the medical technology community.

In addition to these major projects, preliminary research has been conducted on focus areas of local concern to the CIMIT community. An example of this work is research focusing on prospective regulatory treatment of "plug and play" diagnostic medical equipment, as envisioned in the BodyLan project.

Plan: Considerable Program effort will come to fruition with the October 2002 conflict of interest forum. A consensus document, suitable for publication in the academic literature, is the minimum work product envisioned. Depending on discussion direction and content, follow-up projects or even additional meetings may be required.

Discussions with CMS, industry, and HSPH continue, and are expected to result in a formal agreement for an on-going CMS internship in fall 2002. Project focus areas with be determined in conjunction with CMS.

In addition to the internship program, the Regulatory Affairs Program will build on preliminary discussions for a collaborative research project with HSPH, with preliminary agreement expect in fall-early winter 2002. Extramural funding for this project, expected to focus on the impact of CMS National Coverage Decisions on the adoption of new medical technology, will then be jointly sought.

Specific Aim 3: Maintain an infrastructure for addressing systemic regulatory and coverage/payment issues in device development; maintain adequate capacity to address product-specific questions, as well as educate the CIMIT community on regulatory issues.

Progress: The Regulatory Affairs Program maintains a robust capacity to identify and assess systemic issues in medical device regulation and coverage/payment. These efforts have been

augmented by the hire of a full-time research associate and administrative director in January 2002, now fully integrated into Program operations.

In addition the Program's focus on systemic issues, the Program continues to address regulatory needs in the CIMIT Community. The well-received Regulatory Affairs Newsletter expanded its distribution in FY '02, and it now available across the Partners Healtcare community, and well as to CIMIT's industrial partners and interest parties in academia and government. Program resources are also available to assist CIMIT investigators with general issues involving FDA and CMS-related matters, as well as to develop coherent regulatory strategy, generally before industry becomes involved.

The Program has also engaged in an educational effort within the CIMIT community and beyond, with the Director of Regulatory Affairs delivering several invited lectures. Web-based resources have also been expanded, providing access to Program white papers as well as frequently-asked regulatory questions.

Plan: The Regulatory Affairs Program will continue to employ its current methodology to identify and assess systemic issues, using the results to guide research and produce the monthly Regulatory Newsletter. In addition, product-specific regulatory and coverage/payment services will continue to be offered to CIMIT investigators, in close cooperation with the Office of Technology Development.

APPENDIX D: OFFICE OF TECHNOLOGY DEVELOPMENT PROGRAM

Program Director: Jonathan Rosen, Ph.D.

The CIMIT Office of Technology (OTD) provides technology transfer guidance and support services to CIMIT, our investigators, and their institutions. The OTD also provides CIMIT with its primary interface to the investor community, and participates in the design and application of advanced partnering and new venture business models.

During the past year, the CIMIT Office of Technology Development has focused its activities on preparing for the successful transfer of several major CIMIT technologies including Tissue Engineering, Optical Diagnostics, and Medical Simulation. The OTD has also designed and implemented a new proposal evaluation process, the individual Patient Impact Profile (iPIP), as part of the CIMIT Awards Program. For every proposal CIMIT has chosen to support during the coming year, the OTD is designing a customized implementation plan to prepare for the successful transfer of the anticipated technology innovations. The OTD has initiated a series of inter-institutional intellectual property working groups to improve the portfolio management process for CIMIT Consortium patents. Finally, the OTD, in co-operation with the CIMIT Industrial Liaison Program, has conducted a series of discussions with leading health-care venture funds and selected members of their investment portfolio companies. These activities can be summarized by the following four Specific Aims:

Specific Aim 1: Facilitate and support the successful transfer of CIMIT technologies.

Progress: During this past year, CIMIT invention disclosures and patents have been filed by each of the four institutions in the CIMIT Consortium. In each case, the OTD is working with the respective licensing offices to identify appropriate and interested licensing partners and potential investors.

Tissue Engineering: Because of the strongly collaborative nature of this program, relevant intellectual property ownership is shared by several consortium member institutions. The OTD has designed, coordinated and implemented a targeted marketing and technology transfer program intended to introduce a series of patient care improvements based on break-through advances that CIMIT has supported. CIMIT is working with a leading healthcare corporation in the management of end-stage kidney failure to design a broad combination license-sponsored research partnership with Dr. Vacanti and the institutions involved in the CIMIT Tissue Engineering Program.

Optical Diagnostics: This program includes the design and testing of a series of advanced optical instrument systems including Optical Coherence Tomography (OCT), Spectrally Encoded Confocal Microscopy (SECM), Speckle Imaging, and related technologies. The CIMIT OTD and the licensing office of the Massachusetts General Hospital (CSRL) have worked cooperatively to design application-specific patent portfolios to advance patient care in the management of Barrett's esophagus, in the identification of Vulnerable Plaques, and in creating an Optical Biopsy System. Discussions are in progress on both licensing and new venture opportunities.

Medical Simulation: CIMIT and the OTD have been working with the Medical Simulation team to establish a working portfolio of intellectual property and supplier agreements that will allow for successful production of advanced training systems for both military and civilian

applications. These include field-tested chest-tube simulation systems (VIRGIL), and training systems directed to teaching laproscopic procedures.

Plan: To continue to facilitate and support the successful transfer of CIMIT technologies.

Specific Aim 2: Maximize the potential for each CIMIT technology to improve Patient Care.

Progress: The OTD has designed and implemented a new evaluation tool called the individual Patent Impact Profile (iPIP). This technique is used to anticipate the potential for patient impact, new intellectual property and key drivers for successful implementation and was applied to each of the proposals submitted to CIMIT for funding in FY03. The iPIP considers to what extent the proposed work has the potential of (1) positively impacting patient care, (2) creating new intellectual assets (3) contributing to high value markets, and (4) returning education, financial or equity opportunities to CIMIT. A 'due diligence' process has been established that may include patent and publication searches, interviews, corporate profiles and internal data searches to help in determining the most likely exit strategies for each project as part of the selection process.

For each of the proposals selected for CIMIT funding, the OTD is preparing an individual plan for the eventual and successful transfer of the innovative technologies we are promoting.

Plan: To complete the design of customized implementation plans for each funded project and to continue to maximize the potential for each CIMIT technology to improve Patient Care.

Specific Aim 3: Establish improved inter-institutional communications channels to facilitate the management of jointly-owned CIMIT-funded intellectual properties.

Progress: During the past year, the CIMIT OTD has hosted a series of working sessions between the licensing professionals representing various CIMIT Consortium members to discuss both specific issues relating to ongoing patent prosecutions, and IP management strategies that anticipate future obstacles and plan for anticipated successful resolutions. The OTD has worked to establish a series of standing multi-institutional IP committees that meet periodically to discuss both the science and the patent activities associated with CIMIT-sponsored multi-institutional translational research.

Within the Partners HealthCare System, Dr. Rosen serves on the Internal Patent Review Committee that oversees all new IP generated by researchers within the Partners system.

Plan: To continue to improve inter-institutional communications channels to facilitate the management of jointly-owned CIMIT-funded intellectual properties.

Specific Aim 4: Establish and expand a network of selected Investors and their medical device portfolio companies.

Progress: In collaboration with the CIMIT ILP Program, the OTD has hosted a series of discussions with leading health care venture capital funds and individual investors interested in new ventures resulting from CIMIT research. These meetings have also included introductions to selected health care companies that are high-value candidates for licensing of CIMIT-supported research.

Plan: To continue to establish and expand a network of selected Investors and their medical device portfolio companies.

APPENDIX E: LIST OF CIMIT PROJECTS AND PRINCIPAL INVESTIGATORS

ENDOVASCULAR DEVICES PROGRAM

Cardiomyocyte repopulation
Principal Investigator: Craig Thompson, M.D., MGH

Radio frequency ablation with needle-tipped catheter
Principal Investigator: William Stevenson, M.D., BWH

Atrial fibrillation ablation with MR guidance
Principal Investigator: David Keane, M.D., MGH

MINIMALLY-INVASIVE SURGERY PROGRAM

Blake OR-Advanced Procedure Room, APRIL
Principal Investigator: David Rattner, M.D., MGH

Patient monitoring and communications
Principal Investigator: Nathaniel Sims, M.D., MGH and John Guttag, Ph.D., MIT

Robotics in cardiac surgery
Principal Investigator: David Torchiana, M.D., MGH

Gallbladder extraction device
Principal Investigator: David Whittaker, M.D., MGH and David Rattner, M.D., MGH

Laparoscopic ultrasound
Principal Investigator: Kirby Vosburgh, PhD, MGH and James Ellsmere, MD, MGH

IMAGE-GUIDED THERAPY PROGRAM

Cellular resolution endoscope and catheter-based optical imaging
Principal Investigator: Brett E. Bouma, Ph.D., MGH

Non-invasive image-guided opening of the blood-brain barrier
Principal Investigator: Kullervo Hynynen, Ph.D., BWH

Automated segmentation of anatomy from CT and MRI
Principal Investigator: Carl-Fredrik Westin, Ph.D., BWH

TISSUE ENGINEERING PROGRAM

Degradable conductive polymers
Principal Investigator: Robert Langer, Sc.D., MIT

Mullerian Inhibiting Substance (MIS) for ovarian cancer
Principal Investigator: David MacLaughlin, Ph.D., MGH

Tissue engineering: vascular systems and angiogenes is
Principal Investigator: Joseph Vacanti, M.D., MGH

Tissue engineering: 3D tissue design
Principal Investigator: Joseph Vacanti, M.D., MGH

Tissue engineering vascularized tissue *in vitro* for implant
Principal Investigator: Jeffrey Borenstein, Ph.D., Draper

MEDICAL SIMULATION PROGRAM

Enabling technologies for medical simulation
Principal Investigator: Steven Dawson, M.D., MGH

BIODETECTION PROGRAM

Real-time blood assay
Principal Investigator: Christopher Dube, Ph.D., Draper

Developing diagnostic and monitoring technology for circulatory shock states
Principal Investigator: Andrew Reisner, M.D., BWH and Harry Asada, Ph.D., MIT

Development and characterization of pyrolysis: FAIMS analyzer for the detection of Bacillus spores
Principal Investigator: Jeffrey Borenstein, Ph.D., Draper

COMBAT CASUALTY CARE PROGRAM

RAFTS/Bioglove
Principal Investigator: Geoffrey Ling, M.D., Ph.D., USUHS

Parallel computer processing and modeling use in medical monitoring
Principal Investigator: William Wiesmann, M.D., Harvey Mudd College

VULNERABLE PLAQUE PROGRAM

Vulnerable Plaque
Principal Investigator: James Muller, M.D., MGH and Thomas Brady, M.D., MGH

Characterization of vulnerable plaque
Principal Investigator: Thomas Brady, M.D., MGH and Brett Bouma, Ph.D., MGH

Detection of vulnerable atherosclerotic plaques with radionuclide technology
Principal Investigator: Alan Fischman, M.D., MGH

Magnetic resonance compatible devices
Principal Investigator: Jerome Ackerman, Ph.D., MGH

STROKE PROGRAM

Continuous monitoring of stroke using diffuse optical tomography
Principal Investigator: David Boas, Ph.D., MGH

MGH XMR suite
Principal Investigator: R. Gilberto Gonzalez, M.D., Ph.D., MGH

TECHNOLOGY ASSESSMENT AND OUTCOMES ANALYSIS PROGRAM

Technology Assessment Program Core
Principal Investigator: G. Scott Gazelle, M.D., Ph.D., MGH

Operating Room of the Future outcomes
Principal Investigator: G. Scott Gazelle, M.D., Ph.D., MGH

Vulnerable Plaque outcomes
Principal Investigator: G. Scott Gazelle, M.D., Ph.D., MGH

APPENDIX F: LIST OF PERSONNEL RECEIVING PAY

Project: Magnetic resonance compatible devices
Personnel: Jerome Ackerman, Ph.D., MGH

Blake OR-Advanced Procedure Room and Innovation Laboratory, APRIL
David Rattner, M.D. MGH and Keith Isaacson, M.D., MGH

Minimally Invasive Surgery outcomes
G. Scott Gazelle, M.D., Ph.D., MGH and James Stahl, M.D., MGH

Patient monitoring and communications
Nathaniel Sims, M.D., MGH and John Guttag, Ph.D., MIT

Cellular resolution endoscope and catheter-based optical imaging
Brett E. Bouma, Ph.D., MGH

Non-invasive image-guided opening of the blood-brain barrier
Kullervo Hynynen, Ph.D., BWH

Automated segmentation of anatomy from CT and MRI
Carl-Fredrik Westin, Ph.D., BWH

Mullerian Inhibiting Substance (MIS) for ovarian cancer
David MacLaughlin, Ph.D., MGH

Tissue Engineering: 3D tissue design
Joseph Vacanti, M.D., MGH

Enabling technologies for medical simulation
Steven Dawson, M.D., MGH

Endpoints of cellular resuscitation in hemorrhagic shock
Harry Asada, Ph.D., MIT

Vulnerable Plaque Program
James Muller, M.D., MGH and Thomas Brady, M.D., MGH

Vulnerable Plaque Program outcomes
G. Scott Gazelle, M.D., Ph.D., MGH

Continuous monitoring of stroke using diffuse optical tomography
David Boas, Ph.D., MGH

Tele-stroke
Lee Schwamm, M.D., MGH

MGH XMR suite
R. Gilberto Gonzalez, M.D., Ph.D., MGH

G. LIST OF PERSONNEL RECEIVING DEGREES

Tissue Engineering Program

Ernest S. Kim, MS Mechanical Engineering, MIT, June 2002, "Design of a Single Capillary-Parenchymal Co-Culture Bioreactor."

Kevin R. King, MS Health Science and Technology, MIT/Harvard, August 2002, "Development of Biodegradable Microfluidic Networks for Tissue Engineering."

Joann C.C. Wang, BS, Chemical Engineering, June 2002.

Eli J. Weinberg, BS, Mechanical Engineering, June 2002.

Biodetection Program

Thomas Buckley, IV, B.S. Chemical Engineering, Northeastern University, June 2002