

AD _____

Award Number: DAMD17-99-2-9001

TITLE: Center for Integration of Medicine and Innovative Technology

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

CONTRACTING ORGANIZATION: The Massachusetts General Hospital Corporation
dba Massachusetts General Hospital
Boston, MA 02114

REPORT DATE: November 2006

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

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE 01-11-2006		2. REPORT TYPE Annual		3. DATES COVERED 15 Oct 2005 – 14 Oct 2006	
4. TITLE AND SUBTITLE Center for Integration of Medicine and Innovative Technology				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER DAMD17-99-2-9001	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) John A. Parrish, M.D.				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Massachusetts General Hospital Corporation dba Massachusetts General Hospital Boston, MA 02114				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. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES Original contains colored plates: ALL DTIC reproductions will be in black and white.					
14. ABSTRACT 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. CIMIT develops technologies to advance the diagnosis and treatment of patients using minimally invasive and less costly approaches. CIMIT coordinates and implements research programs in cardiovascular disease, cancer, trauma, and critical care, supported by basic science and engineering development in biomaterials, endoscopic tools, energy delivery, medical imaging, and other novel technologies. This unique military/civilian partnership allows DoD the transfer to the military of successful minimally invasive approaches developed at CIMIT. The overall goal of CIMIT is to create a national program that combines clinical and technological excellence and educational components to generate, develop, and reduce-to-practice innovative and high-impact concepts in minimally invasive therapy.					
15. SUBJECT TERMS NOT PROVIDED					
16. SECURITY CLASSIFICATION OF:			UU	18. NUMBER OF PAGES 62	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

Attachment 2

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.

Signature

Date

DAMD17-99-2-9001

**CENTER FOR INTEGRATION OF MEDICINE AND INNOVATIVE TECHNOLOGY
Annual Progress Report – October 1, 2005 - September 30, 2006**

TABLE OF CONTENTS

1.0 INTRODUCTION	7
2.0 ENABLING TECHNOLOGIES	12
2.1 ENDOVASCULAR DEVICES	12
Task 1: Cardiomyocyte Repopulation using Percutaneous Delivery of Tissue Engineered Systems	12
Task 2: Fellowship: Application of Automation and Tissue Engineering to Construct Heart Valves	13
2.2 MINIMALLY INVASIVE SURGERY	14
Task 1: Minimally Invasive Cardiac Surgery – Endoscopic Coronary Anastomosis	14
Task 2: Endothelial Activation Markers as Molecular Targets for Innovative, Minimally Invasive Diagnosis and Therapy in Cardiovascular Disease	15
Task 3: Develop a Computer-Based Three-Dimensional Imaging Treatment Planning System to Drive an Endoscopically Placed, Miniature, Facial Skeletal Distraction Device.	16
Task 4: Virtual Fixtures for Robot-Assisted Minimally Invasive Cardiac Surgery	17
Task 5: Operating Room of the Future	18
2.3 IMAGE GUIDED THERAPY	20
Task 1: MRI-guided Focused Ultrasound Treatment of Breast Cancer	20
Task 2: Early Detection and Ablation of Epithelial Cancers	21
Task 3: Segmentation of Bone From CT and Vessels From MRA Data	23
Task 4: Real-time Registration of Intra-operative Ultrasound with Pre-operative CT/MR for Image Guided Therapy	24

2.4 TISSUE ENGINEERING	24
Task 1: Degradable Conductive Polymers	24
Task 2: Polymer-based Gene Delivery Platform	25
Task 3: Transdermal Drug Delivery and Chemical Sensing for Neonates	28
2.4 TISSUE ENGINEERING, continued:	
Task 4: Synthesize Vascularized Living Systems from the Platform of Two-Dimensional Silicon Microfabrication Technologies and Adapt to Three-Dimensional Living Devices	29
Task 5: Synthesize Vascularized Living Systems from the Platform of Three-Dimensional Printing Technology	29
Task 6: Minimally Invasive Meniscal Repair with Tissue Engineered Cartilage	31
Task 7: Development of a Novel <i>in vivo</i> Recombinant Protein Delivery Device Designed to Regress Abnormal Tissue: Recombinant Human Müllerian Inhibiting Substance (rhMIS) Producing Cells on Biodegradable Matrices	32
Task 8: Determine the Role of MSCs in Fetal Tissue Engineering	33
2.5 SIMULATION	35
Task 1: Discover Enabling Technologies for Medical Simulation	35
2.6 NEW INITIATIVES	37
Task 1: Lung Volume Reduction Using a Bronchoscopic Approach	37
Task 2: Outcome Assessment in Menorrhagia	38
3.0 CLINICAL CHALLENGES	39
3.1 TRAUMA AND CRITICAL CARE	39
Task 1: Microsensors – Real-Time Blood Assay	39
Task 2: Application of Microwave Imaging to Rapid Non-Invasive Detection of Intracranial Hematoma	40
Task 3: Near-Infrared Reflectance Spectroscopy (NIRS) to Assess Regional Ischemia both during Trauma Resuscitation and at the Bedside in the Intensive Care Unit	42

Task 4: Noise-Enhanced Tactile Sensation for the Management of Sensory Deficits in Patients with Stroke	43
3.2 VULNERABLE PLAQUE	45
Task 1: Vulnerable Plaque Detection and Treatment	45
Task 2: Detection of Vulnerable Plaque using Optical Coherence Tomography	44
3.3 STROKE	46
Task 1: Acute Stroke Management – Neuro-Protection	46
Task 2: MRI Guided Rapid Laser Endovascular Photoacoustic Recanalization (LEPAR) for Hyperacute Stroke and Stroke Predictive Modeling	46
Task 3: Optical Monitoring and Imaging of Stroke	47
Task 4: Neuronal Injury and Neuroprotection in Epilepsy: Proton Beam Radiation for Intractable Epilepsy	49
Task 5: Measurement of Vascular Reactivity by Functional MRI in Cerebral Amyloid Angiopathy	50
4.0 TECHNOLOGY ASSESSMENT AND OUTCOMES ANALYSIS	52
5.0 REFERENCES	56
6.0 APPENDICES	58
A. LIST OF CIMIT PROJECTS AND PRINCIPAL INVESTIGATORS	58

CENTER FOR INTEGRATION OF MEDICINE AND INNOVATIVE TECHNOLOGY Annual Progress Report – October 1, 2005 - September 30, 2006

1.0 INTRODUCTION

The Center for Integration of Medicine and Innovative Technology (CIMIT) has completed the fiscal year 10/1/05 to 9/30/06 under Cooperative Agreement Number DAMD17-99-2-9001. 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, Charles Stark Draper Laboratory and the Beth Israel Deaconess Medical Center. The overall goal of the program has evolved beyond minimally invasive therapy to include 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 – Cardiomyocyte Repopulation – Steven Oesterle, MD, MGH

The major accomplishment for the Cardiomyocyte Repopulation project was the first feasibility testing of a novel, catheter-based method for autologous bone marrow stem cell transplantation to heart muscle. This completes this project.

Minimally Invasive Surgery – Heart Valve Construction – Jennifer White, MD, MGH

Fabrics have been integrated into the leaflets of tri-leaflet valve scaffold constructed using methods previously developed in our laboratory. In order to maximize the data regarding the interaction of the leaflet fabric with the living body gained from the pending chronic animal studies, these valves have been constructed as chimeric implants in which each leaflet of a tri-leaflet valve is a different fabric. This completes this project.

Minimally Invasive Surgery – Endoscopic Anastomosis – David Torchiana, MD, MGH

Chronic studies in a large animal model demonstrated that FocalSeal surgical sealant is an effective hemostatic adjunct without associated tissue toxicity when applied to blood vessel anastomoses sites. This completes this project.

Minimally Invasive Surgery - Craniofacial Surgery Planning – Leonard Kaban, MD, MGH

The CIMIT team has developed a user interface for six degree-of-freedom manipulation of 3-D graphical objects using a standard computer mouse. Also, an upgraded version of a 3-D axis manipulation tool was implemented in the current version of the 3-D Slicer. This completes this project.

Minimally Invasive Surgery - Robot-Assisted Surgery – Robert Howe, PhD, HMS

The CIMIT team is implementing a new approach that uses an electromagnetic tracker attached directly to the tip of the instrument. Based on this more accurate sensor, the team has developed a navigational aid that shows the location of the instrument tip relative to the internal mammary artery. This completes this project.

Image Guided Therapy - Focused Ultrasound for Cancer Tx – Ferenc Jolesz, MD, BWH

Several phased array systems were tested and results used to develop the final 208-channel phased array system in collaboration with a commercial manufacturer. This system was tested in rabbits. The results are good, demonstrating the ability of the system to coagulate tumor tissue similar in size and location to breast cancer. This completes this project.

Image Guided Therapy - Automated Image Segmentation – Carl-Fredrik Westin, PhD, BWH

The CIMIT team has introduced a new image feature, based on local phase, which describes local edge symmetry independent of absolute gray value. The phase is a natural bi-product from the filters used in the adaptive filtering scheme presented. Because phase is amplitude invariant, the measurements are robust with respect to smooth variations, such as bias field inhomogeneities present in all MR images. In order to enable validation of the phase-wire segmentation software, a system has been created that continuously records user interaction and automatically generates a database containing the number of user interactions, such as mouse events, and time stamps from various editing modules. This completes this project.

Tissue Engineering - Degradable Conductive Polymers – Robert Langer, ScD, MIT

The CIMIT team proposed a novel approach to the creation of bioerodible polypyrrole (Ppy). In this novel paradigm the rate of erosion of Ppy is controlled by the hydrolysis and ionization of pendant groups followed by the solubilization of Ppy oligomers. The team has verified the hypothesis that solubilization of Ppy solid and thin film substrates, via ionizable side chain moieties, can occur under physiological conditions. This completes this project.

Tissue Engineering - Polymer-Based Gene Delivery Platforms – Robert Langer, ScD, MIT

The CIMIT team has continued development on the first accelerated discovery approach for finding synthetic transfection vectors. This year the team has begun the synthesis of a library containing up to 3,500 individual polymers. In the near future, this library will be screened for gene transfer efficiency. Work has also been done to further characterize the polymers in the original poly(β -amino ester) library. The library was characterized along the following dimensions: (1) effective diameter of polymer-DNA complexes, (2) zeta potential of polymer-DNA complexes, and (3) relative uptake of complexes by 3T3 cells. This completes this project.

Tissue Engineering - Trans-Dermal Drug Delivery – James Weaver, PhD, MIT

A new approach to computer simulation of spatially complex systems was identified. The CIMIT team has obtained very encouraging results for a simulation of the transport of potent agents through the skin due to exposure of a small amount of the compound to the surface of the skin. This completes this project.

Tissue Engineering - Synthesis of Vascularized Living Systems – Joseph Vacanti, MD, MGH

Significant milestones in both fabrication and testing of microfabricated vascular scaffolds have been reached during this project. Polymer fabrication in both biocompatible and biodegradable matrices is moving ahead swiftly. Molds produced from PolyDiMethylSiloxane (PDMS), a biocompatible polymer, have been produced in both two- and three-dimensions. Three-dimensional vascular beds have been connected in parallel and run through initial fluid dynamic qualification studies. Bonded layers of biodegradable PLGA molded films have also been produced, a major milestone. This completes this project.

Tissue Engineering - Structures to Enable Vascularization – Jeffrey Borenstein, PhD, Draper

Major milestones in the design of scaffolds for endothelial cell seeding have been achieved. Several generations of networks have been produced, each representing a significant advance over previous designs. The first design with fully uniform flow, TEP-2, was generated on the wafer level and utilized to produce large numbers of silicon and polymer scaffolds for cell seeding. Design efforts were then transitioned to the modular networks TESTNET0 and TESTNET1, which are more suited to fluid dynamic experiments and biocompatibility studies. In a major advance, a new technique for generating mask layouts has been developed in which computational techniques are used to automatically produce vascular networks with desired flow characteristics. This new layout tool has been applied to the generation of photomasks for vascular designs, thereby reducing the cost of photomasks from \$700 to \$15 and the layout time required from 2 weeks to 1 day. This completes this project.

Tissue Engineering - Minimally Invasive Meniscal Repair – Thomas Gill, MD, MGH

This research has demonstrated that a cell-based therapeutic approach can be used in the articular environment in a large animal model of meniscal tears. Further investigation during the second year sought to define the best delivery material and the best pre-seeding conditions of the reparative cells onto candidate scaffolds. A clinically applicable approach combining this technique with arthroscopic surgery might be developed based on these studies. This completes this project.

Tissue Engineering – Treatments for Ovarian Cancer – David MacLaughlin, PhD, MGH

In these studies, resorbable polyglycolic acid biopolymer matrices impregnated with cells transfected with the MIS gene were successfully implanted in over 80 immuno-compromised mice and bioactive MIS produced and absorbed by the blood stream. The effect of different sized biopolymer implants on the resulting serum MIS concentrations was also determined. This completes this project.

Tissue Engineering - MSCs for Tissue Engineering – Scott Adzick, MD, UPENN

The CIMIT team has made significant progress toward the clinical utilization of mesenchymal stem cells. Due to progress from other investigators in the field, it is clear that a mesenchymal stem cell of small phenotype, rather than the large fibroblastic phenotype used in our previous studies, has significantly greater differentiative capacity *in vitro*, and contains a higher frequency of Colony Forming Units-f forming cells. This completes this project.

New Initiatives - Outcome Assessment in Menorrhagia – Johanna Bosch, PhD, MGH

The CIMIT team has developed a self-administered questionnaire including the Health Utilities Index and EuroQol-5D to collect quality-of-life data in patients with menorrhagia. This completes this project.

Simulation – Procedural Simulation – Steven Dawson, MD, MGH

The CIMIT team continued to see strong interest in the VIRGIL® system from emergency physicians, paramedics, and business people who have visited the CIMIT facility. The team has invested considerable time in redesigning the system so that it can be more easily transportable. New design considerations for the beta version of VIRGIL® include significant modifications to the instrument tracking system, a key component of the augmented reality tracking system, new

containment methods for the hemothorax blood flow scenario, and new cooling and ventilation methods. This completes this project.

Trauma and Critical Care – Microsensors – Christopher Dube, PhD, Draper

Among the key results from this year is the repeatable detection of the microbial pathogen *E. coli* O157:H7 using individually functionalized μ CANARY elements. In the previous quarter the team demonstrated detection of *E. coli* O157:H7 using commercially available antibodies. This completes this project.

Trauma and Critical Care – Hematoma Detection – Geoffrey Ling, MD, PhD, USUHS

The team has successfully completed a study of the RAFTS as it is applied to diagnosis of intracranial hematomas, pneumothorax and compartment syndrome. The results from this work demonstrate that the RAFTS can differentiate hematomas from brain and skull. Subsequently, the team reported the completed *in vivo* study that was performed in live anesthetized pigs. These studies show that the RAFTS can accurately detect the presence of hematomas at epidural, intraventricular, subdural and intraparenchymal sites in a clinically relevant model. Also in pigs, RAFTS can also detect as little as a 10% pneumothorax and as little as 2cc of either blood or saline in the muscle compartment. This completes this project.

Vulnerable Plaque – VP Detection and Treatment – James E. Muller, MD, MGH

Vulnerable Plaque Program continued to meet its goals and establish new ones. The main activity of the Program continues to be the scientific projects focusing on methods of detection and treatment of vulnerable plaque. Leadership of the Program continues to address thematic, administrative and support issues in an attempt to enhance the overall quality and scope of the Program. This completes this project.

Vulnerable Plaque – OCT for Vulnerable Plaque Detection – Brett Bouma, PhD, MGH

The CIMIT team has advanced the capabilities of OCT for imaging *in vivo* by resolving three key technical issues. First, the team has developed methods for displacing blood from the iliac and aorta using balloon occlusion and saline flush. Second, the team has demonstrated a sufficient image acquisition rate to avoid motion artifact due to respiration and pulsatile blood flow. Finally, the team has demonstrated that characteristic features in plaques can be resolved using a catheter that provides a resolution of approximately 10 microns. This completes this project.

Stroke - Optical Monitoring of Stroke – David Boas, PhD, MGH

Significant progress was made in diffuse optical technology for characterizing layered media. This technology is central to cerebral oximetry in which the layered structure of scalp, skull and brain must be characterized. The key developments include: 1) New time resolve near infrared spectroscopy instrumentation for improved optical property determination, 2) time resolved Monte-Carlo modeling of layered media and 3) composing and submitting a Human protocol for cerebral oximetry measurements on healthy people. This completes this project.

Stroke - Functional MRI in Cerebral Amyloid Angiopathy – Steven Greenberg, MD, MGH

Thus far, 4 control subjects and one CAA subject have been studied using fMRI. Data analysis revealed a robust response in blood flow to both visual stimulation and CO₂ inhalation in the control subjects. This completes this project.

Technology Assessment - Inpatient Costs in Stroke – G. Scott Gazelle, MD, PhD, MGH

The Technology Assessment and Outcomes Analysis Program has evolved over three years with the support and guidance of CIMIT leadership. In view of changes in CIMIT over the years, the Program has been reshaped to concentrate our research efforts in two major focus areas: Vulnerable Plaque and the Operating Room of the Future. Also, service, policy and administrative components of the Program are now concentrated in a Program Core. This completes this project.

2.0 ENABLING TECHNOLOGIES

2.1 ENDOVASCULAR DEVICES

Task 1: Cardiomyocyte Repopulation using Percutaneous Delivery of Tissue Engineered Systems

Principal Investigator: Stephen Oesterle, MD and Craig Thompson, MD, MGH, Boston, MA

Over 1.5 million adults experience acute myocardial infarction each year. More than 500,000 die from the event. Many others survive with significant impairment of left ventricular function. A multitude of diseases unrelated to Atherosclerosis can also result in varying degrees of heart failure, including sustained hypertension, viral myocarditis, and valvular insufficiency frequently lead to intractable ventricular dysfunction. Congestive heart failure (CHF) is amongst the most frequent diagnoses for patients admitted to acute care hospitals. CHF is associated with the longest lengths of stay for any of the cardiac Diagnostic Related Groups (DRGs). Acute and chronic care of patients with heart failure consumes billions of health care dollars. Beyond diuretics and other pharmaceutical preparations that “unload” failing hearts, there are few effective treatments for advanced heart failure. Adult mammalian myocardial cells are generally believed to be terminally differentiated with little or no capacity for repair or proliferation. Unlike skeletal muscle, irreversible injury to myocardial tissue predictably leads to akinesis, fibrosis and thinning.

The purpose of this project is to develop a tissue engineered device to replace myocardial muscle damaged by ischemia or inflammation and to develop a percutaneous catheter system for delivery to the heart using an *in vivo* porcine model.

Key Results: The major accomplishment for the Cardiomyocyte Repopulation project was the first feasibility testing of a novel, catheter-based method for autologous bone marrow stem cell transplantation to heart muscle. This completes this project. It should be noted that as of December 1, 2001, Dr. Stephen Oesterle assumed the position of Vice President of Medtronic, and has there for left Massachusetts General Hospital and CIMIT. Dr. Donald Baim has assumed the role of Acting Program Leader for the Endovascular Devices Program.

Specific Aim 1: To refine percutaneous catheter devices to achieve quantitative myocardial cell transfer.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 2: To develop a tissue engineered system of cardiomyocytes in hydro gel polymer for delivery into both healthy and damaged ventricles.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 3: To evaluate applicability of adult and fetal cardiomyocytes and stem cells as catheter-delivered donors. To devise proper mixtures of hydro gel polymers, and growth factors to support cardiac cells for catheter delivery.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Task 2: Fellowship: Application of Automation and Tissue Engineering to Construct Heart Valves

Principal Investigator: *Jennifer White, MD, MGH, Boston, MA*

Project Completed.

2.2 MINIMALLY INVASIVE SURGERY

Task 1: Minimally Invasive Cardiac Surgery – Endoscopic Coronary Anastomosis

Principal Investigator: David Torchiana, MD and Jennifer White, MD, MGH

This project entails laboratory development of a robotic interface in cardiac surgery to ensure safe and effective clinical application of the technology. 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 sixty-eight laboratory animals. Advancements have been made in the anatomical positioning of instrument ports, internal mammary artery harvesting, and surgical skill in performing a non-beating heart anastomosis using the robotic interface. An upgraded Zeus robotic interface acquired in December 2000 reduced surgical case interruption due to computer errors. Novel instruments including a proximal anastomotic device ("Symmetry", St. Jude Medical, Inc.) and surgical clips ("U-Clip", Coalescent Surgical, Inc.) have been integrated into the procedure.

In the course of this work, it has been appreciated that endoscopic robot-assisted dissection of the internal mammary artery is time consuming and difficult. In humans the vessel tends to course deep in the transversus thoracic muscle and out of the thorascopic view of the surgeon. In an attempt to overcome this problem, manipulation of the robotic interface through CT-image guidance has been developed to assist in the video-endoscopic dissection of the internal mammary artery. Professor Howe's group from Harvard's Department of Engineering has undertaken a joint effort with our laboratory to augment the internal mammary artery (IMA) takedown procedure using computer-assisted computerized tomography (CT) guidance with 3-dimensional surgical instrument registration. The procedure could lead to safer clinical left internal mammary artery (LIMA) dissection, since the intra-operative movement of the robotic interface would be linked directly to the anatomical course of the vessel as "mapped out" by the patient's pre-operative CT scan. In addition, it is expected that successfully linking data obtained from these pre-operative images to the procedure will enable instrument port placement to be optimized for each individual. This new emphasis on pre-operative image guidance should reduce instrument mechanical conflicts and increase the freedom of the instrument's movements to perform the task at hand.

Key Results: The MGH is one of two clinical sites in what will eventually be a five center clinical trial of IMA takedown with plans to enroll 250 patients in all. The institutional and DoD human use approval process is underway for this project. Dr. Torchiana is the Principal Investigator for this trial.

Specific Aim 1: Characterization of FocalSeal surgical sealant as a hemostatic adjunct.

Progress: Project completed. See Quarterly Progress Report for the period January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report for the period January 1, 2001 through March 31, 2001.

Specific Aim 2: Perform acute and chronic evaluation of a new micro-anastomotic device on coronary arteries.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Minimally-Invasive Cardiac Surgery under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 3: Development of a method for video-endoscopic coronary anastomosis.

This Specific Aim is to develop the closed chest E-CABG procedure in the laboratory during the pre-clinical investigation and move into the clinical setting in a four-step process. Laboratory studies directed towards device development and training of the surgical team will continue throughout all four phases. The clinical application will progress over a two-year period with phases of increasing surgical complexity and technical difficulty. Laboratory studies directed towards device development and training of the surgical team will continue throughout all phases.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Minimally-Invasive Cardiac Surgery under Cooperative Agreement No. DAMD17-02-2-0006.

Task 2: Endothelial Activation Markers as Molecular Targets for Innovative, Minimally Invasive Diagnosis and Therapy in Cardiovascular Disease

Principal Investigator: *Michael Gimbrone, MD, Brigham and Women's Hospital, (BWH), Boston, MA*

The endothelial cells (EC) that comprise the lining of the cardiovascular system constitute a dynamically mutable interface in health and disease. In response to various inflammatory, thrombotic and atherogenic pathophysiologic stimuli (e.g., cytokines, coagulation factors, bacterial and tumor products, advanced glycation endproducts, oxidized lipoprotein components, injurious agents, biomechanical stresses), EC can undergo phenotypic modulation to a dysfunctional state that is marked by expression of "activation antigens", such as E-selectin (ELAM-1) and VCAM-1 (Athero-ELAM). The detection of soluble/shed forms of these cell surface markers in serum/plasma is already being utilized as a surrogate index of endothelial dysfunction in certain clinical studies. The team proposes to further exploit these EC phenotypic markers as molecular targets for innovative, minimally invasive diagnostic and therapeutic applications.

Specific Aim 1: To develop a reproducible, robust small rodent model of endothelial activation that combines the use of adenoviral vectors (which can efficiently mediate high-level, localized expression of a given EC activation antigen, precisely where they are introduced into the vascular system), with a simple method of introduction into an anatomically defined vascular

bed. Note: all work involving rats in this overall project has been funded by sources other than the DoD, see Annual Progress Report October 1, 1998 through September 30, 1999.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Specific Aim 2: To apply radiolabeling method(s) that result in high specific activity of labeling of Fab'2 fragments of EC activation antigen-specific monoclonal antibodies, and validate the retention of specificity and avidity of binding to a cultured activated EC monolayer that expresses the target antigen(s) of interest.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Task 3: Develop a Computer Based Three-Dimensional Imaging Treatment Planning System to Drive an Endoscopically Placed, Miniature, Facial Skeletal Distraction Device.

Principal Investigator: *Leonard B. Kaban, MD, DMD and Maria Troulis, MD, MGH*

The significance of this project relates to the development of innovative, minimally invasive techniques for surgical treatment of patients with congenital and acquired craniomaxillofacial deformities. The combination of minimally invasive surgical techniques with the design and implementation of buried, miniature distractors guided by computer manipulated 3-D CT data, will increase operator and patient acceptance, and expand the applications of distraction osteogenesis (DO) to a variety of common craniomaxillofacial problems. There is no currently available system for surgical treatment of craniomaxillofacial deformities which links minimally invasive techniques, miniaturization, and a computer-based treatment-planning program. This concept is unique to the Massachusetts General Hospital, Skeletal Bone Research Center and the BWH Surgical Treatment Planning Laboratory project on DO.

Specific Aim 1: To develop a computer software application for the planning and simulation of an osteotomy and for analysis of the results. To accomplish this Specific Aim the following items will be addressed:

- To document reproducibility of the selected landmarks using both "Multiplanar" and "freehand" methods,
- To update the software and make it compatible with the new version of the "Slicer" and "Visualization Tool Kit" of the Surgical Planning Laboratory (SPL),
- To analyze skeletal changes in 25 pre and postoperative patients treated by distraction osteogenesis,
- To apply the software prospectively for treatment planning a selected variety of

distraction cases, and

- To make the program more user-friendly for clinicians and accessible as a product.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Task 4: Virtual Fixtures for Robot-Assisted Minimally Invasive Cardiac Surgery

Principal Investigator: Robert D. Howe, PhD

This project develops new computer assistance techniques to improve efficiency and increase safety in robot-assisted minimally invasive surgery. Although these techniques will be applicable to a wide variety of robotically assisted surgical procedures, the immediate focus is coronary artery bypass graft (CABG) procedures, where robotic assistance enables minimally invasive techniques, but current robotic procedures are slow and cumbersome.

Specifically, this study develops image-guided virtual fixtures for the internal mammary harvest portion of robot-assisted CABG. In the experiments, the animal undergoes a CT scan before surgery. Small metal pins are inserted percutaneously between the ribs, to provide fixed landmarks for reference during surgery. The resulting image set is processed to define the location of the artery relative to the registration pins. In surgery, the surgeon brings the tip of a robot-mounted calibration instrument into contact with each of the pins. This permits the robot to determine the location of the pins, and thus the location of the artery from the CT image data. A virtual fixture constrains the instrument's motions, as commanded by the surgeon, to appropriate paths adjacent to the artery. In the next implementation, a surgical macro will move the robot along the path adjacent to each artery to dissect it free of the chest wall.

Key results: The CIMIT team is implementing a new approach that uses an electromagnetic tracker attached directly to the tip of the instrument. Based on this more accurate sensor, the team has developed a navigational aid that shows the location of the instrument tip relative to the internal mammary artery.

Specific Aim 1: Develop control techniques for "virtual fixtures" and "surgical macros" that assist the surgeon in guiding robotically positioned instruments.

Progress: The CIMIT team is implementing a new approach that uses an electromagnetic tracker attached directly to the tip of the instrument. Based on this more accurate sensor, the team has developed a navigational aid that shows the location of the instrument tip relative to the internal mammary artery.

Plan: The next step will be implementation of the virtual fixture based on this sensor, which will require interfacing the sensor with the ZEUS robot controller.

Specific Aim 2: Develop image-guided fixtures and macros that use preoperative 3-D patient images to help direct instruments to the appropriate tissues.

Progress: The team is testing the navigational aid described above *in vitro*.

Plan: *In vivo* animal trials of the navigational aid are planned for the immediate future. Once the electromagnetic tracker has been interfaced with the ZEUS controller, the team will proceed with tests of the virtual fixture using this more accurate sensing approach.

Specific Aim 3: Measure the performance of the enhanced system in surgical procedures on animal models in terms of: (i) the improvement in control of surgical tasks; and (ii) the precision attainable with these techniques.

Progress: No activity this year.

Plan: Following implementation of the navigational aid and the new virtual fixture control algorithm based on the electromagnetic tracker, the team will test accuracy and evaluate performance enhancement.

Task 5: Operating Room of the Future

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

The Massachusetts General Hospital (MGH) Surgical Executive Committee and CIMIT have been collaborating over the past year to design and build the Operating Room (OR of the Future). The team has grown in size to include 25 members with backgrounds in Surgery, Gynecology, Anesthesia, Nursing, Biomedical Engineering, Information Systems, Operating Room Management, Architecture, Engineering and Outcomes Measurement. Targeted industrial partners joined the team and are listed below.

The overall goal 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.

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

Team formation, finalizing goals

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Establishing Industry Collaborators

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Testing, Finalizing Room Design

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Identifying Needs, Methods of Tracking Equipment and People

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Identifying Needs and Facilitating Design of Information Integration

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue to design and build the Operating Room of the Future under Cooperative Agreement No. DAMD17-02-2-0006.

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. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue to design and build the Operating Room of the Future under Cooperative Agreement No. DAMD17-02-2-0006.

2.3 IMAGE GUIDED THERAPY

Virtually every device that supports minimally invasive procedures relies on processed images. These images provide preoperative data and guide surgery. While already useful for brain, spine and musculoskeletal surgery, current systems have limitations: the integration is awkward, they slow down the procedures they are intended to facilitate, and data preparation in clinical setting is too time consuming. To overcome such limitations Image Guided Therapy Enabling Technology is developing robust and flexible algorithms that incorporate knowledge about anatomy and pathology and provide intuitive user interfaces.

Task 1: MRI-guided Focused Ultrasound Treatment of Breast Cancer

Principal Investigator: Ferenc Jolesz, MD, BWH

The overall goal of this project is to develop a magnetic resonance imaging (MRI) guided focused ultrasound system for thermal coagulation of breast cancer. The first accomplishment for making clinical breast treatments practical is to develop and test phased array ultrasound applicators that allow the focal spot size to be increased. This is needed for two reasons: A large focal spot allows the tumors to be coagulated in a shorter time, making the treatment time practical. It also reduces the nonuniformities in the temperature field thus assuring better treatment response. Overall, the team has made significant progress using an animal model that will make noninvasive MRI guided thermal coagulation of breast tumors practical for clinical testing.

To study this hypothesis in a clinical setting the team needs to develop sonication and MRI thermometry methods for practical treatments and to test them in animal experiments.

Key Results: The several phased array systems were tested using an animal model and the results were used to develop the final 208-channel phased array system in collaboration with a commercial manufacturer. The results are good, demonstrating the ability of the system to coagulate tumor tissue similar in size and location to breast cancer.

Specific Aim 1: Develop treatment-plan procedures utilizing 3D-MRI information to determine the target volume and execute treatment:

- To evaluate the feasibility of inducing temperatures between 60 and 100°C in tissue volumes required for breast cancer treatments during a 10-60 second sonication.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 2: Study the accuracy of MRI-derived temperature history for calculating the thermal exposure of tissue.

The goal of this Specific Aim is to test and evaluate the feasibility of using MRI thermometry to estimate the temperature and thermal dose induced by the sonications and to test its accuracy. The team used *in vivo* animal tissues for these tests.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 3: Establish the thermal exposure required to assure complete tumor coagulation.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 4: To test Specific Aim 3 in implanted rabbit tumors.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 5: To evaluate the influence of fat and tissue motion on the MRI dosimetry.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Task 2: Early Detection and Ablation of Epithelial Cancers

Principal Investigator: *Norman S. Nishioka, MD, MGH*

Subtask 1: ALA Enhanced Fluorescence Imaging of Barrett's Epithelium

Note: We will be forwarding written correspondence regarding our intention to withdraw this study.

This study will investigate the use of aminolevulinic acid (ALA) to enhance the fluorescence signal from dysplastic cells in the esophagus in the specific case of Barrett's esophagus. High-grade dysplasia in Barrett's esophagus has been known to progress into adenocarcinoma. Patients diagnosed with Barrett's usually require long-term endoscopic surveillance. While

Barrett's epithelium is easily detected on endoscopy, regions of dysplasia cannot be easily visualized with white light. The results of previous studies have demonstrated the potential of this method to identify and localize pre-malignant regions of the esophagus that cannot be seen during routine endoscopy. This study will determine the accuracy of orally administered ALA in marking dysplasia and develop, test and improve the endoscopic system for fluorescence detection in the esophagus.

Specific Aim 1: Determine the accuracy of orally administered ALA for marking dysplasia occurring in Barrett's esophagus.

Progress: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Plan: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Subtask 2: OCT Imaging of Esophageal Lesions

Principal Investigator: *Norman S. Nishioka, MD, MGH*

Note: We will be forwarding written correspondence regarding our intention to withdraw this study.

The goal of this project was to determine the clinical utility of OCT for imaging lesions in the gastrointestinal (GI) tract. Modern gastrointestinal endoscopy is a potent diagnostic and therapeutic technique for the management of a wide variety of GI disorders. However, one limitation of conventional endoscopy is the inability to visualize structures beneath the mucosal surface of the GI tract. The advent of endoscopic ultrasound has made it possible to visualize subsurface structures in many settings, but the instrumentation is expensive and the spatial resolution is limited by the transducer operating frequency (<30 MHz). Optical coherence tomography (OCT) is an alternate technique for obtaining high-resolution cross-sectional images of tissue. The operating principles of OCT are analogous to ultrasound except that light waves are used to image tissue rather than acoustic waves. The spatial resolution of OCT is approximately 10 times better than that of the best ultrasound devices.

Specific Aim 1: Perform a pilot trial of OCT in unselected patients undergoing upper endoscopy to assess the spatial resolution and clinical usability of the present system.

Progress: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Plan: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Task 3: Segmentation of Bone from CT and Vessels from MRA Data

Principal Investigator: Carl-Fredrik Westin, PhD and Ron Kikinis, MD, BWH

The broad goal of this 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: The team has introduced a new image feature, based on local phase, which describes local edge symmetry independent of absolute gray value. The phase is a natural bi-product from the filters used in the adaptive filtering scheme presented last year in the project. Because phase is amplitude invariant, the measurements are robust with respect to smooth variations, such as bias field inhomogeneities present in all MR images. In order to enable validation of the phase-wire segmentation software, a system has been created that continuously records user interaction and automatically generates a database containing the number of user interactions, such as mouse events, and time stamps from various editing modules.

Specific Aim 1: To implement a data enhancement scheme for segmentation of bone from CT and vessels from MRA.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To implement a data enhancement scheme for segmentation of bone from CT and vessels from MRA.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3: Optimization and Validation: to quantitatively validate and optimize the automated segmentation method results.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3.1: Optimization and Validation: validation of phase-wire segmentation software.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 4: Extend out current implementation of adaptive filtering to incorporate interpolation to a finer grid.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 5: To develop a segmentation model based on the team's experience on adaptive filtering and surface evolution.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Task 4: Real-time Registration of Intra-operative Ultrasound with Pre-operative CT/MR for Image Guided Therapy

Principal Investigator: *Eric Grimson, PhD, Massachusetts Institute of Technology (MIT), Cambridge, MA*

The utility of minimally invasive therapy depends, in no small measure, on the ability to precisely deliver therapy to the targeted site. The efficacy of image-guided therapies is now well documented in the literature for such applications as tissue biopsy, cryotherapy, brachytherapy, and energy delivery. For the most part, however, image guidance requires expensive intra-operative equipment (e.g., intra-operative MRI), ionizing radiation (e.g., fluoroscopy, CT), or is limited to surface (e.g., luminal) imaging of areas accessible through videoendoscopic tools. Although inexpensive, non-ionizing, subsurface-capable, and portable, ultrasound imaging has not found the widespread usage that one might expect, due largely to the poor-contrast, specular noise, and unintuitive nature of ultrasound imagery. In this proposal the team aimed to demonstrate a novel new method for improving the visualization quality of intra-operative ultrasound imagery. Specifically, because of the overwhelming preference of users for high-contrast CT/MR imagery, and since such imagery are frequently acquired pre-operatively, the team aimed to demonstrate the ability to register these high contrast pre-operative imagery to yield the same view as the intra-operative ultrasound. The approach enabled, effectively, an intra-operative CT/MR imagery from which image guidance can be performed, but without incurring the costs and risks associated with continuous CT/MR imaging.

Specific Aim 1: Demonstrate the ability to register pre-operative CT/MR, in a non-real-time manner, so that point-to-point correspondence to an intra-operative ultrasound can be obtained.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Specific Aim 1.1: Select a set of surface points from MR/CT, and use ICP to match the points to edges in ultrasound. This result provides an initial correspondence between the two data sets.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Specific Aim 1.2: Explore numerous variations on polynomial warping methods which included the following: variation of the number of corresponding points; variation of polynomial order; variation of the point set distribution; and error verification to measure sensitivity in our computed registration errors.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

2.4 TISSUE ENGINEERING

The field of Tissue Engineering is now maturing and undergoing explosive growth. Virtually every tissue and organ of the body has been studied. Many tissue engineering technologies are becoming available for human use. Over time, several techniques to engineer new living tissue have been studied. Technologies include the use of growth factors to stimulate wound repair and regeneration, techniques of guided tissue regeneration using non-living matrices to guide new tissue development, cell transplantation, and cell transplantation on matrices. Recent studies in stem cell biology has led to studies of populations primordial cells, stem cells or embryonic stem cells to use in tissue engineering approaches.

Task 1: Degradable Conductive Polymers

Principal Investigator: Robert Langer, ScD, MIT

Electroactive polymers, which constitute a unique class of synthetic polymers, possess the ability to inter-convert chemical, mechanical, thermal and optical perturbations into tiny electrical currents. This property can be exploited to play an important role in the interfacing of the external environment with biological systems. Electronically conductive polymers are especially attractive in that, they can not only be employed as guidance channels or substrates for tissue culture but can also potentially be utilized as a medium to subject the adhered tissue (cells) to an electrical stimulus. The team has shown that electrical stimulation of neuronal and mesenchymal progenitor cells adhered to conductive oxidized polypyrrole (Ppy) substrates, in presence of soluble morphogens and growth factors can aid in the lineage specific differentiation of these cells. In its traditional chemical form oxidized Ppy is non-degradable and is minimally processible. A more processible and bioerodible Ppy would be particularly important for applications wherein a PPy coating is used to alter the surface characteristics or tissue response to a prosthetic for a well-defined period such as coating of a vascular stent to minimize smooth muscle proliferation and restenosis. One can also envision coating of metal or carbon composite or other polymeric orthopedic prosthesis with conductive polymers such as polypyrrole to improve tissue compatibility and adherence of the implant to surrounding tissue. Furthermore, from a tissue-engineering standpoint, it would be ideal if the conductive polymer matrix served as a template for the desired period and underwent degradation thereafter thus eliminating any potential long-term undesirable tissue response.

Key Results: The team has synthesized and characterized a novel family of Ppy's. These polymers have been shown to undergo dissolution/erosion under physiologically relevant conditions *in vitro*. The team has also demonstrated that the erosion rate of these substrates may be modulated by the judicious choice of the ionizable end group in the alkyl moiety at the beta position on the pyrrole ring.

Specific Aim 1: To synthesize degradable analogs of the conductive polymer PPy, as well as water soluble analogs, and to study the degradation and cytocompatibility characteristics of these polymers.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: Project completed.

Task 2: Polymer-based Gene Delivery Platform

Principal Investigator: Robert Langer, ScD, 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 of the current grant period has been directed toward the continued development of new polymeric "proton sponge" materials and the development of a mechanistic understanding through which these materials mediate transfection. The team is nearing completion of a collaborative effort with investigators at the University of California at San Francisco to investigate their most promising polymers for the delivery of therapeutic HIV vaccines in mouse models. The work conducted toward Specific Aim 2 in recent quarters has been directed toward the development of a parallel synthesis and screening strategy for the discovery of new degradable polycations useful as gene delivery vectors and pH-responsive materials for enhanced intracellular delivery.

Key Results: The team has continued development on the first accelerated discovery approach for finding synthetic transfection vectors. This year, the team has begun the synthesis of a library containing up to 3,500 individual polymers. In the near future, this library will be screened for gene transfer efficiency. Work has also been done to further characterize the polymers in the original poly(β -amino ester) library. The library was characterized along the following dimensions: (1) effective diameter of polymer-DNA complexes, (2) zeta potential of polymer-DNA complexes, and (3) relative uptake of complexes by 3T3 cells.

Specific Aim 1: To synthesize a polymer-based gene delivery system that on the molecular level mimics viruses.

Progress: As discussed in the previous quarter, the team initiated a collaborative project with Prof. Chris Locher in the Department of Virology at the University of California at San Francisco (currently at Maxygen, Inc.) to conduct a head-to-head *in vivo* comparison of naked DNA, liposome formulations, and the team's "proton sponge" polymers using a therapeutic HIV vaccine and a mouse model. Based on experiments concluded this year, Prof. Locher has recently submitted a paper for publication.

Specific Aim 2: To synthesize new degradable polymers for use as gene transfer vectors, and to investigate the degradability, cytotoxicity, and ability of these polymers to condense and/or encapsulate DNA into particles suitable for transfection.

Progress: Last quarter, the team used preliminary high-throughput screening assays to identify two polymers that yield gene expression in model cell lines at levels surpassing those of both PEI and Lipofectamine 2000, two leading polymeric and liposomal transfection agents. The team continues to investigate 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 year, the team has characterized this library along the following dimensions: (1) effective diameter of polymer-DNA complexes, (2) zeta potential of polymer-DNA complexes, and (3) relative uptake of complexes by 3T3 cells. See Figures 1-3 below.

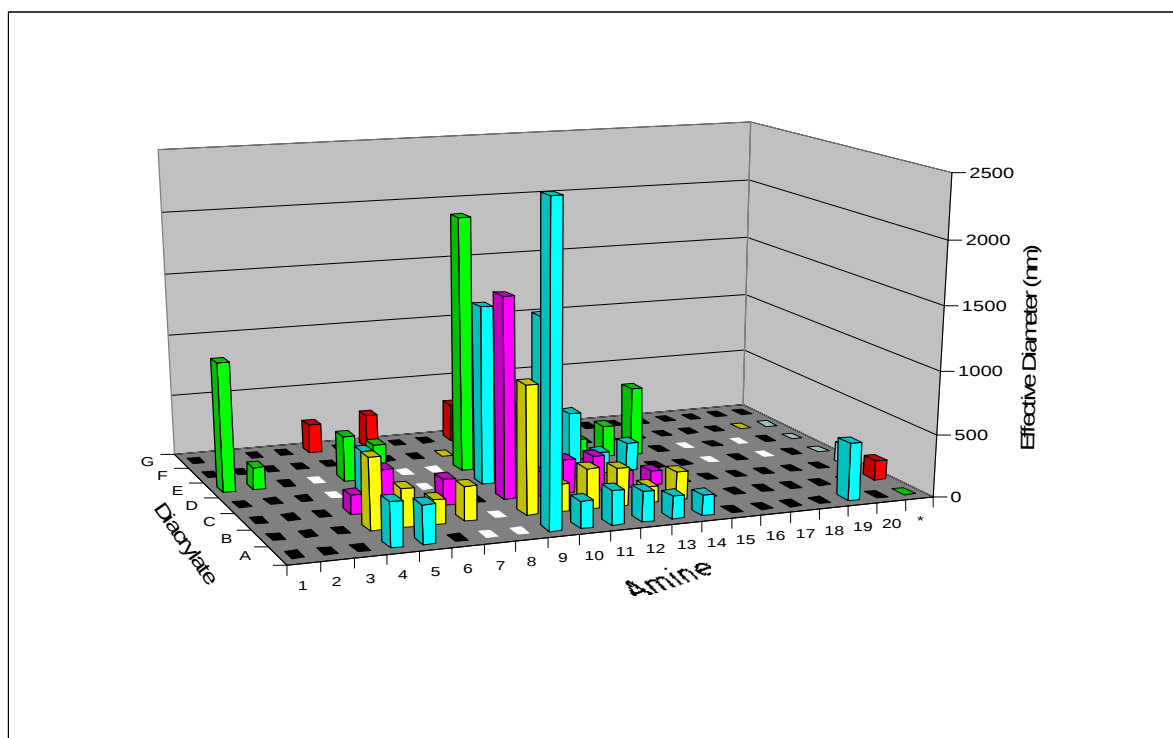


Figure 1: Effective Diameter as a function of polymer structure. Complexes were formed at DNA:polymer weight ratios of 1:20. Effective diameter determined using laser-light scattering in 10 mM Hepes buffer pH 7.2.

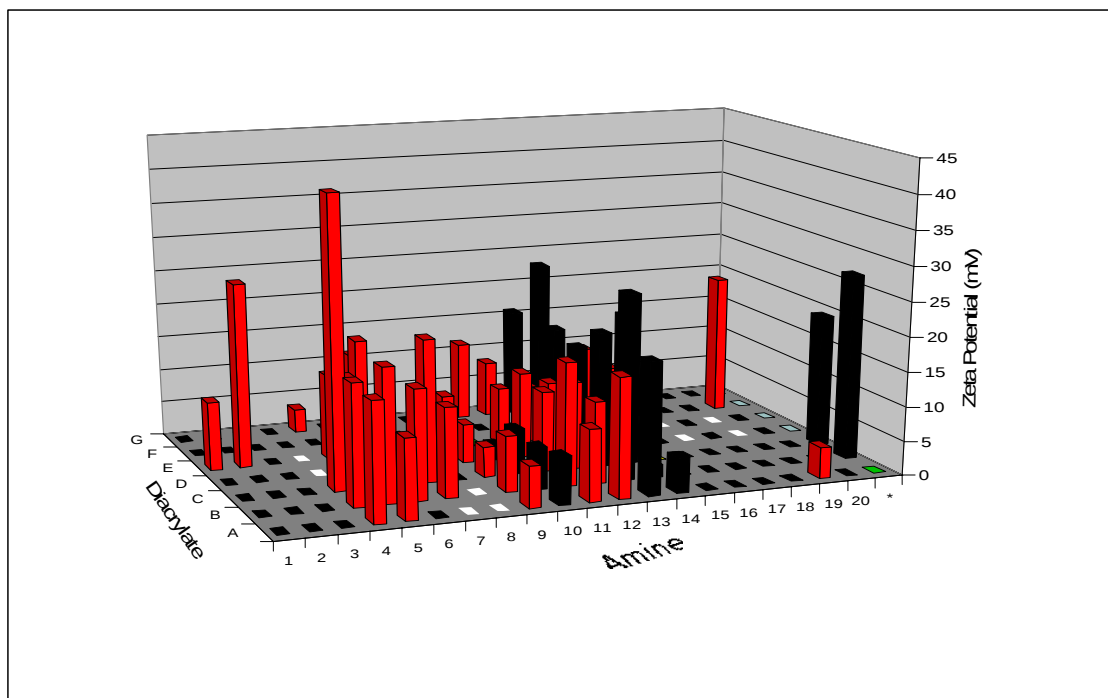


Figure 2: Zeta potential of DNA-polymer complexes as a function of polymer structure. Red bars indicate positive zeta potential values, while black bars indicate negative zeta potential values.

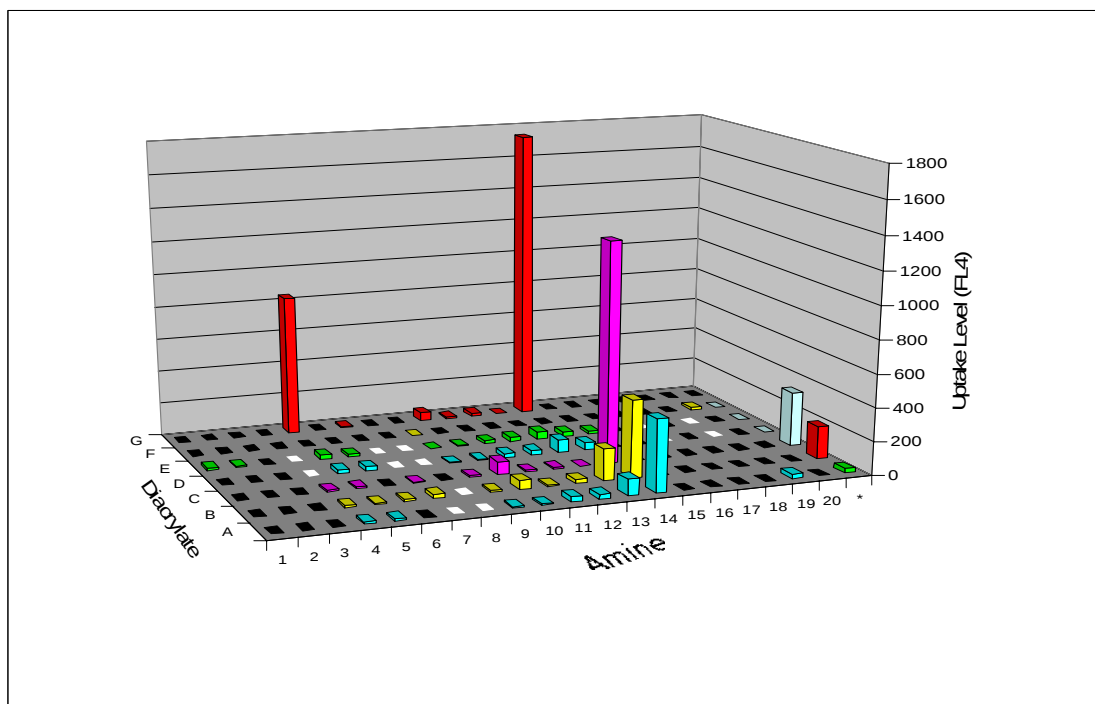


Figure 3: Relative uptake level of DNA-polymer complexes by NIH 3T3 cells as a function of polymer structure. Red bars indicate positive zeta potential values, while black bars indicate negative zeta potential values.

The team has also initiated the synthesis of larger libraries of polymers (up to 3,500 chemically distinct structures) based on their initial technology. In the near future, these libraries will be screened to identify polymers that mediate high levels of gene transfer.

Plan: To continue new research in Degradable Conductive Polymers under Cooperative Agreement No. DAMD17-02-2-0006.

Task 3: Transdermal Drug Delivery and Chemical Sensing for Neonates using Skin Electroporation

Principal Investigator: James C. Weaver, PhD, MIT

Our research into an improved method of transdermal drug delivery has yielded two major results. First, a new method for creating transdermal microconduits has been developed, which will be reported in a paper to be submitted for publication. Microconduits can be used for drug delivery and for interstitial fluid sampling. Second, a new method for carrying out function-based simulation of transport of charge, heat and molecules has been developed, and this will also be reported in a manuscript that is being written for submission to a scientific journal. The simulation has the potential to increase the productivity of research and development of minimally invasive technology, such as drug delivery protocols and devices that interface with tissue. This new, presently unpublished method was partially developed during our investigation of the skin's response to electrical pulses.

While investigating the optimization of microconduit creation in the skin's stratum corneum (SC), the team has continued to seek understanding about how the multilamellar bilayer membranes within the SC are electroporated. This remains key to understanding how safe keratolytic agents are delivered into the SC, and how brief, highly localized heating takes place.

Key Results: During the past year new approach to computer simulation of spatially complex systems was identified. The team has obtained very encouraging results for a simulation of the transport of potent agents through the skin due to exposure of a small amount of the compound to the surface of the skin.

Specific Aim 1: Optimize parameters for creation of microconduits in hairless rat skin *in vitro*.

Specific Aim 2: Determine transdermal transport of aqueous solution through microconduits *in vivo* in hairless rats.

Specific Aim 3: Creation and partial optimization of microconduits in neonatal skin *in vitro*.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Task 4: Synthesize Vascularized Living Systems from the Platform of Two-Dimensional Silicon Microfabrication Technologies and Adapt to Three-Dimensional Living Devices***Principal Investigator: Joseph Vacanti, MD, MGH***

See section 1.2, Highlight Project on page 11.

Task 5: Synthesize Vascularized Living Systems from the Platform of Three-Dimensional Printing Technology***Principal Investigator: Joseph Vacanti, MD, MGH and Jeffrey Borenstein, PhD, Draper Laboratory, (DL), Cambridge, MA***

Significant progress in the development of new microfluidic designs, materials and fabrication processes has been made in the previous quarter. New fluidic network designs for the extension of existing 2D networks into the third dimension have been generated, and preliminary fabrication work on the 3D networks has begun. A novel material known as biorubber, recently developed by Professor Robert Langer's group at MIT, has been tested using microfabrication processes. Finally, significant progress on the development of high-resolution microfabrication processes for biodegradable polymers has been made.

Key Results: Over the past year, the new designs described in the last progress report have become the baseline for cell culture studies. These designs, labeled TESTNET0, TESTNET1 and TESTNET2, are smaller, more modular and simpler to produce. They are based upon low-cost layout and mask-making technology and provide for uniform flow.

Specific Aim 1: Design and fabricate silicon and Pyrex based systems providing an array of etched channels to act as a mold for generating a living network in two dimensions. To accomplish this Specific Aim the following items will be addressed:

- Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold,
- Design bioreactors to house the device during tissue formation and folding,
- Develop assays to study the generation of tissue and its histologic, biomechanical, and biochemical parameters,
- Investigate mechanisms of tissue development using molecular markers for gene developmental programs and programs of wound healing and regeneration, and
- Begin animal implantation studies to begin to understand perfusion, survival, and function of the living device, and
- Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold.

Design and fabricate silicon and pyrex based systems providing an array of etched channels to act as a mold for generating a living network in 2 dimensions

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Tissue Engineering under Cooperative Agreement No. DAMD17-02-2-0006.

Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Tissue Engineering under Cooperative Agreement No. DAMD17-02-2-0006.

Task 6: Minimally Invasive Meniscal Repair with Tissue Engineered Cartilage***Principal Investigator: Thomas J. Gill, MD and David J. Zaleske, MD, MGH***

Recent findings demonstrate that a cell-based therapy could be one therapeutic approach for repairing tears in the avascular zone of the knee meniscus cartilage. In previous studies in the nude mouse model, articular chondrocytes seeded onto a devitalized meniscal cartilage scaffold were able to bond the edges of a meniscal tear. Those studies were performed in a vascular subcutaneous environment, which is different from the avascular articular environment of the knee joint. The studies performed over the past year demonstrated that the same goal could be achieved in the articular environment in a large animal model. The results of the first year of investigation demonstrated that this tissue engineered approach could repair the knee meniscus when a lesion involves the avascular inner third. Although further investigation is still needed to define the best delivery material and the best pre-seeding conditions of the reparative cells onto such a scaffold, the team believes that a clinically applicable approach combining this technique with arthroscopic surgery might be soon developed.

The Specific Aims of this project are: 1) to demonstrate that chondrocytes, seeded onto a matrix scaffold, can be used as valid therapeutic approach to achieve a secure meniscus repair in a preclinical orthotopic model; and 2) to investigate other cell sources and different absorbable materials for cell scaffolding to accomplish a minimally invasive meniscus repair technique. In previous studies in the nude mouse model, articular chondrocytes seeded onto a devitalized meniscal cartilage scaffold were able to bond the edges of a meniscal tear. Results from these studies demonstrate that a cell-based therapy could be a useful therapeutic approach for repairing tears in the avascular zone of the knee meniscus cartilage.

Key Results: Studies performed over the past year demonstrated that a cell-based therapeutic approach can be used in the articular environment in a large animal model of meniscal tears. Further investigation during the second year sought to define the best delivery material and the best pre-seeding conditions of the reparative cells onto candidate scaffolds. A clinically applicable approach combining this technique with arthroscopic surgery might be developed based on these studies.

Specific Aim 1: To demonstrate that chondrocytes, seeded onto a matrix scaffold, can be used as valid therapeutic approach to achieve a secure meniscus repair in a preclinical orthotopic model.

Rationale: During the past year, the team has demonstrated meniscal healing in a nude mouse model, using articular cartilage chondrocytes as the cells source and devitalized meniscal chips as structural support for chondrocytes. The central hypothesis of this project is that a lesion in the meniscus can be repaired using isolated autologous cells seeded onto a scaffold material. The scaffold could be allogeneic devitalized meniscal tissue or other synthetic materials to be investigated. The cells could be chondrocytes or other cell population, stimulated to chondrogenic differentiation. The cell-seeded construct would be then interposed in the meniscal lesion and secured in place. Healing would be achieved by the bonding capabilities of the cells. The goal of this section will be to develop and refine the model for creating a reproducible meniscal injury in the medial meniscus of pigs. Once this goal is achieved, new constructs or variables to be investigated in subsequent stages of the project will be tested in the same fashion for consistency.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 2: To investigate other cell sources and different absorbable materials for cell scaffolding to accomplish a minimally invasive meniscus repair technique.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Task 7: Development of a Novel *in vivo* Recombinant Protein Delivery Device Designed to Regress Abnormal Tissue: Recombinant Human Müllerian Inhibiting Substance (rhMIS) Producing Cells on Biodegradable Matrices

Principal Investigator: David T. MacLaughlin, PhD, MGH

A major problem impeding progress in using complex human proteins as therapeutic agents against disease including cancer is producing sufficient quantities for use in a cost-effective manner and the development of a suitable and effective system to deliver these proteins to patients. Most of these proteins are complex macromolecules consisting of subunits and/or covalently attached substituent groups. In Nature they are produced in extremely small quantities and it is impossible to purify enough for use in the clinic. Therefore, there are significant problems to overcome before the cost-effective production of sufficient quantities of highly purified proteins as drugs can be accomplished. Modern cloning strategies have created organisms that produce large quantities of the proteins that still needed to be purified for clinical use. These methods are expensive, have modest yields and they reduce biological potency. Our project is designed to eliminate both the requirement for *in vitro* production facilities and the need to purify the proteins. We used Müllerian Inhibiting Substance (MIS) as a model protein and the treatment of ovarian cancers *in vivo* as a biological assay to test the hypothesis that bio-engineered implantable tissue could be used as a drug delivery system.

Key Results: Resorbable polyglycolic acid biopolymer matrices impregnated with cells transfected with the MIS gene were successfully implanted in over 80 immuno-compromised mice and bioactive MIS produced and absorbed by the blood stream. The effect of different sized biopolymer implants on the resulting serum MIS concentrations was also determined.

Specific Aim 1: Determine *in vivo* pharmacokinetics of recombinant human MIS produced on degradable biopolymer matrices implanted into SCID mice by transfected clonal CHO B9 cells.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new MIS research under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 2: Determine if the recombinant human MIS produced by transfected CHO B9 cells inhibit growth of human ovarian carcinoma cell lines transplanted beneath the renal capsule of SCID mice.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new MIS research under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 3: Harvest autologous fibroblasts from patients with ovarian cancer, transfect them with the human MIS cDNA, and re-implant mesh impregnated with the patients own MIS producing transfected cells into the peritoneal cavity, using laparoscopic minimally invasive techniques.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue new MIS research under Cooperative Agreement No. DAMD17-02-2-0006.

Task 8: Determine the Role of Mesenchymal Stem Cells in Fetal Tissue Engineering

Principal Investigator: *N. Scott Adzick, MD, University of Pennsylvania (UPenn) and Children's Hospital of Philadelphia (CHOP) and Alan W. Flake, MD, CHOP*

The overall goal of this research is to define the tissue engineering potential of mesenchymal stem cells (MSC). During this past year, the team has made considerable progress in isolating, expanding, and documenting the *in vitro* multipotential differentiative capacity of fetal liver derived mesenchymal stem cells in sheep. The team has also established site-specific differentiation of adult bone marrow derived human mesenchymal stem cells in the fetal sheep model after prenatal systemic administration.

The team has successfully tissue engineered bone marrow using principles derived from known mesenchymal stem cell biology and tissue engineering. These accomplishments have been documented in a number of oral and poster presentations at national meetings as well as in manuscripts, either published or in progress.

The team has formed collaborations with Dr. Catherine Verfaillie at the University of Minnesota (human and mouse MSCs), Dr. Johnny Huard at the University of Pittsburgh (muscle progenitor cells), and Dr. Paul Simmons from Melbourne (Mouse MSC) to investigate the relative merits of these various promising cells in our fetal models. In addition, the team is applying their low density culture techniques to sheep fetal liver derived MSC to isolate a small phenotype fetal cell with multipotential capacity. Simultaneously, the team has been developing lentiviral vectors to apply to these cells to manipulate their *in vivo* biology. The team has developed lentiviral vectors for MyoD (drives MSCs toward muscle differentiation), Pax7 (an upstream transcription factor from MyoD which regulates MSC to muscle progenitor differentiation), and are working on a

vector for Hox4B (a stem cell proliferation regulatory homeobox transcription factor) which the team will test *in vivo* in future experiments.

Key Results: The team made significant progress toward the clinical utilization of mesenchymal stem cells. Due to progress from other investigators in the field, it is clear that a mesenchymal stem cell of small phenotype, rather than the large fibroblastic phenotype used in our previous studies, has significantly greater differentiative capacity *in vitro*, and contains a higher frequency of CFU-f forming cells.

Specific Aim 1: Determine the multipotential differentiation of sheep mesenchymal stem cells *in vitro*.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 2: Determine site-specific differentiation of mesenchymal stem cells in the developing fetus.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 3: Establish clinically applicable methods to isolate and expand mesenchymal stem cells in the sheep.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 4: Apply the principles of mesenchymal stem cell differentiation to the concept of tissue engineering by organizing mesenchymal stem cells on a biodegradable polymer and implanting the construct *in vivo* for tissue reconstruction.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

2.5 SIMULATION

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: Discover Enabling Technologies for Medical Simulation

Principal Investigator: Steven L. Dawson, MD, MGH

The CIMIT Simulation Group continued to make progress on multiple fronts during the past year. On the research side, the team has begun design of the CAML framework for simulation development, began collaborations on source code sharing with Stanford University, and started new initiatives in validation of the VIRGIL® system and surgical skills trainers. On the applications side, the team has redesigned the VIRGIL Training System infrastructure to improve reliability and robustness, the team has designed a skills assessment training system. Also, the team has installed the equipment needed to provide on-site manufacturing capability on the Landsdowne Street facility.

From the intellectual property perspective, the team has continued negotiations with Limbs and Things on patent protection, and we were notified that the VIRGIL trademark has been accepted, so that VIRGIL is now VIRGIL®. The technological advances that VIRGIL® represents attracted the attention of Ascension Technologies, the manufacturer of the mini-BIRD tracking devices used in the system. As a result of our creative use of tracking, Ascension has joined the CIMIT Industrial Liaison Program, and will be working closely with us to further refine the abilities of position tracking tools in medical applications.

Together with TATRC, the team participated in the 2002 Medicine Meets Virtual Reality meeting in Newport Beach, California, demonstrating VIRGIL® to computer scientists and simulation developers as a member of the TATRC demonstration booth. Group members presented at the TATRC principal investigator's review and the Simulation Challenges Workshop, and presented an original scientific paper on tissue property measurements ("*In vivo* measurement of solid organ visco-elastic properties").

While at the MMVR meeting, the team convened two separate sessions of the CAML consortium, bringing together representatives from MGH, the National Center for Medical Simulation, the Stanford CASS group, the National Biocomputation Center at Stanford, ETH Zurich, and the University of Tübingen.

Over the last year, group members have submitted two scientific papers to the Medical Image Computing and Computer Aided Interventions (MICCAI) 2002 meeting. We anticipate that these works will be accepted for this rigorous and prestigious international meeting. Mark Ottensmeyer collaborated with Cynthia Bruyns at the National Biocomputation Center at Stanford University on a work comparing *in vitro* soft tissue properties and finite element models in a virtual animal model ("The Development of a Physically Based Virtual Animal Model using

Soft-Tissue Parameter Testing”). We also submitted a paper that presents the early results of our new initiative in validation of surgical skills (“Metrics for Laparoscopic Skills Training: The Weakest Link”).

In February, Daniel Kalanovic, a research surgeon from Tübingen, Germany began a six-month research fellowship with the Simulation Group, funded by a grant from the German government. Daniel will be working with Mark Ottensmeyer, comparing experimental methods and results from the Tübingen group with our results.

Lastly, the CIMIT Simulation team hosted a visit to VIRGIL® by Representatives Murtha, Capuano, and Lynch from the US Congress, during their CIMIT visit on March 18th.

Specific Aim 1: Tissue Modeling - Develop tools capable of *in vivo* measurement of soft tissue characteristics, including:

- Haptics-Enabled force feedback of tissue data to render tissue manipulation realistic,
- Geometric modeling and visual feedback - recreate on the monitor screen a believable representation of tissue-tool interactions,
- Integration of physiology into computerized representations of procedures, and
- Development of a common anatomic modeling language (CAML) to achieve integration of physiology into computerized representations.

Progress: Project completed.

Plan: To continue Medical Simulation research under Cooperative Agreement No. DAMD17-02-2-0006.

2.6 NEW INITIATIVES

The New Initiatives Enabling Technology provides an incubator for approaches to clinical problems that are likely to evolve into novel therapies and outcomes analyses that can be applied to a variety of medical problems. As these approaches mature, they will be made available to other Enabling Technologies.

Task 1: Lung Volume Reduction Using a Bronchoscopic Approach

Principal Investigator: *Edward P. Ingenito, MD, BWH*

The objective of lung volume reduction is to eliminate dysfunctional, overinflated regions of the lung. Results similar to surgical resection have been obtained by plication and stapling without tissue removal, as well as by laser directed tissue ablation. These observations suggest that removal of the dysfunctional tissue is not required. A procedure that eliminated the participation of dysfunctional tissue in the breathing process would suffice.

There have been no detailed studies on the lung mechanical effects of experimental emphysema in large animals. It is useful to know the specific changes in lung mechanics with emphysema induction to deploy the animal model for studies of novel emphysema interventions. Specifically, the team wished to understand the effects of papain to induce emphysema on airway and tissue resistance and elastance, since diseases such as emphysema may harbor both parenchymal and airway abnormalities concomitantly. To do so, the team employed a method of optimal waveform ventilation for measurement of dynamic airway and tissue mechanics, and static measurements of elastic recoil and functional residual capacity. The goal was to demonstrate that parenchymal disease induced by papain was similar to human emphysema. Hence, this project entailed two scientifically novel features: 1) the development of a reproducible model of diffuse emphysema in sheep using aerosols of papain, and 2) the characterization of the disease process using optimal waveform ventilation (OWV) in addition to static mechanics.

Specific Aim 1: To compare short term (1 month) and long term (3 month) survival, physiological responses, surgical complications and lung histopathology in control sheep (untreated, non-emphysema) following either standard surgical plication lung volume reduction or bronchoscopic lung volume reduction (BVR).

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To compare short and long term survival, physiological responses, complications, and lung histopathology in sheep with emphysema (generated by papain exposure) treated either with SPVR or BVR.

Volume reduction therapy (VRT) for emphysema involves removal of hyper-expanded, dysfunctional lung, which increases recoil, improves tethering, and recruits previously

compressed lung. This has traditionally been accomplished by surgical means. The team describes a bronchoscopic method of VRT in which fibrin glue containing pro-fibrotic growth factors is used to collapse and scar emphysematous lung.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Task 2: Outcome Assessment in Menorrhagia

Principal Investigator: *Johanna Bosch, PhD, MGH*

Minimally invasive treatments have been developed to treat menorrhagia. Evaluation studies comparing these therapies with traditionally performed therapies, such as hysterectomy, are needed to help physicians, patients and policy makers to make informed decisions. Therefore, appropriate (i.e., preference based and from the community at large) quality-of-life data and the assessed relative benefits and cost-effectiveness of new therapies are needed. In this study, we assess the quality of life in women with menorrhagia using existing utility assessment instruments, a simple preference-based instrument (the binary-gamble method) will be developed further to assess community preferences, and a decision model to perform cost-effectiveness analyses of minimally invasive therapies for menorrhagia is being developed.

Key Results: The CIMIT team has developed a self-administered questionnaire including the Health Utilities Index and EuroQol-5D to collect quality-of-life data in patients with menorrhagia. Upon the patient survey and its data analyses, the binary-gamble method will be used to assess community preferences for menorrhagia in a sample of the general population.

Specific Aim 1: To assess quality of life in women with menorrhagia using the HUI and the EuroQol-5D.

Progress: Currently, the CIMIT team has developed the questionnaire with the research staff at the DATA Group, and research staff in the Department of Gynecology to evaluate quality of life, general health status, and out-of-pocket and time costs in patients with menorrhagia. Innovative quality-of-life methods have been incorporated into the cross-sectional survey. Because standard quality-of-life instruments such as EuroQol, HUI, or the visual analogue scale are intended for chronic conditions, they are unsuitable for use for patients with menorrhagia, a condition that primarily affects women in monthly episodes. A modified version of these instruments is being used and the feasibility of this type of research will be assessed. We believe that this type of methodology can be applied to other episodic health conditions as well. The research staff at the Department of Gynecology has recently moved to another hospital, which has delayed the recruitment of patients. The team will now seek final DoD approval of the staff relocation before initiating the study.

To estimate out-of-pocket expenses, patients are asked about their extra expenses due to the condition (such as clothes, underwear, bedlinen, furniture, tampons, pads). To estimate time

costs, patients are asked about the number of days unable to go to work and/or unable to do their normal activities due to the condition.

This completes this project.

3.0 CLINICAL CHALLENGES

3.1 TRAUMA AND CRITICAL CARE

The Trauma and Critical Care Clinical Challenge is developing new, efficient technologies that reduce morbidity and mortality from trauma and critical illness. These developing technologies lessen: the time required for recovery, the pain and suffering associated with therapy, and the overall cost of patient care.

Task 1: Microsensors – Real-Time Blood Assay

Principal Investigator: Christopher Dube, PhD, Draper Laboratory, Cambridge, MA

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.

Key Results: The key milestones of the past year include: **1)** Repeatable detection of the microbial pathogen *E. coli* O157:H7 using individually functionalized μ CANARY elements. In the previous quarter the CIMIT team demonstrated detection of *E. coli* O157:H7 using commercially available antibodies. This past year we have repeated *E. coli* O157:H7 detection and verified the detection sensitivity; **2)** Demonstration of specific binding of *E. coli* O157:H7 to the anti-*E. coli* O157:H7 by showing a lack of binding of *E. coli* O157 knockout strain that does not express the O157 antigen. This was a very significant milestone because our detection relies on the specificity of the affinity coating for the target organism, and this was nicely demonstrated this past year; **3)** Refinement of the molded PDMS microfluidic flow distributor and adoption of a SOP for detection of *E. coli*. 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 μ CANARY sensor into a sensor system since this system requires that the sensor be replaced periodically. The projects final accomplishment (4) relates to the identification of peptide sequences that are specific to the three different *E. coli* variants under investigation. This work was done in conjunction with 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. These ALRs will be used in conjunction with the μ CANARY sensors for detection of microbial pathogens. Although we have had very good results with our efforts to detect *E. coli* organisms, the team has been less successful with detection of DNA. This past year we began development of the μ CANARY sensor for DNA hybridization reactions. This involves attachment of biotinylated ssDNA to the μ CANARY surface, followed by detection of the complementary strand using the μ CANARY sensor. We were not able to detect the hybridization of the trial target sequences with the μ CANARY sensor, and so the team went back to developing a fluorescent assay (Rhodamine dye) to evaluate the attachment of the ssDNA to the surface, to be used in parallel with the μ CANARY sensor. The eventual application for DNA-based sensing is the identification of *E. coli* strains, based on the strain typing polymorphs developed by our MGH partner Dr. Stephen Calderwood and his group.

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.
- Sensor system development.
- Sensor surface chemistry.
- 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.

Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue Microsensor research under Cooperative Agreement No. DAMD17-02-2-0006.

Task 2: Application of Microwave Imaging to Rapid Non-Invasive Detection of Intracranial Hematoma

Principal Investigator: *Lt Col Geoffrey S. F. Ling, MD, PhD, Uniformed Services University of the Health Sciences, (USUHS), Bethesda, Maryland*

Trauma care has advanced remarkably over the past 20 years. A leading contributor is the introduction of treatment algorithms taught in Advanced Trauma Life Support (ATLS) and Advanced Cardiac Life Support (ACLS) courses. In practice, to use these algorithms, medical providers must have adequate training and appropriate diagnostic tools. It is the lack of both that has prevented military first providers (combat medics) from meeting this standard of care.

The Radio Frequency Triage System (RaFTS) unit is a handheld device facilitating the diagnosis of severe combat injuries directly on the far-forward battlefield. The prototype concept utilizes the detection of the physical modulation of radio frequencies by living tissue to transmit or backscatter radio frequencies based on the physical dielectric constant inherent in different tissues. This device will provide combat medics with patient vital signs, electrocardiogram (EKG), percent blood oxygenation and ability to diagnose common occult trauma conditions, e.g., intracranial hemorrhage and pneumothorax.

Specific Aim 1: To demonstrate the feasibility of applying the microwave diagnostic tool to accomplish the following:

- to identify pneumothorax,
- to identify the presence of blood in the epidural space,
- to identify compartment syndrome,
- to detect intraventricular hematoma, and
- to detect intraparenchymal hematoma.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To perform additional *in vivo* studies of pneumothorax and compartment syndrome in pigs using the RAFTS system.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3: Using RAFTS, perform baseline studies in normal human volunteers to determine the RF signals under normal uninjured conditions:

- Determine baseline signature of the head,
- Determine the baseline signature of the chest,
- Determine the baseline signature of the leg, and
- Characterize RAFTS signal response to blood, bone and bone-blood interface.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue this research under Cooperative Agreement No. DAMD17-02-2-0006

Task 3: Near-Infrared Reflectance Spectroscopy (NIRS) to Assess Regional Ischemia both during Trauma Resuscitation and at the Bedside in the Intensive Care Unit***Principal Investigator: Juan Carlos Puyana, MD, University of Pittsburgh Medical Center***

The overall objective of this research effort is to use Near-Infrared Reflectance Spectroscopy NIRS and other new minimally invasive technologies to determine the severity and reversibility of hemorrhagic shock by means of assessing organ specific cellular function and metabolism.

Presently the team is focusing on establishing the effects of spontaneous breathing on tissue blood gases. Previous experiments so far have shown that the PCO₂ of the muscle correlates well with the severity of shock. However these data has not been obtained in shocked animals without ventilatory support and without controlling for ventilation and arterial CO₂

The work completed so far has allowed us to show that the use of a multi-parameter sensor facilitates the identification of a specific organ response to hemorrhage. That changes in baseline tissue PCO₂, PO₂ and pH occur promptly after hemorrhage and that these responses are similar in all organs studied (liver, gut peripheral muscle, and stomach). Also, the team has demonstrated that changes in tissue pH and PCO₂ in peripheral muscle correlate well with severity of blood volume lost and with the resuscitative interventions used to replace hypovolemia.

Key Results: Validation studies at the University of Pittsburgh Medical Center will begin once all animal use approvals have been granted.

Specific Aim 1: To develop minimally invasive techniques to measure peripheral organs (Bladder) pH in the victim of hemorrhagic shock and evaluate the potential of this method as a predictor of multiple organ dysfunction syndrome (MODS) and a guide for resuscitation.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 2: Validation of NIR for tissue pH measurement

Progress: Validation studies at the University of Pittsburgh Medical Center will begin once all animal use approvals have been granted.

Plan: To initiate validation studies.

Task 4: Noise-Enhanced Tactile Sensation for the Management of Sensory Deficits in Patients with Stroke

Principal Investigator: *D. Casey Kerrigan, MD, Spaulding Rehabilitation Hospital (SRH), Boston, MA*

The overall goal of this research is to gain an increased understanding of how noise affects the detection and discrimination of mechanical cutaneous stimuli in subjects with impaired sensation, and also to establish a scientific foundation for the development of a clinically useful noise-based technique for improving tactile sensation in humans.

Key Results: Twenty-one subjects were screened for the project which included a mental status examination and a comprehensive battery of sensory tests of both hands. Sensory tests included light touch with monofilaments, hot-cold and 2 point discrimination, proprioception and muscle strength testing. It was demonstrated that electrical noise can, in fact, slightly enhance the ability of patients with stroke to detect subthreshold mechanical stimuli.

Specific Aim 1: Design and construct a suitable apparatus for patient experiments.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: Demonstrate the feasibility of both the apparatus and an experimental protocol through implementation in patients with stroke; collect data on patients with stroke.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001

Specific Aim 3: Analyze data to test the hypothesis that electrical noise can enhance the ability of patients with stroke to detect subthreshold mechanical stimuli.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

3.2 VULNERABLE PLAQUE PROGRAM

Task 1: Vulnerable Plaque Detection and Treatment

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

Key Results: Vulnerable Plaque Program continued to meet its goals and establish new ones. The main activity of the Program continues to be the scientific projects (see below for project reports). Leadership of the Program continues to address thematic, administrative and support issues in an attempt to enhance the overall quality and scope of the Program. The following represents the programmatic accomplishments during the past quarter.

Specific Aim 1: Establish a Vulnerable Plaque Lecture Series.

Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue Vulnerable Plaque research under Cooperative Agreement No. DAMD17-02-2-0006.

Task 2: Detection of Vulnerable Plaque using Optical Coherence Tomography

Principal Investigator: Brett Bouma, PhD, MGH

The specific goal of this research was to apply optical coherence tomography (OCT) for monitoring plaque development and response to systemic therapy in an animal model for atherosclerosis. Prior to this work, no longitudinal studies have been conducted within individual animals. The advantage of OCT is that cross-sectional images with a resolution approaching that of histopathology can be obtained *in vivo* (without sacrifice) so that disease can be monitored over time in individual animals. In order to make longitudinal studies with OCT practical, several technical issues have been addressed including imaging in the presence of blood, avoiding motion artifacts and providing sufficient resolution for plaque characterization.

Atherosclerotic disease in rabbits was generated using a high-cholesterol diet and focal balloon injury in the aorta and iliac arteries. The goal of the study was to monitor plaque response to diet modification and systemic therapy. Balloon injury was performed at the initiation of high-cholesterol diet. The first imaging time point was at 4 months. At that time, the rabbits were divided into separate arms of the study including diet modification and systemic therapy. The final imaging time point was intended to identify plaque response. The primary technical challenges addressed in this work were associated with the *in vivo* imaging. Balloon injury was performed using femoral access. OCT images of the rabbit iliac arteries and aorta were obtained by insertion of the imaging catheter through the carotid artery.

A second goal of the research was to investigate the ability of OCT to characterize plaque composition. As there is no existing gold standard for plaque characterization *in vivo*, the team has conducted an extensive *in vitro* study.

Key Results: The team has advanced the capabilities of OCT for imaging *in vivo* by resolving three key technical issues. First, the team has developed methods for displacing blood from the iliac and aorta using balloon occlusion and saline flush. Second, the team has demonstrated a sufficient image acquisition rate to avoid motion artifact due to respiration and pulsatile blood flow. Finally, the team has demonstrated that characteristic features in plaques can be resolved using a catheter that provides a resolution of approximately 10 microns.

The team has demonstrated that OCT imaging of the rabbit iliac and distal aorta can be performed in live animals without sacrifice. The images have demonstrated that OCT provides adequate resolution and contrast to identify focal lipid rich plaques and that the extent of disease can be quantified. At the first OCT imaging time point the team has uncovered two problems suggesting that the time scale of our study must be extended. First, the young age of the rabbits acquired for the study results in small vessel sizes. This has made vessel ligation a challenging problem following imaging. Failure to adequately ligate the carotid has resulted in the death of three rabbits. A second problem is that the frequency of observing localized lipid rich plaques in the iliac and distal aorta is less than anticipated based on our preliminary studies. Extending the timeframe of the study should lessen the impact of both of these problems. The team is therefore requesting a no-cost extension for a period of six months so that both imaging time points can be delayed in all remaining rabbits.

Specific Aim 1: To develop, optimize and apply OCT imaging for the detection of vulnerable atherosclerotic plaques. To accomplish this Specific Aim the following items will be addressed:

- To identify OCT morphologic features that distinguish vulnerable from stable plaques,
- To determine catheter and imaging characteristics in a porcine model, and
- Validation of a rabbit atherosclerosis model.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue Vulnerable Plaque research under Cooperative Agreement No. DAMD17-02-2-0006.

3.3 STROKE

Stroke is the third leading cause of death and a major disability for over 4 million stroke survivors in the United States. There are 700,000 new stroke cases every year. Stroke has an economic impact of \$30 billion a year.

The Acute Stroke Program at Partners HealthCare System has offered immediate evaluation and advanced emergency treatment over the last decade. Construction of a specially designed angiographic suite, which includes both state of the art MRI and digital subtraction angiographic (DSA) instruments, is nearing completion at the MGH and is expected to be operational by the spring of 2001. This MRI/DSA unit will enable physicians to optimize delivery of existing stroke treatments, and, at the same time, provide CIMIT investigators with access to this facility for the rapid advancement of novel therapies in the management of acute stroke.

The overall goals of the CIMIT Stroke Program are: 1) to protect the brain from ischemic brain injury with brain hypothermia, 2) to treat clots that obstruct brain blood flow before they cause permanent brain injury; 3) to develop better means of non-invasively monitoring the brain for dangerously low blood flow and brain hemorrhage, 4) to develop non-human primate models to predict brain injury, and 5) to provide technology assessment to evaluate new therapies for the treatment of stroke.

Task 1: Acute Stroke Management – Neuro-Protection

Principal Investigator: *Walter J. Koroshetz, MD, MGH and Albert S. Lee, MD, MGH*

Brain cooling is the most potent neuroprotective strategy in the management of acute stroke. Its use as a neuroprotectant in ischemic brain injury is limited only by the lack of the means to achieve cerebral hypothermia in a rapid, safe fashion. Ongoing CIMIT funded research is focused on the development of novel interventional modalities to selectively cool the surface of the cerebral cortex to provide neuroprotection for stroke patients.

Specific Aim 1: Develop a means to quickly cool the brain cortex to afford neuroprotection.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Task 2: MRI Guided Rapid Laser Endovascular Photoacoustic Recanalization (LEPAR) for Hyperacute Stroke and Stroke Predictive Modeling

Principal Investigator: *R. Gilberto Gonzalez, MD, PhD, MGH*

The emphasis of this project remains the same as for the previous year. In the last year the team has been working in two main areas on this project: experiments with the arterial bypass device to supply blood to ischemic brain regions via the microcatheter (a potential therapeutic approach

for human stroke as well) and experiments with the survival macaque stroke model (needed to assess the longer term effect of potential therapies as well as to obtain control MRI data on stroke evolution in this new model). The arterial bypass device was improved via more bench top experiments and the purchase of a dual channel ultrasonic flow meter, allowing us to measure two flow streams at once (i.e. arterial blood and a second flow of dilutant solution, e.g. saline, or other solution mixed into the blood stream). Additional *in vivo* experiments utilizing this setup were partially successful.

The second focus area has been the survival macaque stroke model. So far the team has recovered one animal following the acute stroke procedures. This animal was recovered after 60 minutes of MCA occlusion, and was survived successfully for 24 hours. Observations at 24hrs after stroke induction showed that the animal appeared healthy with no noticeable deficits. This is an important advance as it demonstrates successful recovery from acute stroke, which is necessary for the long terms plans for this stroke model.

Key Results: Four animals were studied with the bypass setup: in two animals the correct flow rate was achieved and brain tissue in the lesion area was maintained viable for 60-90 minutes, while in one animal the flow rate was too low and the lesion tissue infarcted, while in one animal the flow rate was too high and hemorrhage resulted. These results identify the future directions for this part of the project: to improve flow stability using a better blood pump and to improve the means of obtaining the correct flow rate in each animal by measuring or calculating accurately the fluid pressure at the tip of the microcatheter within the brain.

Specific Aim 1: To demonstrate efficacy and tissue safety of the LEPAR device and to maximize patient safety by defining the irreversible brain injury probability by diffusion MRI in a primate model.

Progress: Project completed. See Annual Progress Report, October 1, 2000 to September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 to September 30, 2001.

Task 3: Optical Monitoring and Imaging of Stroke

Principal Investigator: *Walter J. Koroshetz, MD, MGH and David A. Boas, PhD, MGH*

Note: We will be forwarding written correspondence regarding our intention to withdraw this study.

The ischemic brain injury (stroke) program is targeted at developing better means of non-invasively monitoring brain for dangerously low blood flow and for brain hemorrhage; treating clots that obstruct brain blood flow before they cause permanent brain injury; protecting brain from ischemic brain injury with brain hypothermia. The optical imaging project is focused on developing a new bedside capable imaging modality for continuous quantitative monitoring of cerebral perfusion and oximetry.

Key Results: During the last quarter significant progress was made in diffuse optical technology for characterizing layered media. This technology is central to cerebral oximetry in which the layered structure of scalp, skull and brain must be characterized. The key developments include: 1) New time resolve near infrared spectroscopy instrumentation for improved optical property determination, 2) time resolved Monte-Carlo modeling of layered media and 3) composing and submitting a Human protocol for cerebral oximetry measurements on healthy people.

Specific Aim 1: To finish the construction and testing of the 3rd generation CW instrument and the 1st generation RF instrument.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Specific Aim 2: Develop quantitative 3D reconstruction algorithms.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Specific Aim 3: To cross-validate the sensitivity and quantitative accuracy of the optical measurements with structural and functional information obtained with MRI, and to obtain preliminary results for “spin-off” projects.

Progress: No activity this quarter.

Plan: Once DoD animal use approval is received, piglet measurements will be initiated. The piglet data will provide preliminary feed back to complete instrument.

Specific Aim 4: Establish feasibility of translating technology to humans.

Progress: Toward this Specific Aim an IRB protocol entitled “Continuous Monitoring of Cerebral Hemoglobin Oxygenation Using a Hybrid Time-Domain/Continuous-Wave Diffuse Optical Tomography System.” (Accession #2001P 001632) was composed and submitted.

Plan: Depending on progress with approval this study of healthy humans will be started. Also, preparation will begin for a subsequent protocol to look at chronic patients with head trauma.

Task 4: Neuronal Injury and Neuroprotection in Epilepsy: Proton Beam Radiation for Intractable Epilepsy**Principal Investigator: Jonathan L. Brisman, MD, MGH**

A new model of proton beam radiosurgery (stereotactically focused irradiation) of the rat hippocampus has been developed. This model appears to be robust with brain necrosis evidenced reliably after a 3 month latency using doses of 90 Cobalt Gray Equivalents (CGE) or greater. This unilateral necrosis has been shown to correlate with increased T2 signal on MRI, decreased ability to perform the Morris Water Maze and the diminution of excitatory post-synaptic potentials and granule cell field spike obtained using *in vivo* microelectrode recordings. Positive alterations in heat shock protein, parvalbumin, calbindin and calmodulin have been detected. Upregulation of heat shock protein at non-necrotic doses may be important in explaining why low-dose irradiation reduces seizure activity in humans. These findings have been presented orally at the Congress of Neurological Surgeons Annual Meeting, September 2000, at the Spring Hippocampal Research Conference in spring 2000 and presented at the national Radiology Conference in fall 2000.

Two additional time points after irradiation have been employed to further study the time course of irradiation effects on the rat brain. Twelve animals have been studied five hours after irradiation and eighteen animals ten months after irradiation. The animals studied at the five hour point show apoptotic cell death in the irradiated hippocampus in a dose-dependent fashion. The ten month animals appear to show physiologic changes even at the lower doses used; histologic analysis has not yet been done.

A cohort of 40 animals has been irradiated after receiving pilocarpine status epilepticus. These animals have been analyzed physiologically and their brains stained for histologic and immunochemical analysis. In addition to the immunochemistry previously used in the normal rat brain irradiation study, a "Timm Stain," that typically shows axonal sprouting after pilocarpine seizures, was employed to determine whether irradiation has any effect on this neuronal response to status epilepticus. Preliminary results suggest that the pattern is altered with the higher doses employed.

Specific Aim 1: To characterize the histologic and electrophysiologic effects of proton beam irradiation in the normal rat brain.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To determine whether proton beam radiation can alter the neurophysiology or anatomic changes in animals that have undergone 24 hours of perforant pathway stimulation.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3: To determine the brain MRI appearance of rodents subjected to varying dosages of proton beam irradiation as well as rodents that have undergone 24 hours of perforant pathway stimulation.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Task 5: Measurement of Vascular Reactivity by Functional MRI in Cerebral Amyloid Angiopathy

Principal Investigator: *Steven M. Greenberg, M.D., Ph.D.*

In cerebral amyloid angiopathy (CAA), the β -amyloid peptide is deposited in small and medium-sized vessels of the leptomeninges and cerebral cortex. Amyloid replaces vascular smooth muscle, transforming vessels into rigid structures. In severe cases, this leads to rupture of the vessel wall and cerebral hemorrhage. Current diagnostic methods for CAA are limited to pathologic examination of the brain or radiographic demonstration of multiple hemorrhages in a characteristic distribution. Although CAA often affects a large number of cerebral vessels, whether the disease changes the flow characteristics of these vessels is unknown. Functional MRI (fMRI) can reliably assess human cerebral oxygenation, blood flow, and, with gadolinium injection, cerebral blood volume. We are investigating two stimuli that reliably increase cerebral blood flow in humans: visual stimulation using a flashing checkerboard pattern and CO₂ inhalation. Because cerebral blood flow is intimately tied to oxygen demand, visual stimulation increases flow through the normal activation of neuronal activity, and the recording of such changes has been the cornerstone of fMRI. By increasing CO₂ in the blood, CO₂ inhalation results in dilation of cerebral vessels and increased cerebral perfusion. We hypothesize that changes in blood vessels secondary to amyloid deposition alter the degree to which vascular tone can respond to both increased neuronal activity and CO₂ inhalation. This project investigates whether fMRI can document a difference in the response of cerebrovascular tone to these two stimuli between patients and controls. These techniques may enable us not only to diagnose cerebral amyloid angiopathy before the first hemorrhagic stroke, but also to follow patients over time, assessing the progress of their disease and response to potential therapies.

Key Results: Thus far, 4 control subjects and two CAA subjects have been studied using fMRI. Data analysis revealed a robust response in blood flow to both visual stimulation and CO₂ inhalation in the control subjects, although we have not detected any quantitative differences between CAA subjects and controls with this limited sample size. We are eager to investigate whether this observation is true in other CAA subjects.

Specific Aim 1: To develop a protocol for measuring cerebrovascular dilation in response to visual stimulation and 5% CO₂ inhalation in the elderly.

Progress: Cerebrovascular reactivity to visual stimulation has been measured in 4 control subjects by examining the changes in blood oxygen level dependent (BOLD) signal and regional cerebral blood flow. MRI revealed increased regional cerebral blood flow responses to visual stimulation (Figure 1) in 3 patients and CO₂ inhalation in 2 subjects (Figure 2). Two subjects were not administered CO₂ and a fourth subject, in whom no blood flow response was measured during visual stimulation, likely closed her eyes during much of the MRI.

One additional CAA subject was scanned this year, but did not undergo CO₂ inhalation during the study.

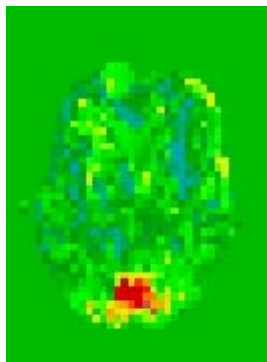


Figure 1. (WN) BOLD sequence from a 68-year-old control patient exposed to a visual stimulus. Areas colored red and orange demonstrate increased regional cerebral blood flow.

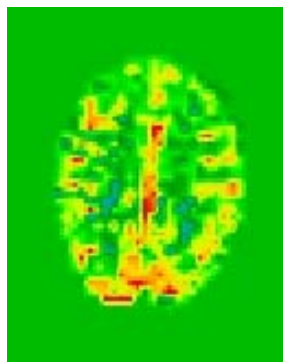


Figure 2. (FS) BOLD sequence from a 67-year-old control subject exposed to 5% CO₂ demonstrates more diffusely distributed changes in regional cerebral blood flow when compared to the BOLD response obtained with visual stimulation.

Plan: Project completed.

4.0 TECHNOLOGY ASSESSMENT AND OUTCOMES ANALYSIS PROGRAM***Principal Investigator: G. Scott Gazelle, MD, MPH, PhD***

The Technology Assessment and Outcomes Analysis Program represents an evolution of the Program established three years ago with the support and guidance of CIMIT leadership. As a result of discussions with members of the Operations Group, and in view of changes in CIMIT over the years, we have reshaped the Program to concentrate our research efforts on two major focus areas. Service, policy and administrative components of the Program are now concentrated in a Program Core. The Technology Assessment and Outcomes Analysis Program will be an important component of ongoing CIMIT technology development efforts. The Program will help CIMIT focus resource allocation for the development of innovative technologies that can result in improved patient care; perform studies to assess the effectiveness, cost and cost-effectiveness of technologies under development; and demonstrate the value of these technologies to the public, physicians, payers, industry, and legislators in order to facilitate appropriate clinical implementation. Our overall goal is to help CIMIT determine and optimize the outcomes of its research efforts, and more generally to redefine the manner in which healthcare interventions are valued.

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.

The two Outcomes Projects were developed in response to the needs of CIMIT major focus areas and are the result of ongoing collaborations. The models developed and research results from each of these projects are expected to be resources not only for CIMIT, but also for collaborators in government and industry.

TECHNOLOGY ASSESSMENT PROGRAM CORE

Within the larger Technology Assessment and Outcomes Analysis Program, the 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. With CIMIT support and guidance, the 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.

Moving forward, 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 (i.e., the Vulnerable Plaque and Operating Room of the Future Outcomes Projects). 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: The CIMIT Operations Group with resource allocation decisions via preliminary analysis of technologies identified in requests for funding.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

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

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

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: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

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. In the next two years, the team will build a decision model and use it to investigate a number of clinical and policy issues which face those developing, using, or funding these interventions.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

OPERATING ROOM OF THE FUTURE OUTCOMES PROJECT

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 is impossible to perform a truly randomized controlled trial in the surgical environment, the team has 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, the team 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, the team 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 of the work to be done.

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

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

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

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

5.0 REFERENCES

- Abukawa H, Kaban LB, Williams WB, Terada S, Vacanti JP, **Troulis MJ**. Effect of interferon-alpha-2b on porcine mesenchymal stem cells. *J Oral Maxillofac Surg*. 2006 Aug;64(8):1214-20.
- Abukawa H, Papadaki M, Abulikemu M, Leaf J, Vacanti JP, Kaban LB, **Troulis MJ**. The engineering of craniofacial tissues in the laboratory: a review of biomaterials for scaffolds and implant coatings. *Dent Clin North Am*. 2006 Apr;50(2):205-16.
- Bosch JL**, Beinfeld MT, Muller JE, Brady T, Gazelle GS. A cost-effectiveness analysis of a hypothetical catheter-based strategy for the detection and treatment of vulnerable coronary plaques with drug-eluting stents. *J Interv Cardiol*. 2005 Oct;18(5):339-49.
- Brisman JL**, Cosgrove GR, Thornton AF, Beer T, Bradley-Moore M, Shay CT, Hedley-Whyte ET, Cole AJ. Hyperacute neuropathological findings after proton beam radiosurgery of the rat hippocampus. *Neurosurgery* 56(6):1330-7; discussion 1337-8, 2005.
- Chen TC, Cense B, Pierce MC, Nassif N, Park BH, Yun SH, White BR, **Bouma BE**, Tearney GJ, de Boer JF. Spectral domain optical coherence tomography: ultra-high speed, ultra-high resolution ophthalmic imaging. *Arch Ophthalmol*. 2005 Dec;123(12):1715-20.
- Chung C, Mesa J, **Randolph MA**, Yaremchuk M, Burdick JA. Influence of gel properties on neocartilage formation by auricular chondrocytes photoencapsulated in hyaluronic acid networks. *J Biomed Mater Res A*. 2006 Jun;77(3):518-25.
- Dawson S**. Procedural simulation: a primer. *Radiology*. 2006 Oct;241(1):17-25.
- Diamond SG, Huppert TJ, Kolehmainen V, Franceschini MA, Kaipio JP, Arridge SR, **Boas DA**. Dynamic physiological modeling for functional diffuse optical tomography. *Neuroimage*. 2005 Oct 19; [Epub ahead of print]
- Fuchs JR, Nasser BA, Vacanti JP, **Fauza DO**. Postnatal myocardial augmentation with skeletal myoblast-based fetal tissue engineering. *Surgery*. 2006 Jul;140(1):100-7.
- Gonzalez RG**. Imaging-guided acute ischemic stroke therapy: From "time is brain" to "physiology is brain". *AJNR Am J Neuroradiol*. 2006 Apr;27(4):728-35.
- Henderson AC, **Ingenito EP**, Salcedo ES, Moy ML, Reilly JJ, Lutchen KR. Dynamic lung mechanics in late-stage emphysema before and after lung volume reduction surgery. *Respir Physiol Neurobiol*. 2006 Jun 3; [Epub ahead of print]
- Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, Cury RC, Abbata S, Joneidi-Jafari H, Achenbach S, **Brady TJ**. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol*. 2006 Apr 18;47(8):1655-62.

Ishii O, Shin M, Sueda T, **Vacanti JP**. *In vitro* tissue engineering of a cardiac graft using a degradable scaffold with an extracellular matrix-like topography. J Thorac Cardiovasc Surg. 2005 Nov;130(5):1358-63.

Kamegaya Y, Farinelli WA, Vila Echague AV, Akita H, Gallagher J, Flotte TJ, Anderson RR, **Redmond RW**, Kochevar IE. Evaluation of photochemical tissue bonding for closure of skin incisions and excisions. Lasers Surg Med. 2005 Oct;37(4):264-70.

Khalil AS, Chan RC, Chau AH, **Bouma BE**, Mofrad MR. Tissue elasticity estimation with optical coherence elastography: toward mechanical characterization of *in vivo* soft tissue. Ann Biomed Eng. 2005 Nov;33(11):1631-9.

Liu Y, D'Arceuil H, He J, Duggan M, Seri S, Hashiguchi Y, Nakatani A, **Gonzalez RG**, Pryor J, de Crespigny A. Dynamic susceptibility contrast perfusion imaging of cerebral ischemia in nonhuman primates: comparison of Gd-DTPA and NMS60. J Magn Reson Imaging. 2005 Oct;22(4):461-6.

Mesa JM, Zaporozhan V, Weinand C, Johnson TS, Bonassar L, Randolph MA, **Yaremchuk MJ**, Butler PE. Tissue engineering cartilage with aged articular chondrocytes *in vivo*. Plast Reconstr Surg. 2006 Jul;118(1):41-9; discussion 50-3.

Muller JE, **Tawakol A**, Kathiresan S, Narula J. New opportunities for identification and reduction of coronary risk: treatment of vulnerable patients, arteries, and plaques. J Am Coll Cardiol. 2006 Apr 18;47(8 Suppl):C2-6.

Peretti GM, Xu JW, Bonassar LJ, Kirchhoff CH, Yaremchuk MJ, **Randolph MA**. Review of injectable cartilage engineering using fibrin gel in mice and swine models. Tissue Eng. 2006 May;12(5):1151-68.

Terada S, Yoshimoto H, Fuchs JR, Sato M, Pomerantseva I, Selig MK, Hannouche D, **Vacanti JP**. Hydrogel optimization for cultured elastic chondrocytes seeded onto a polyglycolic acid scaffold. J Biomed Mater Res A. 2005 Dec 15;75(4):907-16.

Wang PY, Koishi K, McGeachie AB, Kimber M, **MacLaughlin DT**, Donahoe PK, McLennan IS. Mullerian inhibiting substance acts as a motor neuron survival factor *in vitro*. Proc Natl Acad Sci U S A. 2005 Nov 8;102(45):16421-5.

Weinand C, Peretti GM, Adams SB Jr, Bonassar LJ, Randolph MA, **Gill TJ**. An Allogenic Cell-Based Implant for Meniscal Lesions. Am J Sports Med. 2006 Jul 26; [Epub ahead of print]

Yelick PC, **Vacanti JP**. Bioengineered teeth from tooth bud cells. Dent Clin North Am. 2006 Apr;50(2):191-203, viii.

Zhang Y, Brooks DH, **Boas DA**. A haemodynamic response function model in spatio-temporal diffuse optical tomography. Phys Med Biol. 2005 Oct 7;50(19):4625-44.

6.0 APPENDICES

APPENDIX A. LIST OF CIMIT PROJECTS AND PRINCIPAL INVESTIGATORS

CIMIT RESEARCH PROJECTS

ENDOVASCULAR DEVICES

Cardiomyocyte Repopulation using Percutaneous Delivery of Tissue Engineered Systems

Stephen Oesterle, MD MGH

Application of Automation and Tissue Engineering to Construct Heart Valves

Jennifer White, MD MGH

MINIMALLY INVASIVE SURGERY

Minimally Invasive Cardiac Surgery – Endoscopic Coronary Anastomosis

David Torchiana, MD MGH

Endothelial Activation Markers as Molecular Targets for Innovative, Minimally Invasive Diagnosis and Therapy in Cardiovascular Disease

Michael Gimbrone, MD BWH

Develop a Computer-Based Three-Dimensional Imaging Treatment Planning System to Drive an Endoscopically Placed, Miniature, Facial Skeletal Distraction Device

Leonard B. Kaban, MD, DMD and Maria Troulis, MD, MGH

Operating Room of the Future

David Rattner, MD, MGH

Application of a Robotics Interface in Surgery

Robert Howe, PhD, HMA

IMAGE GUIDED THERAPY

MRI-guided Focused Ultrasound Treatment of Breast Cancer

Ferenc Jolesz, MD BWH

ALA Enhanced Fluorescence Imaging of Barrett's Epithelium

Norman Nishioka, MD MGH

OCT Imaging of Esophageal Lesions

Norman Nishioka, MD MGH

Segmentation of Bone From CT and Vessels From MRA Data

Carl-Fredrik Westin, PhD and Ron Kikinis, MD, BWH

Real-time Registration of Intra-operative Ultrasound with Pre-operative CT/MR for Image Guided Therapy

Eric Grimson, PhD MIT

TISSUE ENGINEERING**Degradable Conductive Polymers**

Robert Langer, ScD MIT

Polymer-based Gene Delivery Platform

Robert Langer, ScD MIT

Transdermal Drug Delivery and Chemical Sensing for Neonates Using Skin Electroporation

James Weaver, PhD MIT

Synthesize Vascularized Living Systems from the Platform of Two-Dimensional Silicon Microfabrication Technologies and Adapt to Three-Dimensional Living Devices

Joseph Vacanti, MD MGH

Synthesize Vascularized Living Systems from the Platform of Three-Dimensional Printing Technology

Joseph Vacanti, MD MGH and Jeffrey Borenstein, PhD, Draper Laboratory

Minimally Invasive Meniscal Repair with Tissue Engineered Cartilage

Thomas J. Gill, MD and David J. Zaleske, MD, MGH

Development of a Novel *in vivo* Recombinant Protein Delivery Device**Designed to Regress Abnormal Tissue: Recombinant Human Müllerian Inhibiting Substance (rhMIS) Producing Cells on Biodegradable Matrices**

David MacLaughlin, PhD MGH

Determine the Role of Mesenchymal Stem Cells in Fetal Tissue Engineering*N. Scott Adzick, MD, University of Pennsylvania (UPenn) and Children's Hospital of Philadelphia (CHOP) and Alan W. Flake, MD, CHOP***SIMULATION****Design, Fabricate and Validate Procedural Medical Simulators***Steven L. Dawson, MD MGH***NEW INITIATIVES****Lung Volume Reduction Using a Bronchoscopic Approach***Edward Ingenito, MD BWH*

Outcome Assessment in Menorrhagia

Johana L. Bosch, PhD GH

TRAUMA AND CRITICAL CARE

Microsensors – Real-Time Blood Assay

Christopher Dube, PhD Draper Laboratory

**Application of Microwave Imaging to Rapid Non-Invasive
Detection of Intracranial Hematoma**

*Geoffrey Ling, MD, PhD Uniformed Services University of the Health Sciences,
USUHS, Bethesda, MD*

**Near-Infrared Reflectance Spectroscopy (NIRS) to Assess Regional
Ischemia both during Trauma Resuscitation and at the Bedside in the
Intensive Care Unit**

Juan Carlos Puyana, MD BWH

**Noise-Enhanced Tactile Sensation for the Management
of Sensory Deficits in Patients with Stroke**

Casey Kerrigan, MD Spaulding Rehabilitation Hospital

VULNERABLE PLAQUE

Detection of Vulnerable Plaque using Optical Coherence Tomography

Brett Bouma, PhD MGH

STROKE

Acute Stroke Management – Neuro-Protection

Walter Koroshetz, MD MGH

**MRI Guided Rapid Laser Endovascular Photoacoustic Recanalization
(LEPAR) for Hyperacute Stroke and Stroke Predictive Modeling**

R. Gilberto Gonzalez, MD, PhD MGH

Optical Monitoring and Imaging of Stroke

David Boas, PhD MGH

**Neuronal Injury and Neuroprotection in Epilepsy: Proton Beam
Radiation for Intractable Epilepsy**

Jonathan Brisman, MD MGH

Telemedicine – Remote Stroke Videoconferencing Project

Lee Schwamm, MD MGH