Words from the Chairman

Surgical Research is part of any contemporary, first class, Department of Surgery and the Beth Israel Deaconess Medical Center is no exception. As the Department grew, so did its research effort and level of funding. Until recently, continual growth in research funding for the Department of Surgery was gratifying indeed. The Department's research funding from all sources, both NIH and non-NIH, increased from about $10 to more than $21 million annually, during the period of 2002-2005. This growth was impressive, taking the Department from approximately 22nd in the country in total NIH funding, to about 5th or 6th. It is difficult to obtain our exact position amongst NIH-funded Departments of Surgery because this number is calculated by the NIH as a total of all Departments of Surgery at Harvard Medical School, including totals for all Harvard affiliated hospitals.

Since 2005, our NIH and other funding for research have been declining. The NIH seems to view its funding for research as discretionary, which is particularly unfortunate given the number of people and planning that must go in to building one's research holdings, and also the nature of individuals that need to be supported. When there is little money, as there currently is not going to various military needs and other non-discretionary activity, NIH funding declines. Just as others have experienced a downturn in NIH funding, so have we. Our NIH and other funding have diminished, including a reduction in the total dollar amount for each awarded grant and the total number of NIH grants that are funded, including competing renewals of long-standing projects. It is unlikely that this trend will reverse soon and from my conversations with other Department chairs, this downturn is being experienced all over.

Nonetheless, the Department of Surgery at the Beth Israel Deaconess Medical Center has a robust research effort and continues to pursue academic productivity as well as research productivity with its excellent faculty. This fact is demonstrated in the following report that summarizes our research effort in 2007. Whether or not the current trend in NIH funding will reverse, is anybody's guess. At present, it looks like it will not. However, we are grateful for the fine clinical and research faculty that we have and the ability to support first class research that goes on in the Department. We look forward to better days.

Josef E. Fischer, MD
Chairman, Department of Surgery
Beth Israel Deaconess Medical Center

William V. McDermott Professor of Surgery
Harvard Medical School

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Director of Endocrine Surgery
George H. A. Clowes, Jr. Professor of Surgery

Susan J. Hagen, PhD — Associate Director for Surgical Research
Associate Professor of Surgery

Sabrina Pinder, BS — Administrative Coordinator

A. Introduction

In this section of the Annual Report, we provide an overall description of the goals and responsibilities of the Division of Surgical Research, a summary of research faculty in the Department, funding and publications generated by researchers in the Department of Surgery, and other aspects of research within the Department. More detailed research updates are found for individual members of the different Divisions in subsequent sections of the report.

The Division of Surgical Research is an administrative division with an aim to facilitate both basic and clinical research in the Department of Surgery at the Beth Israel Deaconess Medical Center (BIDMC). The Division of Surgical Research is headed by Per-Olof Hasselgren, MD, PhD, who is Vice Chairman for Research in Surgery at BIDMC and the George H.A. Clowes Jr. Professor of Surgery at Harvard Medical School, and Susan J. Hagen, PhD, who is Associate Director for Surgical Research in Surgery at BIDMC and Associate Professor of Surgery at Harvard Medical School. The division is also supported by an administrative coordinator, Ms. Sabrina Pinder.

The Division of Surgical Research has the following responsibilities: 1) Pre-award review and approval of all grant submissions in the Department of Surgery. This includes assisting in the process of submission of grant applications and interaction with the BIDMC Office of Sponsored Programs. 2) Management of research space, including laboratory and office space, and shared research equipment. For this, the allocation of research space within the Department is overseen, shared tissue culture facilities are maintained, and the Department is represented at various institutional committees and subcommittees dealing with research space at the BIDMC. 3) Organizing monthly Surgical Research Seminars, open for both clinical and research faculty in the Department as well as other members of the BIDMC community. 4) Preparing the Department of Surgery Annual Research Report. 5) Organizing laboratory and shared equipment maintenance and telecommunications. 6) Supporting and mentoring junior faculty in the establishment of research laboratories. 7) Interacting with and providing information to Surgical Residents who plan to spend time in the research laboratory. 8) Obtaining visas for foreign scholars in

Research and in preparing applications for Harvard Medical School appointments for Research Fellows and Instructors in Surgery Research. 9) Making recommendations concerning research faculty appointments and reappointments in Surgery (working together with the Department of Surgery Appointment, Reappointment, and Promotion Committee). 10) Assisting the Chairman with the development of existing and new research areas within the Department of Surgery, including both short- and long-term strategic planning and recruitment.

B. Research Faculty

The number of individuals involved in research (basic and clinical research) in the Department of Surgery has varied between 122 and 148 over the last 6 years. Currently, research in the Department is conducted by 51 faculty, 44 postdoctoral research fellows, 9 surgical residents, 20 research associates and assistants, 2 visiting scientists, 1 nurse educator, 1 dietitian, 1 medical writer, and 17 undergraduate, graduate, and medical students. Numerous research coordinators, administrative assistants, and administrative coordinators provide important administrative support for research efforts in the Department.

Many faculty members in the Department of Surgery have received and continue to receive both national and international prominence related to research. Several faculty members continued to serve or were appointed to NIH study sections or serve as ad hoc members of study sections, and a number of research faculty members serve on Editorial Boards or are Editors for National and International journals.

In 2007, most of the Research Faculty in Surgery were invited speakers around the world. Faculty members were invited speakers in interesting locations that varied from Thailand (Blackburn) to Belgium (Hasselgren) to Australia (Kiessling and Koulmanda).

Research Faculty in the Department of Surgery also participates in significant teaching endeavors. These include acting as mentors in the NIH in-service teacher program, MIT Bioengineering Undergraduate Research Program, Biomedical Science Careers Program, Project Success, Undregraduate Research Opportunities Program, and Research Scholars Institute Summer Program. The Vascular and Endovascular Surgery Division remains actively involved in the William J von Leibig research training program for both medical and postdoctoral students. Several of the Surgical Research Faculty teach at Harvard Medical School in the Body, Cell Biology, Pharmacology, and GI Pathophysiology courses and most of the surgeons in the Department participate in the surgical clerkships.

C. Research Activities and Funding

Research activities within the Department of Surgery at the Beth Israel Deaconess Medical Center are strong and have shown a robust growth over the last 6 years (2002-2007). Research and development constitute one of the cornerstones and missions of the Department, in addition to patient care and teaching. The strength and growth of the various research programs within the Department of Surgery are illustrated by **a 119% increase in external funding from 2002-2005,** making the Department one of the top five surgery departments in the country with regards to NIH funding. Since 2005 funding has declined somewhat, reflecting budget restrains imposed on NIH during the past few years, but is still **increased 55% over 2002 external funding levels**. All Divisions within the Department presently conduct NIH-funded research. **The number of R01 grants held by faculty in the Department has increased from 23 to 38 (a 65% increase)** during the 6-year period 2002-2007 and in 2007, **22 faculty in Surgery held R01 grants**. During the same period of time, the **number of publications originating from the Department increased by nearly 67%.**

Both basic and clinical research programs are active in the Department. From a thematic standpoint, the following areas of research are represented: Cancer Biology, Inflammation, Development, Vascular Biology, Cardiothoracic research, Transplantation-Immunology, Obesity-Nutrition-Metabolism, Wound Healing, Epithelial Biology, Stem Cell Biology, and Clinical Outcomes. All research, both basic and clinical, in the Department of Surgery is supported by external funding and more than 2/3 of this funding has been in the form of NIH grants. Although the amount of external funding decreased during 2007, the level of funding is remarkable considering that a number of those faculty members who contribute substantial grant funds to the research effort are also clinically very active. The federal (almost exclusively

NIH), non-federal, and total external funding during the 6-year period 2002-2007 are illustrated below in Table 1 and Figure 1.

Table 1. *Total (Direct and Indirect) Awarded Funds from Fiscal Year (FY) 2002-2007*

FY	Federal	Non-Federal	Total
2002	6,205,560	3,509,366	9,714,966
2003	9,120,376	5,189,335	14,309,711
2004	9,546,640	6,432,878	15,979,518
2005	13,709,118	7,532,073	21,241,191
2006	12,536,470	5,164,713	17,701,183
2007	10,818,988	4,247,367	15,066,355

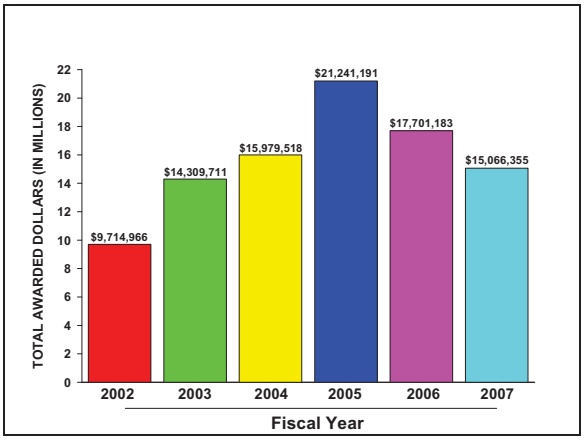

Figure 1 (left) Total (direct and indirect, federal and non-federal) awarded funds during the 6-year period 2002-2007.

The current distribution of external funding between the different Divisions in the Department of Surgery is illustrated by the diagram in Figure 2. The Transplant Surgery and General Surgery Divisions have the largest external funds constituting approximately 30-40% each of the total departmental funding.

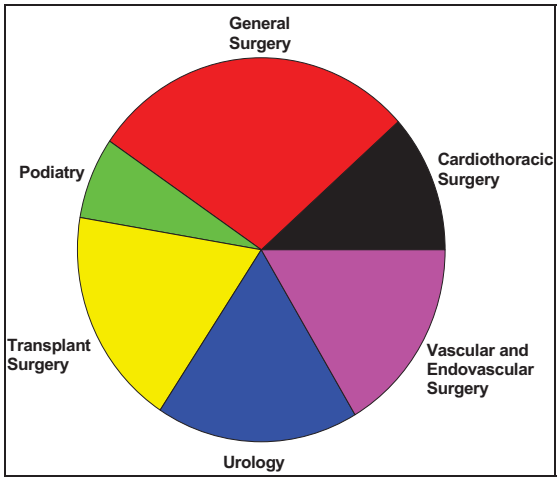

Figure 2 (left) Total (federal and non-federal) funding in 2007 by Division.

It should be noted that the figures provided here for awarded funds in Table 1 and Figs 1 and 2 are greater than the corresponding figures provided in previous Annual Research Reports from the Department. The reason for this discrepancy is that the BIDMC Research Administration has not previously been able to provide figures for actual awarded funds and in previous years the awarded funds were calculated on the basis of expended dollars. This is the first year in which the BIDMC Research Administration has provided information about actual awarded funds and that is why the figures provided in this report are accurate. During the last 5 years we have actually underestimated grant awards in the Annual Research Reports.

D. Training Grants

The Department presently holds two active NIH training grants, one in Cardiovascular Surgery (PI, Dr. Frank Sellke) and one in Vacsular Surgery (PI, Dr Frank LoGerfo). In addition, investigators in Surgery actively participate in a GI Surgery Training Grant. This is a joint training grant between the three HMS

teaching hospitals led by Dr. Soybel (PI) at the Brigham and Women's Hospital, Dr. Hodin (Co-IP) at the Massachusetts General Hospital and Dr. Hasselgren (Co-IP) at BIDMC. An additional NIH training grant for Surgery at the BIDMC, submitted by Transplantation (Dr. Hanto, PI), was awarded by the NIH and will begin in 2008.

E. Surgical Residents and Research

Over the last 6 years, approximately 10 residents per year elected to spend time in a basic or clinical research laboratory as part of their surgical training (Figure 3). Most of the residents performed research in a basic science laboratory doing bench research. Although not obligatory, the present policy is to have residents dedicate time to research between their second and third clinical years. This extends the surgical residency from 5 years to 7-8 years, but learning to do bench research an important and worthwhile experience, regardless of whether the resident plans a career in academic surgery or in private practice.
The majority of residents perform research in laboratories within the Department of Surgery, but some residents have spent time in other Departments at the Beth Israel Deaconess Medical Center or in laboratories off-site in Boston (for example MIT, Massachusetts General Hospital, and Children's Hospital) or other institutions, including places abroad.

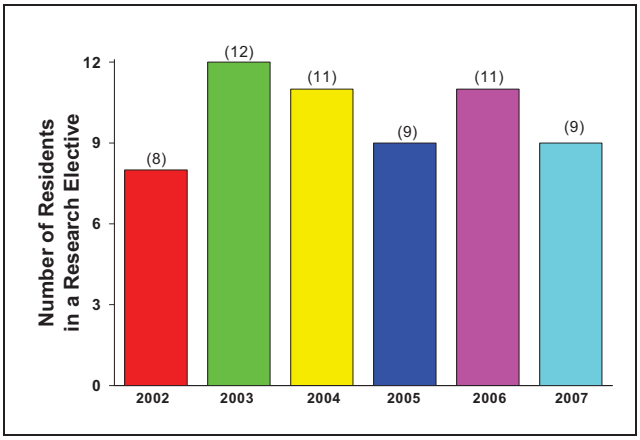

Figure 3 (left) Number of surgical residents per year spending time (2-3 years) in a research elective.

An important aspect of a Residents' research is obtaining funding. The process that has been adopted in the Department over the last 6 years is for the resident who plans to go into the laboratory to write and submit at least two credible grant/fellowship applications (typically applying at sources such as various National Surgical Societies, NIH, and the American College of Surgeons) – those applications are usually written together with and supported by the research mentor with whom the resident will work. If the applications are not funded, training grants in the Department or other funds within the individual laboratories can frequently provide support and it is only exceptionally that the resident has to rely on Departmental financial support for the time in the laboratory. To assist residents in obtaining funding, the Division of Surgical Research has made available a 70 page booklet entitled "Funding Sources for Surgical Residents" (right), which describes various funding sources, deadlines, financial support available, and application forms. This booklet is also available electronically at http://www.bidmc.harvard.edu/content/bidmc/Departments/Surgery/Funding.pdf?node_id=10717 and was updated in 2007.

In 2004, an **Annual Residents' Research Competition** was instituted. This competition is open for all residents who are or have recently been in a research laboratory or who are involved in a clinical research project. Fifteen abstracts were submitted this year and they were scored by a committee consisting of Faculty in the Department. Four finalists presented their papers at a Surgical Grand Rounds in June and the winner was selected among the 4 finalists. The presentations at Grand Rounds were evaluated based on both scientific content and delivery.

The 4 finalists in the 4th Annual Residents' Research Competition (2007) were:

Patrick O"Neal: "The Expression of the Muscle Specific Ubiquitin Ligases Atrogin-1 and MuRF1 is Increased during Experimental Hyperthyroidism in Rats"
Mentor: Dr. Per-Olof Hasselgren, Division General Surgery/Section of Endocrine Surgery, BIDMC.

Neel Sodha, MD
"Angiogenic Signaling in the Response to Chronic Myocardial Ischemia in Diabetes"
Mentor: Dr. Frank Sellke, Division of Cardiothoracic Surgery, BIDMC.

Shaun Steigman, MD
"Principal Regulatory Validation of a 3-Stage Amniotic Mesenchymal Stem Cell Manufacturing Protocol"
Mentor: Dr. Dario Fauza, Children's Hospital Boston.

Tsafrir Vanounou, MD
"Selective Administration of Prophylactic Octreatide during Pancreato-duodenectomy: A Clinical and Cost-Benefit Analysis in Low- and High-risk Glands"
Mentor: Drs. Mark Callery and Charles Vollmer, Division of General Surgery, BIDMC.

This year's first price was awarded to Dr. Sodha.

F. Research Seminars

The Division of Surgical Research organizes monthly research seminars with presentations by investigators within the Department of Surgery, from other Departments at the BIDMC, and from other regional institutions. Half of the seminars in 2007 were technique-based presentations with general applicability to all research labs in Surgery. The "Techniques" seminars held during 2007 are summarized below in Table 2. In the fall of 2007 our "Updates" seminar series was re-instated, highlighting the research effort by faculty within the Department. These seminars focused on basic science within the major research emphasis areas of Cancer Biology, Inflammation, Vascular Biology, Cardiothoracic research, Transplantation-Immunology, Obesity-Nutrition-Metabolism, and Wound Healing. This informal seminar series also provides the opportunity for interaction among the research faculty and for increased collaboration between various research groups. A summary of "Updates" seminars in 2007 can be found in Table 2.

Table 2. "Techniques in Surgical Research", 2007

January 8, 2007	**Sue Schadinger, PhD** Drug Discovery Market Specialist Cell Signaling Technologies, Danvers, MA	"Using Antibodies and Probes to Study Cell Signaling Pathways in Basic and Translational Research"
February 12, 2007	**Susan J. Hagen, PhD** Associate Professor of Surgery, HMS Director, Microscopy and Histology Core Facilities, BIDMC	"Imaging Molecular Interactions with New Equipment in the BIDMC Microscopy Core Facility"
March 5, 2007	**Joshua LaBaer, MD, PhD** Director, Harvard Institute of Proteomics Harvard University, Boston, MA	"Functional Proteomics for Biomarker and Target Discovery"
April 9, 2007	**Kioshi Igagaki, PhD** Instructor in Surgery, HMS Hauser Lab, Director BIDMC, Boston	"A Simple and Sensitive Technique to Study Intracellular Ca^{2+} Signaling"

May 14, 2007	**Qinchung Tong, PhD** Research Fellow in Medicine (Tenen Lab) and **Joel Lawitts, PhD** Director, Transgenic Core Facility, BIDMC	"How to Design (Tong) and Produce (Lawitts) Genetically Modified Mice"
September 10, 2007	**Caroline E. Shamu, PhD** Director, Institute of Chemistry and Cell Biology (ICCB)-Longwood Core Facility Harvard Medical School, Boston, MA	"siRNA Resources Available in the ICCB-Longwood Core Facility"
October 10, 2007	**Catherine Lenich, PhD** Research And Academic Affairs, Beth Israel Deaconess Medical Center	"Patenting Your Discoveries"
November 5, 2007	**Jim McIlvain, PhD** Carl Zeiss Inc Biomedical Imaging Consultant	"Choosing the Correct Microscope Equipment for Your Experiments"
December 10, 2007	**Jennifer Sabbagh** Research Administrative Director Beth Israel Deaconess Medical Center	"Research Administration Overview: New Grant Submission Policies"

Table 3. "Updates in Surgical Research", 2007

September 24, 2007	**Maria Koulmanda, PhD** Assistant Professor in Surgery, HMS Non-Human Primate Research Transplant Research Center, Beth Israel Deaconess Medical Center	"The Pathogenic Role of Inflammation in Autoimmune Diabetes Models"
October 29, 2007	**Carl Hauser, MD** Visiting Professor in Surgery, HMS Beth Israel Deaconess Medical Center	"Modifying Inflammatory Cell Signaling With Lipids: Building a Better Raft…."
November 26, 2007	**Frank Sellke, MD** Johnson and Johnson Professor of Surgery, HMS Division of Cardiothoracic Surgery, BIDMC	"Regenerative Therapies for the Treatment of Cardiac Disease"

G. Annual Research Reports

The Division of Surgical Research continues to highlight progress in research by producing an Annual Research Report. The report is made available to all faculty members of the Department, senior leadership of the Hospital including the Chairs of all departments. It is also sent to most Surgical Chairs at major Academic Centers in the country. In addition, the Annual Research Report is an important source of information for Resident Candidates and Postdoctoral Fellows when interviewing for a position in the Residency Program at the BIDMC or in one of the research laboratories. The Report for past years, 2001-2005, can be found within the Department of Surgery web site at **http://bidmc.harvard.edu/display.asp?node_id=6558**.

H. Appointment, Reappointment, and Promotion Committee

In the year 2003, a Departmental Appointment, Reappointment, and Promotion Committee was formed. The purpose of this committee is to review the credentials of faculty members who are being considered for reappointment or promotion at the Harvard Medical School. In addition, the credentials of new faculty being recruited are reviewed by the committee before the individual is being proposed for appointment at HMS. The Committee is chaired by Dr. Hasselgren and presently has 8 members consisting of faculty at the Professor or Associate Professor level. The committee meets at least twice per year.

I. Research Facilities and Space

The Department of Surgery occupies approximately 32,000 square feet of laboratory space including wet labs, special purpose rooms (cold rooms, tissue culture rooms, and shared equipment rooms), and office space. Although the greatest number of research faculty and staff in Surgery are located on the 8th floor of the Dana/Research West building on the East Campus, Surgery has research space in several different locations. These spaces include (in square feet) 10,150 at the HIM (Harvard Institute of Medicine) Building, 11,249 in Dana/Research West, 917 in Slosberg-Landy, 1,755 at 21-27 Burlington Avenue, and 4,818 at Research North. Clinical Research space includes 443 (in square feet) in Palmer and 1,982 in Feldberg. The overall dollar density for research space in the Department of Surgery is approximately $154/sq foot. With new recruitments that have already been completed (in the Divisions of Transplantation and Trauma/Critical Care), the dollar density is expected to increase substantially during the next fiscal year.

J. Bibliography (January – December 2007)

In addition to external funding, the number of publications is an important measure of the success of the research effort conducted in the Department. Over the last 6 years, the number of publications from the Department has increased significantly. In 2007, members of the Department of Surgery published 121 original articles, submitted an additional 90 articles that are in press, wrote 74 reviews and editorials, and published 14 books/textbooks. Overall, this outstanding productivity was significantly greater than in 2006 and represents a **53% increase in published original articles, a 61% increase in submitted or in press articles, a 32% increase in published review articles, and a 133% increase in the publication of books,** including Mastery of Surgery 5th edition, which was edited by Dr. Fischer with contributing chapters by many of the Surgery faculty.

Bold represents Research Faculty in Surgery at BIDMC.

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DIVISION OF CARDIOTHORACIC SURGERY

Malcolm DeCamp Jr., MD

Chief, Division of Cardiothoracic Surgery
Visiting Associate Professor of Surgery

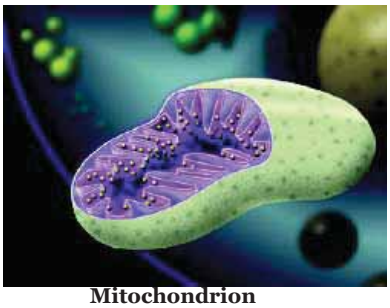
Division Members

Ralph de la Torre, MD	**Instructor in Surgery**
F. Henry Ellis Jr., MD, PhD	**Clinical Professor of Surgery, Emeritus**
Sidharta Gangadharan, MD	**Instructor in Surgery**
Robert C. Hagberg, MD	**Assistant Professor of Surgery**
Kamal Khabbaz, MD	**Assistant Professor of Surgery**
Michael Kent, MD	**Instructor in Surgery**
Sidney Levitsky, MD	**Cheever Professor of Surgery**
James D. McCully, PhD	**Associate Professor of Surgery**
Ioannis K. Toumpoulis, MD	Research Fellow in Surgery
Haripriya Dayalan, PhD	Research Fellow in Surgery
Frank W. Sellke, MA, MD	**Johnson & Johnson Professor of Surgery**
Cesario F. Bianchi, MD, PhD	**Assistant Professor of Surgery**
Jun Feng, MD, PhD	Instructor in Surgery
Richard Clemments, PhD	Research Fellow in Surgery
Yuhong Liu, MD	Research Fellow in Surgery
Robert Osipov, MD	Research Fellow in Surgery
Shu Hua Xu, PhD	Research Associate
Edo Bedzra	Student, Harvard Medical School
Sharon Babcock	Student, Wake Forest University
Ronald M. Weintraub, MD	**David Ginsburg Associate Professor of Surgery**

Sidney Levitsky, MD
James D. McCully, PhD

Basic Research

The primary focus of our laboratory is to elucidate the mechanisms and subcellular localization of biochemical and molecular events contributing to myocardial cell death. In particular, we are interested in the discriminant and/or coordinate contribution of necrosis and apoptosis to myocardial cell death. Study designs utilize models of stunning and ischemia/reperfusion injury in the isolated Langendorff perfused rabbit and the *in situ* blood perfused pig heart to determine the relative contribution of these pathways in the aged as compared to the mature cardiac surgical patient. The laboratory is also involved in the isolation and identification of genes associated with myocardial ischemia/reperfusion amelioration using differential display, selective subtraction hybridization and microarray technology. For this, we use rabbit and pig heart cDNA libraries constructed in our laboratory and non-redundant cDNA's isolated, sequenced and putatively identified by our laboratory for microarray analysis.



Mitochondrion

Current research areas involve identification of mitochondrial changes in morphology, function, respiration, volume and DNA integrity in association with intrinsic and extrinsic apoptotic and necrotic myocardial cell death following ischemia and reperfusion. In addition studies are underway to the identify mitochondrial ATP-sensitive potassium channel regulation of apoptosis and necrosis in the blood perfused pig heart model of acute myocardial infarction; and the role of STAT1/STAT2 signal transduction in myocardial preservation. These studies include comparison between mature and aged populations and differential gender response.

List of Current Employees

Ioannis K. Toumpoulis, MD	Research Fellow in Surgery
Haripriya Dayalan, PhD	Research Fellow in Surgery

List of Current Funding

"Myocardial protection: reperfusion injury amelioration"
National Institutes of Health, **RO1 HL 29077**
Project period: 2004-2009
Principal Investigator: Sidney Levitsky
Collaborating Investigator: James D. McCully

Applications Submitted and Pending Review/Funding

"Mitochondrial transplantation for cardioprotection"
National Institutes of Health, **R01HL092016-01**
Project period: 2008-2013
Principal Investigator: James D. McCully
Collaborating Investigator: Sidney Levitsky

"Myocardial protection: reperfusion injury amelioration "
National Institutes of Health, **RO1 HL 29077**
Project period: 2009-2014
Principal Investigator: Sidney Levitsky
Co-Principal Investigator: James D. McCully

DIVISIONAL ACCOMPLISHMENTS IN THE PAST YEAR

Individual Accomplishments

In the past year we have constructed rabbit heart cDNA libraries and have isolated and 5' sequenced 8647 rabbit heart cDNAs and have identified and stored 2592 non-redundant cDNAs with a mean insert size of 1.67 kb**.** These non-redundant cDNAs have been used to construct rabbit heart microarrays to allow for the parallel determination of multiple gene products and relative mRNA abundance levels and the identification of the co-regulated genes and the functionally related gene groups associated with global ischemia and the enhanced cardioprotection afforded by cardioplegia in the mature and aged male and female heart. This work was performed as current human and mouse cDNA libraries did not allow for analysis with the rabbit heart owing to differences in 3' untranslated regions.

We have also developed an isolated perfused mouse heart model for use with wild type and knock-out mouse models.

Current studies include electreo-mechanical changes and reduction and redistribution of gap junction and adherens proteins during ischemia/reperfusion injury and the effects of cardioplegia.

Age and gender studies have been performed and will continue using mature and aged orchidectomized male rabbits and appropriate shams and ovariohysterectomized female rabbits with appropriate shams and hormone replacement therapy along with *de novo* RNA and protein synthesis inhibition. These studies are designed to utilize microarray technology identify specific up and down regulated RNA's and functionally related gene groups modulated by global ischemia and by cardioplegia with gender and with age. It is expected that these studies will allow for the development of gender and age specific cardioprotective protocols using specific hormonal (17β-estradiol, testosterone) or molecular biological techniques, which will allow for the short-term activation or suppression of RNA transcripts and provide for enhanced post-ischemic recovery following cardiac surgery. The ability to specifically modify the functional and biochemical response for the male and female mature and aged heart through the directed specific activation or suppression of RNA transcripts will ultimately enhance the ischemic tolerance and reduce morbidity and mortality in human cardiac surgery with specific benefit being expected in the aged female cardiac surgical patient.

Abstracts presented at Local, National, and International meetings

He H, Kitahori K, Poutias DN, Balschi JA, Cowan DB, Friehs I, **McCully JD**, del Nido PJ, McGowan FX. Mitochondrial dysfunction causes failure of the pressure-loaded infant right ventricle. Presented at the American Heart Association Scientific Sessions in Orlando, FL. November, 2007.

McCully JD, Cowan DB, Pacak CA, **Levitsky S**. Mitochondrial transplantation for cardioprotection. Presented at the American Heart Association Scientific Sessions in Orlando, FL. November, 2007.

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Lowe J, Luber J, **Levitsky S**, Hantak E, Montgomery J, Schiestl N, Schofield N, Marra S, TISSEEL clinical Study Group. Evaluation of the topical hemostatic efficacy and safety of TISSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: a phase 3, randomized, double-blind clinical study. J Cardiovasc Surg 2007;48(3):323-31.

McCully JD , Rousou AJ, Parker RA, **Levitsky S**. Age and gender differences in mitochondrial oxygen consumption and free matrix calcium during ischemia/reperfusion and with cardioplegia and diazoxide. Ann Thorac Surg. 2007; 83:1102-9.

Original Articles (Submitted or In press)

Gulyasy B, López-Candales A, Reis SE, **Levitsky S**. Quadricuspid aortic valve: An unusual echocardiographic finding and a review of the literature. Int J Cardiol 2007; in press.

Reviews, Chapters, and Editorials

Khabbaz KR, **Levitsky S**. The impact of surgical and percutaneous coronary revascularization on the cardiac myocyte. World J Surg 2008;32:361-5.

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Abstracts

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McCully JD, Cowan DB, Pacak CA, **Levitsky S**. Mitochondrail transplantation for cardioprotection. Circulation 2007; 116 (16): II-496A.

Frank W. Sellke, MD
Cesario Bianchi, MD, PhD

Basic research


Frank Sellke

Drs. Sellke and Bianchi investigate changes in vascular function and signal transduction during cardiac surgery and myocardial ischemia, and therapeutic angiogenesis using protein growth factors in the setting of hypercholesterolemia, diabetes mellitus, and increased oxidative stress.

Clinical research

We continue a genomic-wide study on gene expression profiling in atrial and blood of patients subjected to cardiopulmonary bypass (CPB). Recently, we embarked in studies aiming to characterize candidate biomarkers that would predict diabetic patients prone to complications and biomarkers to predict the development of cognitive decline after CPB.

List of Current Employees

Jun Feng, MD, PhD	Instructor in Surgery
Richard Clemments, PhD	Research Fellow in Surgery
Yuhong Liu, MD	Research Fellow in Surgery
Robert Osipov, MD	Research Fellow in Surgery
Shu Hua Xu, PhD	Research Associate
Edo Bedzra	Student, Harvard Medical School
Sharon Babcock	Student, Wake Forest University

List of Current Funding

"Cardioplegia and coronary microvascular reactivity"
National Institutes of Health, **RO1 HL-46716**
Project Period: 2006-2009
PI: Frank W. Sellke

“Surgical intramyocardial angiogenesis in a swine model”
National Institutes of Health, **RO1 HL-69024-04**
Project Period: 2003-2008
PI: Frank W. Sellke

“Cardiovascular surgery research”
National Institutes of Health, **T32-HL076130-02**
Project Period: 2004-2009
Program Director: Frank W. Sellke

“Research training in vascular surgery”
National Institutes of Health, **T32-HL007734-12**
Project Period: 2004-2009
Program Director: Frank Logerfo
Mentor: Frank Sellke

“Cardiovascular research training grant”
National Institutes of Health, **T32-HL007374-25**
Project Period: 2004-2009
Program Director: Anthony Rosenzweig
Mentor: Frank Sellke

"Effect of the hydrogen sulfide donor IK-1001 on the outcome of myocardial infarction and cardio-pulmonary bypass in the pig"
Ikaria, Inc
Project Period: 2006-2008
PI: Frank W. Sellke

Applications Submitted and Pending Review/Funding

"Surgical intramyocardial angiogenesis in a swine model"
National Institutes of Health, **RO1 HL-69024**
PI: Frank W. Sellke

"Angiogenesis in a model of diabetes and endothelial dysfunction"
National Institutes of Health, **RO1 HL-85647**
PI: Frank W. Sellke

"Cobalt and hydraliazine enhance neovascularization"
National Institutes of Health, **R01 HL093739-01**
PI: Frank W. Sellke

"Small heat shock proteins in surgically-induced myocardial stunning"
National Institutes of Health, K99/R00
PI: Richard T. Clements
Mentor: Frank Sellke

"Small heat shock proteins in surgically-induced myocardial stunning"
American Heart Association: National Scientist Development Grant
PI: Richard T. Clements
Mentor: Frank Sellke

"Enhanced coronary vascular smooth muscle MLC phosphorylation in diabetes"
National Institutes of Health: Loan Repayment Program.
PI: Richard T. Clements
Mentor: Frank Sellke

"Enhanced coronary vascular smooth muscle MLC phosphorylation in Diabetes"
Charles A. King Trust Postdoctoral Fellowship.
PI: Richard T. Clements
Mentor: Frank Sellke

Research Accomplishments in the Past Year

<u>Invited Presentations (Dr. Sellke)</u>

"Regenerative therapies for the treatment of heart disease." Surgery Grand Rounds: Mount Auburn Hospital. Cambridge MA. September 4, 2007.

"Regenerative therapies for the treatment of cardiac disease: where are we and where are we going?" Clowes Visiting Professor PI Research Forum: BIDMC, Boston, MA. November 13, 2007.

"Trasylol: US clinical perspective". Bayer Regional Advisory Board Meeting. Toronto, ON. February, 2007.

Cesario Bianchi

"Myocardial ischemia reperfusion injury." PAR-1 Expert Summit Meeting: Antithormbosis, Inflammation, and Ischemia-reperfusion injury: Annenberg Center for Health Sciences. Palm Springs, CA. April, 2007.

"Regenerative therapies for the treatment of heart disease: Where are we and what is the future?" Emory University School of Medicine. May, 2007.

"Update on SIRS and myocardial ischemia reperfusion injury during cardiac surgery." Emory University School of Medicine, Atlanta, GA. May, 2007.

"Inflammation during cardiac surgery." Montreal Heart Institute. Montreal, Canada. June 15, 2007.

"Regenerative therapies for the treatment of heart disease: where are we and what is the future?" Montreal Heart Institute Research Program: Montreal Heart Institute. Montreal, Canada. June 15, 2007.

"Efficacy of angiogenic therapy for cardiac repair." XXV Meeting of the Society of Cardiac Surgeons. June 22, 2007.

"Basic investigation and the future of cardiac surgery." XXV Meeting of the Society of Cardiac Surgeons. June 23, 2007.

"Angiogenesis for the treatment of coronary disease." The Michael E. DeBakey Summer Vascular Research Institute: Texas A&M University, Texas. July 5, 2007.

"Regenerative therapies for the treatment of heart disease." Department of Surgery Grand Rounds, Beth Israel Deaconess Medical Center, Boston, MA. July 11, 2007.

"Ischemia reperfusion injury and organ protection in cardiothoracic surgery." Norfolk, VA. September 24, 2007.

"Impact of the systemic inflammatory response syndrome in cardiopulmonary bypass." Sentara Heart Center: Eastern Virginia College of Medicine. Norfolk, VA; September 25, 2007.

"Ischemia reperfusion injury and organ protection in cardiothoracic surgery." Richmond, VA; September 25, 2007.

"On pump and off pump CABG: how do they compare?" 60th Annual meeting of the Japanese Association for Thoracic Surgery. Sendai, Japan. October 17, 2007.

"On pump and off pump CABG: how do they compare?" Louis Martini Winery. Napa, CA. October 23, 2007.

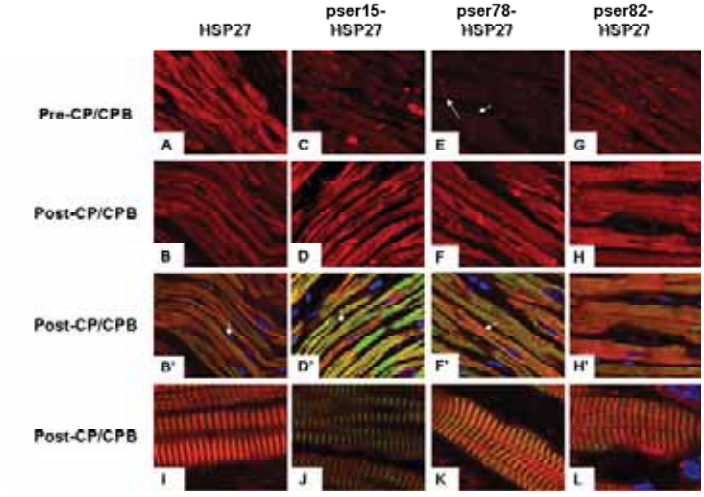

Fig. 1 Effects of CPB on HSP27 phosphorylation and translocation.

Invited Moderator (Dr. Sellke)

Surgical Forum II: Adult cardiac II. Society of Thoracic Surgeons annual meeting in San Diego, CA. January, 2007.

Focused discussion group on angiogenesis and vascular biology. Society of University Surgeons annual meeting in Phoenix, AZ. February, 2007.

AATS Grantsmanship Workshop. Bethesda, MD. March 2, 2007.

Mock Study Section: AATS Grantsmanship Workshop. Bethesda, MD. March 2, 2007.

Cardiac Surgery Biology Club Meeting Program: AATS. May, 2007.

Grant Writing Symposium: American College of Surgeons Meeting. New Orleans, LA. October, 2007.

Targeted Therapy Surgical Forum: American College of Surgeons Meeting. New Orleans, LA. October, 2007.

"Percutaneous and surgical approaches to valvular disease." American Heart Association Scientific Sessions. Orlando, FL. November, 2007.

Abstracts presented at Local, National, and International meetings

Ramlawi B, Mieno S, Sodha NR, **Bianchi C**, Clements RT, Feng J**, Sellke FW.** Oxidative stress levels associated to new onset atrial fibrillation after cardiac surgery: a case-control study. Society of Thoracic Surgeons Meeting. January, 2007.

Mieno S, Clements R, Sodha N, Boodhwani M, Ramlawi B, Feng J, Xu S, **Bianchi C**, **Sellke FW**. Characteristics and functional activity of bone marrow derived endotheial progenitor cells following cryopreservation. This work was presented at the annual meeting of the Society of University Surgeons. February, 2007.

Sodha NR, Feng J, Clements RT, **Bianchi C**, Boodhwani M, Ramlawi B, Mieno S, **Sellke FW**. Protein kinase C modulates microvascular reactivity in the human coronary and skeletal microcirculation. Presented at the annual meeting of the Society of University Surgeons. February, 2007.

Clements RT, Sodha NR, Feng J, Boodhwani M,Emani S, **Bianchi C**, **Sellke FW**. Diabetic impairment of NO-dependent coronary smooth muscle relaxation correlates with enhanced contractile signaling and is normalized by insulin. Presented at the annual meeting of the Federated Societies for Experimental Biology, EB07 in Washington DC. April, 2007.

Boodhwani M, Sodha N, Xu S, Mieno S, Feng J, Ruel M, **Sellke FW.** Insulin treatment enhances the myocardial angiogenic response in diabetes. Presented at the annual meeting of the American Association of Thoracic Surgery. May, 2007.

Sodha NR, Clements RT, Feng J, Szabo C, **Bianchi C**, **Sellke FW.** Exogenous sulfide reduces myocardial apoptosis in response to ischenia-reperfusion injury. Presented at the European Association for Cardio-Thoracic Surgery. September, 2007.

Sodha NR, Boodhwani M, Clements RT, Hua S, **Bianchi C**, **Sellke FW.** Angiostatin and endostatin expression are increased in the skeletal musculature of diabetics. Presented at the annual Meeting of the New England Surgical Society. September, 2007.

Clements RT, Sodha NR, Feng J, Emani S, Senthilnathan S, Khabbaz K, **Bianchi C**, **Sellke FW**. Proteomic profile of differentially regulated proteins in human myocardium before and after cardiac

surgery utilizing cardioplegia and cardiopulmonary bypass. Presented in the research forum: Topics in Myocardial Protection at the annual meeting of the American Heart Association, Orlando, FL. November, 2007.

Liu YH, Feng J, Sodha NR, Khabbaz KR, Senthilnathan V, Alper SL, **Sellke FW**. Calcium activated potassium channels contribute to human coronary microvascular dysfunction after cardioplegia arrest. This work was presented as a poster at the American Heart Association Scientific Session, Orange County, Orlando, FL. November, 2007.

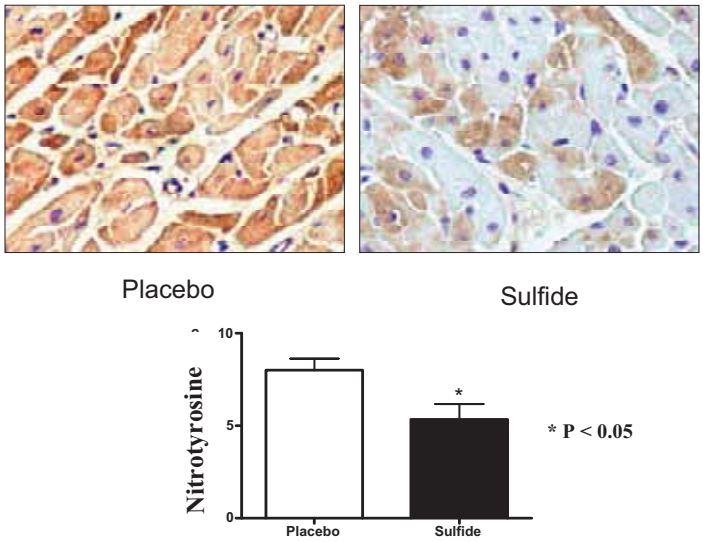

Fig. 2 Sodium sulfite decreases nitrotyrosine formation in acute myocardial infarctions.

Report of Teaching

Cesario Bianchi
Tutor-Harvard Medical School
Molecular and Cellular Basis of Medicine - 1st year M.D. Program – Course director: Randall King

Instructor and Histology Tutor – Harvard Medical School
Human Body Course - 1st year MD Program – Course directors: Cinthia McDermott/Trudy Van Houten

Richard Clements
Tutor-Harvard Medical School
Molecular and Cellular Basis of Medicine - 1st year MD Program – Course director: Randall King

Robert Osipov
Tutor – Harvard Medical School
Human Body Course - 1st year MD Program – Course directors: Cindi McDermott/Trudy Van Houten

Frank W. Sellke
Director of the Cardiothoracic Surgery Research Training Program, where he was responsible for the organization and administration of conferences and training program. Four trainees are enrolled per year.

Bibliography (January – December 2007)

Original articles

Boodhwani M, Sodha NR, Mieno S, Xu SH, **Feng J**, Ramlawi B, Clements RT, **Sellke FW**. Functional, cellular, and molecular characterization of the angiogenic response to chronic myocardial ischemia in diabetes. Circulation 2007; 116(11 Suppl):I31-7.

Boodhwani M, Sodha NR, Mieno S, Ramlawi B, Xu SH, **Feng J**, Clements RT, Ruel M, **Sellke FW**. Insulin treatment enhances the myocardial angiogenic response in diabetes. J Thorac Cardiovasc Surg 2007; 134(6):1453-60.

Clements RT, Sodha NR, **Feng J**, Mieno S, Boodhwani M, Ramlawi B, **Bianchi C**, **Sellke FW**. Phosphorylation and translocation of heat shock protein 27 and alphaB-crystallin in human myocardium after cardioplegia and cardiopulmonary bypass. J Thorac Cardiovasc Surg 2007; 134(6):1461-70.

Feng J, Yano K, Monahan-Earley R, Morgan ES, Dvorak AM, **Sellke FW**, Aird WC. Vascular bed-specific endothelium-dependent vasomomotor relaxation in the hagfish, *Myxine glutinosa*. Am J Physiol Regul Integr Comp Physiol 2007; 293(2):R894-900.

Khan TA, **Bianchi C**, Ruel M, **Feng J**, **Sellke FW**. Differential effects on the mesenteric micro-circulatory response to vasopressin and phenylephrine after cardiopulmonary bypass. J Thorac Cardiovasc Surg 2007; 133(3):682-8.

Ramlawi B, Scott JR, **Feng J**, Mieno S, Raman KG, Gallo D, Csizmadia E, **Chin BY**, **Bach FH**, **Otterbein LE, Sellke FW**. Inhaled carbon monoxide prevents graft-induced intimal hyperplasia in swine. J Surg Res 2007; 138(1):121-7.

Ramlawi B, Otu H, Mieno S, Boodhwani M, Sodha NR, Clements RT, **Bianchi C**, **Sellke FW**. Oxidative stress and atrial fibrillation after cardiac surgery: a case-control study. Ann Thorac Surg 2007; 84(4):1166-72.

Ramlawi B, Otu H, Rudolph JL, Mieno S, Kohane IS, Can H, Libermann TA, Marcantonio ER, **Bianchi C**, **Sellke FW**. Genomic expression pathways associated with brain injury after cardiopulmonary bypass. J Thorac Cardiovasc Surg 2007; 134(4):996-1005.

Sodha NR, **Feng J**, Clements RT, **Bianchi C**, Boodhwani M, Ramlawi B, Mieno S, Khabbaz KR, **Sellke FW**. Protein kinase C alpha modulates microvascular reactivity in the human coronary and skeletal microcirculation. Surgery 2007;142(2):243-52.

Voisine P, Rosinberg A, Wykrzykowska JJ, Shamis Y, Wu GF, Appelbaum E, Li J, **Sellke FW**, Pinto D, Gibson CM, Mitrani E, Laham RJ. Skin-derived microorgan autotransplantation as a novel approach for therapeutic angiogenesis. Am J Physiol Heart Circ Physiol 2007; 294(1):H213-9.

Original Articles (Submitted or In press)

Boodhwani M, Mieno S, **Feng J**, Sodha NR, Clements RT, Xu SH, **Sellke FW**. Atorvastatin impairs the myocardial angiogenic response to chronic ischemia in normocholesterolemic swine. J Thorac Cardiovasc Surg 2007; in press.

Boodhwani M, Voisine P, Ruel M, Sodha NR, **Feng J**, Xu SH, **Bianchi C**, **Sellke FW**. Comparison of vascular endothelial growth factor and fibroblast growth factor-2 in a swine model of endothelial dysfunction. Eur J Cardiothorac Surg 2007; in press.

Feng J, Sellke FW. Invited commentary. Ann Thorac Surg 2007; in press.

Khabbaz KR, Feng J, Boodhwani M, Clements RT, **Bianchi C**, **Sellke FW**. Nonischemic myocardial acidosis adversely affects microvascular and myocardial function and triggers apoptosis during cardioplegia. J Thorac Cardiovasc Surg 2007; in press.

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Reviews, Chapters, and Editorials

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DIVISION OF GENERAL SURGERY

Mark P. Callery, MD, FACS — **Chief, Division of General Surgery**
Associate Professor of Surgery

Division Members

George L. Blackburn, MD, PhD — **S. Daniel Abraham Associate Professor of Nutrition at Harvard Medical School**
Director, Center for the Study of Nutritional Medicine at BIDMC

Center for the Study of Nutrition Medicine

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Ronit Grinbaum, MD	Research Fellow in Surgery
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Katherine Wang	Research Assistant
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Tsafrir Vanounou, MD	Surgical Resident
Teviah Sachs, MD	Surgical Resident
Saju Joseph, MD	Surgical Resident

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Joanna Jung	Research Student
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Noel Irias	Simulation and Skills Center Coordinator
Linda Trainer, RN	Nurse Educator
Maritza Avendano	Administrator
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Ronit Grinbaum, MD	Surgery, MIS Research Fellow

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Kinga Powers, MD, PhD	Surgery, MIS Clinical Fellow
Scott Rehrig, MD	Surgery, MIS Clinical Fellow
Shawn Tsuda, MD	Surgery, MIS Clinical Fellow
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Clinton Koufman, MD	**Clinical Instructor in Surgery**
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Peter M. Mowschenson	**Assistant Clinical Professor of Surgery**
John T. Mullen, MD	**Assistant Professor of Surgery**
Benjamin E. Schneider, MD	**Instructor in Surgery**
Susan L. Troyan, MD	**Instructor in Surgery**
Charles M. Vollmer, MD	**Assistant Professor of Surgery**
Jin-Rong Zhou, PhD	**Assistant Professor of Surgery**
Nutrition Metabolism Laboratory	
Yin Lu, PhD	Visiting Professor
Weijun Pan, MD, PhD	Clinical Research Fellow in Surgery
Derek Liu, PhD	Research Associate in Surgery
Feng Ni, PhD	Research Fellow in Surgery
Hamid Abdolmaleky, MD	Research Fellow in Surgery
Renwang Jiang, PhD	Research Fellow in Surgery
Linglin Li, MS	Research Associate
Fang Wan, BS	Research Student
Jian Qin, BS	Temporary Assistant

Overview of Division Research

With such a large faculty and breadth of clinical and basic science research interests and talents, our Division offers great opportunities for just about any inquiry. From NIH funded laboratories in nutrition, sepsis and inflammation, and muscle wasting cell biology to widely published clinical research programs examining simulation and skills testing in minimally invasive surgery, and quality assessment in high-acuity pancreatic and biliary surgery, there really is something available to all. Please contact any of our Faculty directly to explore research opportunities further.

We hope you enjoy our Division's Research summary.

George L. Blackburn, MD, PhD
Jin-Rong Zhou, PhD

Center for the Study of Nutrition Medicine (CSNM)
Nutrition Metabolism Laboratory (NML)

BASIC RESEARCH

George Blackburn

Research in the NML aims to study the role of diet and nutrition in the prevention and treatment of breast, prostate, and bladder cancers, and obesity/metabolic syndrome, and to investigate the mechanisms of action of active dietary components. To identify active components of the diet, we have established a series of cell-based *in vitro* bioassays for identification of single dietary components and their synergistic combinations to target cancer cell proliferation, apoptosis and invasion/ metastasis, and on tumor angiogenesis. A series of clinically relevant animal models for cancer were established in this laboratory to systematically evaluate the efficacy of candidate components and their synergistic combinations in prevention and treatment of cancer. Advanced techniques for cellular and molecular biology and epigenetics are also applied to elucidate the mechanisms of action of active candidates. By combining efficacy evaluation and mechanistic studies, it is expected to identify effective dietary and nutritional regimens for the prevention and treatment of cancer. The research findings can be directly translated to clinical practice and are designed to provide evidence that strongly establish and support dietary guidelines for prevention and treatment of related diseases.

CLINICAL RESEARCH

Jin-Rong Zhou

The CSNM has over 30-years of extensive experience conducting longitudinal studies particularly in multicenter settings. We are particularly well equipped with the infrastructure to develop clinical investigation and outcomes assessment. CSNM provides sophisticated scientific nutrition interventions that are utilized to support research, training and patient care in many disease states. The CSNM mission is in line with the medical center's "bench-to-bedside" mission. One of our centers accomplishments this year to highlight is the Commonwealth of Massachusetts Betsy Lehman Center for Patient Safety and Medical Error Reduction Expert Panel on Weight Loss Surgery 2007 Update on Patient Safety Recommendations. This report can be found at www.Mass.gov/dph/betsylehman.

LIST OF CURRENT EMPLOYEES

CSNM

Daniel S. Rooks, PhD	Assistant Professor in Medicine
S. Torsten Olbers, MD, PhD	Research Fellow in Surgery
Ronit Grinbaum, MD	Research Fellow in Surgery
Anne McNamara RN	Research Associate
Kristina Day, RD, LD	Research Dietician
Shannon Fischer, MD	Research Assistant
Katherine Wang	Research Assistant
Fabiola Framondi, MS	CME Coordinator
Barbara M. Ainsley, DTR	Administrative Assistant

NML

Yin Lu, PhD	Visiting Professor in Surgery
Derek Liu, PhD	Research Associate in Surgery
Feng Ni, PhD	Research Fellow in Surgery

Hamid Abdolmaleky, MD	Research Fellow in Surgery
Renwang Jiang, PhD	Research Fellow in Surgery
Weijun Pan, MD, PhD	Clinical Fellow in Surgery
Linglin Li, MS	Research Associate
Fang Wan, BS	Student
Jian Qin, BS	Temporary Assistant

List of Current Funding

"Look AHEAD action for health in diabetes"
NIH, **5 U01 DK057154-09**
Project Period: 2007-2008
PI: David Nathan
Co-Investigator: George Blackburn

"The Boston Obesity Nutrition Research Center (BONRC)"
NIH, **5P30DK46200-15**
Project Period: 2003-2008
PI: Barbara Corkey
Co-Investigator: George Blackburn

"Understanding how patients value bariatric surgery"
NIH, **R01 DK073302-01A2**
Project Period: 2007-2011
PI: Christina Wee
Co-Investigator: George Blackburn

"Oldenlandia diffusa for prostate cancer treatment"
NIH, **1R21 CA133865-01A2**
Project Period: 2007-2009
PI: Jin-Rong Zhou

"Parental metabolic status and offspring cancer risks"
NIH, **1RO3 CA130131-01**
Project Period: 2007-2009
PI: Jin-Rong Zhou

"Synergy between phytochemicals for prostate cancer prevention"
NIH, **1RO3 CA130133-01**
Project Period: 2007-2009
PI: Jin-Rong Zhou

"Soy and black tea combinations for prevention of prostate cancer"
Cancer Research and Prevention Foundation
Project Period: 2007-2009
PI: Jin-Rong Zhou

"Choline metabolism in prostate cancers: response to dietary soy phytochemicals"
NIH, **1R21 CA130013-01A1**
Project Period: 2007-2009
PI: Sandra Gaston
Co-Investigator: Jin-Rong Zhou

Applications Submitted and Pending Review/Funding

"LISA (Lifestyle Intervention Study in Adjuvant Treatment of Early Breast Cancer)"
Novartis Pharmaceuticals

Project Period: 2008 -2010
Co-PI: George Blackburn

"Synergy between black tea and soy bioactives for prostate cancer prevention"
NCI/NIH, **1RO1 CA131462**
Project Period: 2008-2013
Co-PI: Jin-Rong Zhou

"Intrauterine exposure to metabolic syndrome and breast cancer risk"
NCI/NIH
Project Period: 2007-2012
Co- PI: Jin-Rong Zhou

"Synergy between black tea and soy bioactives for prostate cancer prevention"
NCI/NIH, **1RO1 CA131462**
Project Period: 2008-2013
PI: Jin-Rong Zhou

"Epigenetic modification of reelin by EGCG in prostate cancer prevention"
NCI/NIH, **R21 CA135194**
Project Period: 2008-2010
PI: Jin-Rong Zhou

"Tanshinones as effective therapeutic agents for prostate cancer progression"
Department of Defense, **PC073988**
Project Period: 2008-2011
PI: Jin-Rong Zhou

"Metabolic syndrome as pancreatic cancer etiology"
NCI/NIH, **R21 CA127794**
Project Period: 2008-2009
PI: Jin-Rong Zhou

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

George L Blackburn, MD, PhD

A) Betsy Lehman Center/Weight Loss Surgery Update

On January 9, 2008 the Betsy Lehman Center's Expert Panel on Weight Loss Surgery released its updated recommendations on patient safety. This report represents a six-month effort in 2007 and involved over 100 specialists from across the state and across the many disciplines involved in the field of weight loss surgery. Massachusetts, Department of Public Health Commissioner, John Auerbach said, "Overwhelming new data highlighted in this report demonstrate reductions in known disease risk factors, improvements in health, and significant reductions in mortality after weight loss surgery," "We expect this report to continue to set the standard for improving the safety of weight loss surgery in the Commonwealth and beyond."

Nationwide, the number of weight loss operations climbed 800% between 1998 and 2004. Between 2005 and 2006, it grew another 11%, increasing from approximately 180,000 procedures to more than 200,000. Across all age groups, the fastest growth occurred among adults aged 55 to 64, with a 20-fold increase between 1998 and 2004. In Massachusetts, the number of weight loss operations climbed from 200 to 3036 procedures between 1998 and 2004. Between 2004 and 2006, it grew another 14% increasing from approximately 3036 procedures to 3447.

New data reflect a trend toward the use of procedures that not only restrict stomach size, as with laparoscopic banding, but also reroute part of the digestive tract, as is done with laparoscopic gastric bypass, the most commonly performed weight loss surgery in the U.S. In 1990, gastric bypass accounted for 55% of all weight loss operations; by 2000, that figure had climbed to 93%.

In 2006, growing popularity of the laparoscopic banding procedure changed the ratio of gastric bypass (both open and laparoscopic) to laparoscopic banding to 70:30.
As the number of weight loss surgeries increased, the national inpatient death rate fell 78.7%, from 0.89% in 1998 to 0.19% in 2004. Male inpatient deaths have historically been higher than those for women, yet the gap narrowed substantially during those years, decreasing by close to 50%. Length of hospital stay also fell by 38.5%, from nearly 5 days to 3.1 days. The oldest patients had the longest length of stay and the highest inpatient mortality rate. Over the past two years, the average inpatient mortality rate for weight loss surgery in the Commonwealth of Massachusetts has been 0.07%, significantly below the national inpatient death rate.

Other new findings show that:

- There are a growing number of surgical options available, including sleeve gastrectomy and biliopancreatic diversion.
- Laparoscopy has displaced open surgery as the predominant approach;
- Weight loss surgery accreditation/credentialing programs have been established within the past three years.
- Weight loss surgery patients have a higher prevalence of mental health disorders, with preliminary evidence indicating substance abuse problems.
- Approximately 4% of U.S. children suffer from extreme obesity.
- Advances in anesthesiology allow for more precise dosing of muscle relaxants and novel applications of anesthetic agents.
- There are new national credentialing standards in perioperative nursing.
- New patient transport and lift technologies can reduce healthcare workplace injuries.
- Optimal treatment requires greater collaboration between members of a multidisciplinary care team.
- 99% of patients who are eligible for weight loss surgery do not receive it.
- The need to accommodate growing numbers of severely obese patients will require wide-ranging changes in new and existing healthcare facilities.
- The Centers for Medicare and Medicaid Services and other payers now only reimburse procedures performed at accredited weight loss surgery centers.

Expert panel on Weight Loss Surgery.
Dr. Blackburn (red circle) was the Chair of this panel.

The Expert Panel included a consumer representative and leading authorities in the fields of obesity treatment, patient safety, nutrition, medical practice, managed care, pediatrics, nursing, and ethics. I had the honor of being the chair of this distinguished panel and Matthew Hutter, M.D., from Massachusetts General Hospital served as the Panel's Vice Chair.

The panel used a state-of-the-art model of evidence-based medicine to develop its findings. The recommendations are based on a comprehensive review of the best and most current literature on weight loss surgery and they are grounded in established methodology and vetted by nationally-recognized experts. The complete report will be published in Obesity in 2008 but can be found at the link, www.Mass.gov/dph/betsylehman.

B) Women's Intervention Nutrition Study (WINS)

The study is currently closed and data is being analyzed. I am please to announce that we are now awaiting publication of a protocol-mandated survival analysis update entitled "Survival Analyses from the Women's Intervention Nutrition Study (WINS) Evaluating Dietary Fat Reduction and Breast Cancer Outcome" (see abstract below). Results indicate a dietary intervention targeting fat intake reduction did not significantly increase overall survival of women with resected breast cancer receiving conventional cancer management. Exploratory analyses suggest dietary intervention influence on survival may be greater in hormone receptor negative subgroups and during the period of active dietary intervention.

ABSTRACT

Survival Analyses From the Women's Intervention Nutrition Study (WINS) Evaluating Dietary Fat Reduction and Breast Cancer Outcome

Chlebowski RT, **Blackburn GL**, Elashoff RM, Hoy KM, Thomson CA, Giuliano AE, McAndrew P, Hudis C, Butler J, Shapiro A.. LABioMed, Torrance, CA; Beth Israel Deaconess Hospital, Boston, MA; University of California, Los Angeles, CA; Cancer Prevention Institute, New York, NY; University of Arizona, Tucson, AZ; St Johns Hospital and Health Center, Santa Monica, CA; Cedars Sinai Hospital, Beverly Hills, CA; Memorial Sloan-Kettering Cancer Center, New York, NY; University of California at Irvine, City of Orange, CA; Park Nicollet Institute, Minneapolis, MN

Background: We previously reported five year results with follow up through October, 2003 of a phase III randomized trial where a dietary fat reduction intervention targeting fat intake reduction, associated with significant weight loss, improved relapse-free survival compared to control in women with resected, early stage breast cancer receiving conventional cancer management (RR 0.79, P=0.034) (JNCI 2006;98:1767-76). After initiating the dietary intervention with 16 visits over 8 weeks, ongoing adherence was addressed by q 3 month nutritionist contacts. Active dietary intervention and contacts with nutritionists ended in May, 2004. We now report a protocol-mandated survival analysis update.

Methods: Updated survival information was obtained through October, 2007 largely through national death registries and randomization group survival differences were examined using Cox proportional hazards models in intention-to-treat analyses. Exploratory analyses examined survival by hormone receptor subgroups and active dietary intervention status.

Results: Although fewer deaths were seen in the intervention group (9.1% vs. 11.1% cumulative mortality, RR 0.83) the difference was not statistically significant (P=0.146). In the 362 women with ER- and PR- disease, a significant overall survival difference was seen for intervention group participants (7.5% vs. 18.1%, cumulative mortality, RR 0.41, P=0.003). The influence of ongoing active dietary intervention was examined by analyses censored six months after contact with nutritionists ended (for survival before and after 12/31/04).

Conclusions: A dietary intervention targeting fat intake reduction did not significantly increase overall survival of women with resected breast cancer receiving conventional cancer management. Exploratory analyses suggest dietary intervention influence on survival may be greater in hormone receptor negative subgroups and during the period of active dietary intervention.

C) Look AHEAD (Action For Health in Diabetes)

Look AHEAD (Action For Health in Diabetes) is a multicenter randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. Look AHEAD is focusing on the disease most affected by overweight and obesity, type 2 diabetes, and on the outcome that causes the greatest morbidity and mortality, cardiovascular disease.

The Look AHEAD trial has completed enrollment of 5,145 obese patients with type 2 diabetes. At study entry, participants were randomly assigned to one of two interventions, the Lifestyle Intervention or Diabetes Support and Education. They will be followed for a total period of up to 11.5 years.

The primary aim of Look AHEAD is to study the effects of the two interventions on major cardiovascular events: heart attack, stroke and cardiovascular-related death. Look AHEAD also will investigate the impact of the interventions on other cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include: diabetes control and complications, fitness, general health, health-related quality of life and psychological outcomes. The cost and cost effectiveness of the Lifestyle Intervention relative to Diabetes Support and Education will be assessed.

DSE-Control Group
- 2 social retention events-"Duck BoatTour" and Holiday Party at Longwood Grille.
- Classes were organized throughout the year for nutrition, exercise and support. Transition into Phase III is complete for 3 groups. This includes a two hour class that covers nutrition and fitness.
- Seasonal Newsletter

Lifestyle Intervention Group
- Retention Events-Duck Boat Tours, Holiday Party at Longwood Grille.
- Weight loss campaigns/refreshers-Strong Roots Campaign. Results were less effective than in the past, attendance were both positive. In speaking with other sites around the country, it was a general consensus that this campaign was not as effective at producing overall weight loss than other campaigns.
- Holiday Weight loss challenge-Continued in 2007. Not a national campaign, only done at Joslin. Participants signed contract during holiday season to either maintain or lose weight during a matter of 8 weeks. Incentive provided if successful as all participants lost weight.

E) Effects of Soy Isoflavones on Menopausal Hot Flashes

In collaboration with OB/GYN, we completed our study on alternatives to hormone replacement therapy in post-menopausal women. We investigated the effect of the novel daidzein-rich isoflavone-aglycone extract from soy germ fermentation on the severity and frequency of hot flashes in postmenopausal women.

The study design was a randomized, double-blind, placebo-controlled trial of menopausal women, aged 38 to 60 years who experienced 4-14 hot flashes/day. After a one-week run-in period, a total of 190 menopausal women were randomized to receive placebo, 40 or 60 mg/day of DRI for 12 weeks. The primary outcome was the mean changes from baseline to week 12 in frequency of hot flashes recorded in the participant dairy. The secondary outcomes included changes in quality of life and hormonal profiles. 147 subjects (77%) completed the study. DRI 40 mg and 60 mg equally improved hot flashes frequency and severity. Hot flash frequency reduced by 43% in 40 mg DRI group and 41% in 60 mg DRI group at 8 weeks when compared to 32% in the placebo group) (p = ns vs placebo). The corresponding numbers for 12 weeks were 52%, 51% and 39% respectively (p = 0.07 and 0.09 vs placebo). When comparing the 2 treatment groups with placebo, there were significant reductions in mean daily hot flash frequency. Supplement reduced hot flashes frequency by 43% at 8 weeks (p =0.08) and 52% at 12 weeks (p = 0.048), but did not cause any significant changes in endogenous sex hormones or thyroid hormones. The study suggests that daidzein-rich isoflavone aglycone supplement may be an effective and acceptable alternative to hormonal treatment for menopausal hot flashes.

E) Calcium Supplementation for Healthy Weight (CaSHew)

The CSNM has been given the opportunity to collaborate with one of our Boston Obesity Nutrition Research groups at the Massachusetts General Hospital to investigate Calcium Supplementation for Healthy Weight (CaSHew). The hypothesis is adding calcium and vitamin D supplementation, via

orange juice, to caloric restriction enhances weight loss and decreases visceral fat in adults with BMI in the range of 25 to 35 kg/m^2. The primary objective of this proposal is to evaluate the effect of calcium and vitamin D supplementation (in form of calcium and vitamin D fortified orange juice beverage) in combination with caloric deficit diet on weight loss in overweight and obese adults. Visceral fat loss will be examined as a secondary outcome. Enrollment is completed, with second arm of the study CaSHew lite patients completing study in April 2007. 83 patients were randomized to the CaSHew lite study and there were no adverse effects, study results are being analyzed and written up for publication.

Jin-Rong Zhou, PhD

In the past year, we continued to investigate the effects of dietary/nutritional components and ingredients from natural resources, alone and in their combinations on the prevention and treatment of cancer. The purpose is to identify potential synergistic combinations of active components to target on different important cellular pathways as effective candidates of preventive regimens. We investigated the activities of a panel of dietary components in inhibiting the growth of pancreatic cancer cells and the growth of endothelial cells as the primary screening steps to identify potential anti-growth and anti-angiogenesis candidates. We identified a few synergistic combination regimens of dietary active components that significantly inhibited the growth of pancreatic cancer cells and angiogenesis in vitro. These candidate combination regimens will be verified for their activities in the clinically relevant orthotopic animal models. We also initiated research on identifying more potent active components in Chinese herbs and botanicals for the prevention and treatment of different types of cancer and to elucidate the mechanisms of action of active components. We have identified certain active anti-prostate cancer components with less cytotoxicity to normal cells from Baihuashishicao and Danshen, and have been funded to continue the proposed research. The results derived from these proposals will be directly translated into clinical investigation for the prevention and treatment of related cancers. In addition, we have started to elucidate how epigenetic modification may play in understanding the mechanisms by which nutritional/natural active components and their combinations may prevent the development and progression of cancer. We focus primarily on the effects of treatments on DNA methylation. Our studies demonstrate that the combination of soy and tea active components indeed synergistically modulate the expression of certain genes via modification of methylation status of their DNA promoters. This mechanistic approach provides a novel strategy to understand how nutritional/natural active components exert their cancer preventive activities.

Abstracts Presentated at Local, National, and International Meetings

Grinbaum R, Stylopoulos N, Aguirre V, **Olbers T, Blackburn G**, Davis PJ, Kaplan L. Sleeve gastrectomy induces durable long-term weight loss and improvement of glucose homeostasis in rats. The Obesity Society 2007 Annual Scientific Meeting, New Orleans, LA. October 2007.

Olbers T, Stylopoulos N, **Grinbaum R**, Aguirre V, **Blackburn G,** Kaplan L. Roux-en-Y gastric bypass in rats decreases the preference for a high fat diet. The Obesity Society 2007 Annual Scientific Meeting, New Orleans, LA. October 2007.

Linglin Li, Ajita Singh, **Jin-Rong Zhou**. The combination of soy and green tea bioactive components synergistically prevents mammary carcinogenesis and modulates metabolic disorders in vivo. 7th International Soy Symposium: Role of Soy in Health and Disease Prevention, Bangkok, Thailand, March 6-9, 2007.

Individual Accomplishments

George L. Blackburn

- Chair, Commonwealth of Massachusetts Betsy Lehman Center for Patient Safety and Medical Error Reduction Expert Panel on Weight Loss Surgery

- Co-Chair, Reality Coalition *Help Not Hype: Getting Real about Weight Loss*
- Invited Reviewer Royal Society of New Zealand Centers of Research Excellance Fund, Grant Review February 9, 2007
- Invited Reviewer NIH 2007 Loan Repayment Grant Review 3/20/07
- Invited Reviewer NIDDK Diabetes Endocrinology Research Centers (DERCs) and Diabetes Research and Training Centers (DRTCs) Special Emphasis Grant Review
- July 22-24, 2007
- Food Research and Action Center, Washington, D.C. Board of Directors
- Obesity Specialist Credentialing Committee, The Obesity Society Representative
- American Society for Nutrition, Medical Nutrition Committee, Member
- Associate Editor, Obesity Research
- Editorial Board, Obesity Management

Jin-Rong Zhou

- Journal Reviewer: *J Urology, BMC Cancer, Cancer Letters, Clinical Cancer Research, International Journal of Cancer, Journal of Nutrition*
- Member, State Key Programs Review Panel, National Science Foundation of China
- Member, Risk and Prevention, Epidemiology Review Panel, Susan G. Komen Breast Cancer Research Foundation
- Visiting Professor: Nanjing University of Traditional Chinese Medicine, Nanjing, China
- Guest Editor: American Journal of Clinical Nutrition
- Managing Editor: Frontiers in Biosciences

Invited Presentations

George L. Blackburn

"Nutrition for the second fifty years." Get Fit and Stay Fit: Women's Health Event: Leventhal Sidman Jewish Community Center. Newton, MA; January 21, 2007.

"Medical nutrition therapy for obesity treatment." Boston Area Dietetic Interns Obesity Day. Boston, MA; January 22, 2007.

"Bariatric surgery." National Business Group on Health. Washington, DC; February 13, 2007.

"Surgical management of obesity." Harvard Nutrition and Metabolism Conference. Athens, Greece; March 31, 2007.

"Diet, behavior modification and exercise." American Gastroenterologist Association Annual Meeting. Washington, DC; May 22, 2007.

"Current and emerging strategies for reducing cardiometabolic risk." Athol Memorial Hospital. Athol, MA; July 26, 2007.

"Current and emerging strategies for reducing cardiometabolic risk." University of Nevada. Reno, NV; September 11, 2007.

"Research in dietetics." Beth Israel Deaconess Medical Center Dietetic Interns: Research Day. Boston, MA; September 24, 2007.

"Making weight control everybody's business." Reality Coalition Meeting: Institute of Medicine. Washington DC; October 11, 2007.

"Permissive underfeeding." HMS-CME: Enhancing the Safety of Parenteral and Enteral nutrition. Cambridge, MA; November 5, 2007.

"Nutrition, immunonutrition, no Nutrition?" HMS-CME: Critical Care and Trauma Symposium. Boston, MA; November 13, 2007.

"Obesity: impact of current non-pharmacologic and pharmacologic treatment options on cardiovascular risk." Joslin Diabetes Center Diabetes: From Research to Clinical Practice. Boston, MA; November 14, 2007.

"Low calorie sweeteners in weight management." Webinar for American Dietetics Association. December 11, 2007.

Jin-Rong Zhou, PhD

"Nutritional manipulations for prevention of bladder and prostate cancers." Urology Club: Beth Israel Deaconess Medical Center. Boston, MA; June 6, 2007.

"Nutritional manipulations for prevention of GU cancers." Department of Urology: Boston University. Boston, MA; April 13, 2007.

"Bioactivity-guided identification of anti-cancer components in Chinese herbal medicines." College of Pharmacy: Nanjing University of Traditional Chinese Medicine. Nanjing, China; December 17, 2007.

"Cellular function-directed development of natural drugs for cancer therapy." Institute of Molecular Experimental Therapy: East China Normal University. Shanghai, China.

"Bioactivity-guided identification of anti-cancer components in Chinese herbal medicines and reformulation with synergy." Institute of Molecular Experimental Therapy: East China Normal University. Shanghai, China.

REPORT OF TEACHING

George L. Blackburn

Undergraduate and Medical School Courses
Preventive Medicine & Nutrition course number PM711.0; Second year HMS Tutor.

Surgical Residents
Nutrition Class on Nutritional Assessment and Enteral Nutrition

CME Courses
HMS, Department of Continuing Medical Education, " Practical Approaches to the Treatment of Obesity: Obesity Medicine: Emergence of a New Discipline" Cambridge, MA. June 21-23, 2007 Course director.

HMS, Department of Continuing Medical Education, Enhancing the Safety of Parenteral and Enteral Nutrition. Cambridge, MA. November 4-6, 2007 Course Director.

Other Teaching Contributions:
9th Postgraduate Nutrition Symposium: Obesity and Inflammation, Harvard Medical School, Division of Nutrition (Associate Director of Division)
Small Steps and Practical Approaches to the Treatment of Obesity
http://www.medscape.com/viewprogram/8204
Nutrition Curriculum Committee at Harvard Medical School

Jin-Rong Zhou

Nutrition Curriculum Committee at Harvard Medical School

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original Articles

Jiang RW, **Zhou JR**, Hon PM, Li SL, Zhou Y, Li L, Ye WC, Xu HX, Shaw PC, But PPH. Lignans from *Dysosma versipellis* with inhibitory effects on prostate cancer cell lines. J Natural Products 2007; 70: 283-6.

Khaodhiar L, Ricciotti HA, Li L, Pan W, Schickel M, **Zhou JR, Blackburn GL.** Daidzein-rich isoflavone aglycones for the treatment of hot flashes in menopausal women. Menopause 2007; 15:125-34.

Mai Z, **Blackburn GL, Zhou JR**. Genistein synergistically increases inhibitory effect of tamoxifen on the growth of HER2-overexpressing human breast cancer cells. Mol Carcinogenesis 2007; 46: 534-42.

Mai Z, **Blackburn GL**, **Zhou JR**. Soy phytochemicals synergistically enhance the inhibitory effect of tamoxifen on the growth of estrogen-dependent MCF-7 human breast tumors in mice. Carcinogenesis 2007; 28: 1217-23.

Pi-Sunyer X, **Blackburn G,** Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007; 30(6):1374-83.

Pan W, **Blackburn GL, Zhou JR**. Effects of a daidzein-rich isoflavone aglycone extract on diet-induced obesity in an ovariectomized mouse model. Clin Exp Pharmacol Physiol 2007; 34: S55-7.

Welty FK, Lee KS, Lew NS, **Zhou JR**. Effect of soy nuts on blood pressure and lipid levels in hypertensive, prehypertensive, and normotensive postmenopausal women. Arch Intern Med 2007; 167: 1060-7.

Welty FK, Lee KS, Lew NS, Nasca M, **Zhou JR**. The association between soy nut consumption and decreased menopausal symptoms. Journal Womens Health (Larchmt) 2007; 16:361-9.

Zhou JR, Li L, Pan W. Dietary soy and tea combinations for prevention of breast and prostate cancers by targeting on metabolic syndrome elements in mice. Am J Clin Nutr 2007; 86:882S-8S.

Original Articles (Submitted or In press)

Abdolmaleky HM, Smith CL, **Zhou JR**, Thiagalingam S. Epigenetic alterations of the dopaminergic system in major psychiatric disorders. Methods Mol Biol. 2007; in press.

Khaodhiar L, Ricciotti HA, Li L, Pan W, Schickel M, **Zhou JR**, **Blackburn GL**. Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. Menopause 2007; in press.

Williams CJ, Fargnoli JL, Hwang JJ, van Dam RM, **Blackburn GL**, Hu FB, Mantzoros CS. Coffee consumption is associated with higher plasma adiponectin concentrations in women with or without type 2 diabetes: a prospective cohort study. Diabetes Care 2007; in press.

Reviews, Chapters, and Editorials

Abdolmaleky HM, Smith CL, **Zhou JR**, Thiagalingam S. Epigenetic modulation of reelin function in schizophrenia and bipolar disorder. In: Fatemi SH, editor. Reelin glycoprotein, biology, structure and roles in health and disease. New York: Springer Publishers; 2007. p 366-84.

Blackburn GL, Wang KA. Dietary fat reduction and breast cancer outcome: results from the Women's Intervenition Nutrition Study (WINS). Am J Clin Nutr 2007; 86(suppl):878S-81S.

Chlebowski RT, **Blackburn GL**. Diet and breast cancer recurrence (letter to Editor) JAMA 2007; 298:2135.

Khaodhiar L, **Blackburn GL**. Enteral nutrition support. In: Fischer JE, editor. Mastery of surgery, 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2007. p.45-56.

Zhou JR, Blackburn GL, Walker WA. Symposium Introduction: metabolic syndrome and the onset of cancer. Am J Clin Nutr 2007;86(suppl):817S-9S.

Reviews, Chapters, and Editorials (Submitted or In press)

Blackburn GL, Olbers T, Schneider BE, Sanchez VM, Brennan A, Mantzoros C, Jones DB. Surgical management of obesity and post-operative care. In: Mantzoros C, editor. Nutrition and metabolism. New Jersey: Humana Press. 2007; in press.

Mark P. Callery, MD, FACS
Charles M. Vollmer, Jr., MD, FACS
Tara S. Kent, MD

CLINICAL RESEARCH

Our work focuses on outcomes research in high-acuity pancreaticobiliary Surgery. Fueled by a robust clinical practice which focuses on treatment of pancreatic malignancies, cystic lesions, and pancreatitis in a multidisciplinary setting, we perform over 100 resection cases and another 75 major pancreaticobiliary operations per annum. A prospective database has been developed and maintained from this practice, and provides the substrate for our investigations.

Areas of emphasis have been the development and critical analysis of clinical pathways and other systems initiatives for optimal patient care. Separate investigations are centered on technical and perioperative management aspects of surgical care. Also explored has been the impact of surgical complications associated with these operations. We are now also embarking on Quality of Life analyses for these disease processes.

LIST OF CURRENT EMPLOYEES

Wande Pratt MSIV	Medical Student
David Odell, MD	Surgical Resident
Patrick Ross, MD	Surgical Resident
Shishir Maithel, MD	Surgical Resident
Tsafrir Vanounou, MD	Surgical Resident
Teviah Sachs, MD	Surgical Resident
Saju Joseph, MD	Surgical Resident

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

Our recent emphasis has been on defining the impact of pancreatic fistula following pancreatic resections. These analyses have demonstrated outcomes within the framework of the recently developed ISGPF clinical grading scale for this postoperative complication. Predictive factors for the development of fistulae have been delineated. We have further identified that the use of Octreotide is most beneficial and cost-effective when selectively applied to high-risk glands. A new clinical entity of the "latent" fistula has been identified. Another concentration has been showing the utility of the POSSUM surgical audit system in predicting morbidity and mortality following pancreatectomy. This work has been extended to illustrate the practical application of POSSUM in defining the interplay of baseline physiology and surgical performance. In addition, through collaboration with our radiology and oncology consultants, we have helped to define the place of state-of-the-art technologies in treatment of these diseases – most notably Cyberknife Radiotherapy and Multi Channel Detector CT Angiography scans for pancreatic cancer.

Abstracts presented at Local, National, and International Meetings

Vanounou T, Pratt WB, **Callery MP**, and **Vollmer CM**. A Novel Cost-Benefit Analysis of Prophylactic Octreotide for Pancreatic Resections. Oral Presentation at The Pancreas Club's 41st Annual Meeting, Washington, DC; May 20, 2007.

Pratt W, **Callery MP**, and **Vollmer CM**. Predictive Risk Factors for Development of Pancreatic Fistula Utilizing the ISGPF Classification Scheme. Oral presentation at the American Hepato-Pancreato-Biliary Annual Congress. Las Vegas, NV; April 21, 2007, and the New England Surgical Society 14th Annual Resident Research Day, May 11th, 2007. Also, this abstract was presented as a short oral presentation at The Pancreas Club 41st Annual Meeting, Washington, DC; May 20, 2007.

Pratt W, Maithel SK, **Vollmer CM,** and **Callery MP**. Clinical Impact of the Reoperative Abdomen in Resective Pancreatic Surgery. Poster presentation at SSAT for Digestive Disease Week. Washington, DC; May 21, 2007, and Poster presentation at The Pancreas Club 41st Annual Meeting, Washington, DC; May 20, 2007.

Pratt W, Maithel SK, **Vollmer CM,** and **Callery MP.** Predictive Risk Factors for Complications of Differential Severity in Resective Pancreatic Surgery. Poster presentation at SSAT for Digestive Disease Week. Washington, DC; May 21, 2007, and Poster presentation at The Pancreas Club 41st Annual Meeting, Washington, DC; May 20, 2007.

Pratt W, Joseph S, **Callery MP**, and **Vollmer CM.** Predictive Risk Assessment Using POSSUM in Pancreatic Surgery. Poster presentation at The Pancreas Club 41st Annual Meeting, Washington, DC; May 20, 2007.

Zamboni G, Kruskal JB, **Vollmer CM**, Baptista J, **Callery MP**, Raptopoulos VD. Accuracy of MDCT Angiography In The Preoperative Evaluation Of Pancreatic Adenocarcinoma. Oral presentation at the Radiological Society of North America Annual National Meeting. Chicago, IL; November 2007.

Odell D, Pratt W, **Callery MP,** and **Vollmer CM.** Prediction of Morbidity in High-Acuity Surgery: The Influence of Surgical Performance on Baseline Physiology. Oral Presentation at the 54th Annual Meeting of the Massachusetts Chapter of the American College of Surgeons (MC-ACS). Boston, MA. December 8, 2007
Note: This abstract won a 3rd place award at the meeting.

Kent TS, Sreeramoju P, Weber TK. Adequate lymph node harvest in colorectal cancer resections independent of specialty training and surgeon volume. Poster presentation at the Society of Surgical Oncology meeting, Washington, DC; March 2007.

Shin J, Mariadson J, Yuan Z, Jhawer M, Arango D, Nasser S, Fordyce K, Sreeramoju P, **Kent TS**, Weber TK. Increased epidermal growth factor receptor (EGFR) gene expression in microsatellite unstable (MSI) human colorectal cancer (CRC) is characterized by mutations in the poly A tract of the 3' untranslated region (UTR) of the EGFR gene. Plenary presentation at the Society of Surgical Oncology meeting, Washington, DC; March 2007.

Individual Accomplishments

Mark P. Callery

- Served as President-Elect of the AHPBA for 2007-2008
- (Incoming President for 2008-2009)
- Served as Treasurer and on Executive Council, AHPBA for 2006-2007
- Served as Program Committee Chairman, and on Board of Trustees, Society for Surgery of the Alimentary Tract (SSAT), 2006-2007
- Served on Board of Governors, SAGES, 2006-2007
- Served on the Editorial Board for the following Journals:
    - Journal of Gastrointestinal Surgery
    - Surgical Endoscopy
    - Journal of Laparoendoscopic & Advanced Surgical Techniques
- Invited Contributor, Selected Summaries, Gastroenterology
- Reviewer for the following Journals:
    - Annals of Surgery
    - Journal of the American College of Surgeons
    - Surgery
    - Annals of Surgical Oncology
    - HPB
- External Advisory Board – NCI Grant "Genetics and Biology of Pancreatic Ductal Adenocarcinoma"

Charles M. Vollmer

- Local Nominee for AAMC National Humanism in Medicine Award (Harvard Medical School)
- Nominee for 2006 Excellence in Mentoring Award (Harvard Medical School)
- Rabkin Fellow in Medical Education; Carl J. Shapiro Institute for Education and Research, Beth Israel Deaconess Medical Center and Harvard Medical School
- Named as Kay Senior Fellow in Medical Education (Carl J. Shapiro Institute for Education and Research, Beth Israel Deaconess Medical Center, Harvard Medical School)
- Named as Co-Chairman of the AHPBA Membership Committee
- Reviewer for the following Journals:
    - Journal of the American College of Surgeons
    - Cancer
    - Annals of Surgery
    - Journal of Surgical Oncology
    - Digestive Diseases and Sciences
    - Journal of the Pancreas (JOP)
    - Surgery
    - Annals of Surgical Oncology
    - CA: A Cancer Journal for Clinicians
- Third Place Award and Oral presentation at the Massachusetts Chapter of the ACS. "Prediction of Morbidity in High-Acuity Surgery: The Influence of Surgical Performance on Baseline Physiology"
- Poster of Distinction – Massachusetts Chapter – ACS
- "The Obstructed Pancreatico-Biliary Limb: Presentation, Management and Outcomes"

Invited Presentations

Mark P. Callery

"Lymphadenectomy for pancreatic cancer." XIV International Course in Hepatopancreaticobiliary Surgery. Mexico City, Mexico; February 8, 2007.

"Surgery vs GUT stents; a review." and "Evidence-based medicine review: gastric outlet obstruction." Rome, Italy; February 21, 2007.

"Surgical aspects of pancreatitis." Gastroenterology and Hepatology Update: Harvard Medical School. Boston, MA; March 26, 2007.

"Quality analysis in high- acuity surgery." Department of Surgery Grand Rounds, Beth Israel Deaconess Medical Center. Boston, MA; April 3, 2007.

"Pancreatic neoplasms." ; "Decompression of malignant biliary obstruction." and "PTBD, endostents, or open biliary drainage?" SSAT Meeting. Washington DC; May 20, 2007.

"Quality analysis in high- acuity surgery." Department of Surgery Grand Rounds, Roswell Park Cancer Institute. Buffalo, New York; June 13, 2007.

"Regionalization for complex operations." Annual SSAT Meeting. Washington DC; May 22, 2007.

"Management of pancreatic masses." Annual SSAT Meeting. Washington, DC; May 22, 2007.

"Management of colorectal metastases." American College of Surgeons Clinical Congress. New Orleans, LA; October 10, 2007.

Charles M. Vollmer, Jr.

"Surgery for chronic pancreatitis." NPF Fellow's Leadership Symposium. Chicago, IL; April 13, 2007.

"Whipple's resection for radiologists." Abdominal Radiology Rounds: BIDMC. Boston, MA; August 30, 2007.

"What is this thing IPMN?" Department of Surgery Grand Rounds: Beth Israel Deaconess Medical Center. Boston, MA; October 17, 2007.

"Practical issues for the new investigator" and "Preparing and training for a career in clinical research." Center for Faculty Development: BIDMC. Boston, MA; May 11, 2007.

"Total pancreatectomy." Americas Hepato-Pancreato-Biliary (AHPBA) Annual Congress. Las Vegas, NV; April 21, 2007.

"Clinical studies in pancreatic cancer." Scientific session of The Pancreas Club: 41st Annual Meeting. Washington, DC; May 20, 2007.

"Quick shots." Society for Surgery of the Alimentary Tract (SSAT) 48th Annual Meeting, Scientific Session. Washington, DC; May 23, 2007.

Workshop on the future of research in pancreatic diseases. National Pancreas Foundation. Baltimore, MD; February 10, 2007.

Charles Vollmer, Jr.

REPORT OF TEACHING

Undergraduate Teaching

Wande Pratt, MSIV has worked under our tutelage for the last 2 ½ years, investigating various aspects of clinical outcomes in high acuity surgery. During that period, he has served as a Doris Duke Clinical Research Fellow (2005-2006), obtained a Masters of Public Health from the Harvard School of Public Health (2006-2007), and is currently preparing to defend his thesis for "Honors in a Special Subject" regarding the topic of pancreatic fistulae.

Principle Clinical Experience (PCE) Faculty (BIDMC) – Part of a core faculty who provide the longitudinal education curriculum to HMS III students.
Role: Case Conference facilitator
Role: Lecturer
"Abdominal Radiology Clinical Correlation"
"Pancreatitis"

Other Teaching Contributions

John Warren Surgical Society (HMS Surgery Interest Group) – Founding Faculty Advisor
Provide leadership for a student-led Surgical Society designed to expose junior medical students to the field and to prepare senior students for a career in surgery. We also developed a topical curriculum and faculty mentorship program.

Resource Faculty (BIDMC Educational Task Force) - Department Representative
Purpose is to promote development of faculty teaching in our department, as well as the institution as a whole, with the overarching goal of improving the quality of education of medical students and residents. Participation in Teaching Consult Service.

Rabkin Fellow in Medical Education (2006-2007) - Studied advanced medical education principles while developing a curriculum in HPB surgery.

Clinical Ultrasound Training - Developed a new curricular offering of for our surgical residency. Through a daylong course, 2nd-Year surgical residents are now taught the Acute Abdominal Ultrasound module of the American College of Surgeons ultrasound process. This certifies them to perform FAST examinations,

and other assessments of critically ill patients. This places us in only a handful (3-5) of surgical residency programs in the country, which offer formal Ultrasound training.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original articles

Brennan DD, Zamboni G, Sosna J, **Callery MP**, **Vollmer CM**, Raptopoulos VD, Kruskal JB. Virtual Whipple: preoperative surgical planning with volume-rendered MDCT images to identify arterial variants relevant to the Whipple procedure. AJR Am J Roentgenol 2007; 188(5):W451-5.

Maithel SK, Khalili K, Dixon E, Guindi M, **Callery MP**, Cattral MS, Taylor BR, Gallinger S, Greig PD, Grant DR, **Vollmer CM.** Impact of regional lymph node evaluation in staging patients with periampullary tumors. Ann Surg Oncol 2007; 14(1); 202-10.

Maithel SK, Pratt W, Kelleher T, Avigan D, Goldman H, Pfeifer W, Pihan GA, **Vollmer CM**. Autoimmune pancreatitis in the setting of castleman's disease. Pancreas 2007; 35(4): 384-438.

Pratt W, Maithel SK, Vanounou T, Huang Z, **Callery MP**, **Vollmer CM**. Clinical and economic validation of the international study group of pancreatic fistula (ISGPF) classification scheme. Ann Surg 2007; 245(3):443-51.

Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C, Traverso LW, and members of the Pancreatic Anastomotic Leak Study Group. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1507 patients: a report from the pancreatic anastomotic leak study group. J Gastrointest Surg 2007; 11:1451-9.

Sahajpal A, **Vollmer CM,** Dixon E, Chan EK, Wei A, Cattral MS, Taylor B, Grant DR, Greig PD, Gallinger S. Chemotherapy prior to liver resection for colorectal cancer hepatic metastases does not adversely affect perioperative outcomes. J Surg Oncol 2007; 95(1):22-7.

Shin J, Yuan Z, Fordyce K, Sreeramoju P, **Kent TS**, Kim J, Wang V, Schneyer D, Weber TK. A del T poly T (8) mutation in the 3' untranslated region (UTR) of the CDK2-AP1 gene is functionally significant causing decreased mRNA stability resulting in decreased CDK2-AP1 expression in human microsatellite unstable (MSI) colorectal cancer (CRC). Surgery 2007; 142:222-7.

Vanounou T, Pratt W, **Callery MP**, **Vollmer CM.** Selective administration of prophylactic octreotide during pancreatoduodenectomy: a clinical and cost-benefit analysis in low- and high-risk glands. J Am Coll Surg 2007; 205:546-57.

Vanounou T, Pratt W, Fischer JE, **Vollmer CM**, **Callery MP**. Deviation based cost modeling (DBCM): a novel model to evaluate the clinical and economic impact of clinical pathways. J Am Coll Surg 2007; 204(4):570-9.

Vollmer CM, Pratt W, Vanounou T, Maithel SK, **Callery MP**. Quality assessment in high-acuity surgery: volume and mortality are not enough. Arch Surg 2007; 142(4):371-80.

Zamboni G, Kruskal JB, **Vollmer CM**, Baptista J, **Callery MP**, Raptopoulos VD. Pancreatic adenocarcinoma: value of multidetector CT angiography in preoperative evaluation. Radiology 2007; 245 (3):770-8.

Original articles (Submitted or In press)

Pratt W, Joseph S, **Callery MP**, **Vollmer CM**. POSSUM accurately predicts morbidity in pancreatic resection. Surgery 2007; in press.

Pratt W, **Callery MP**, **Vollmer CM**. Risk prediction for development of pancreatic fistula utilizing the ISGPF classification scheme. World J Surg 2007; in press.

Pratt W, Steinbrook RA, Maithel SK, Vanounou T, **Callery MP, Vollmer CM**. Epidural analgesia in pancreaticoduodenectomy: a critical appraisal. J Gastrointest Surg 2007; in press.

Shaberg FJ, Miner T, Ng T, Chi D, Chapman WC, Birkett DH, Prinz RA, Libertino JA, **Vollmer CM**. Incidental lesions of the pancreas. Curr Prob Surg 2007; in press.

Reviews, Chapters, and Editorials

Callery MP. Pancreatic disorders: state of the science and future directions. Pancreas 2007; 35:276-80.

Callery MP. Central control of pancreatic cancer pain: protecting the enemy? Gastroenterology 2007; 132(3):1191-2.

Callery MP. Biological therapies for pancreatic cancer. Gastroenterology 2007; 132(7):2607-8.

Callery MP, **Vollmer CM**. Ultrasonography by surgeons. In: Fischer JE, editor. Mastery of surgery, 5th edition. Philadelphia: Lippincott, Williams and Wilkens; 2007; p. 410-20.

Vollmer CM. Necrosectomy for acute necrotizing pancreatitis. In: Fischer JE, editor. Mastery of surgery, 5th edition. Philadelphia: Lippincott, Williams and Wilkens; 2007; p. 1278-80.

Vollmer CM, Pratt W, **Callery MP**. "Clinical and economic validation of the international study group of pancreatic fistula (ISGPF) classification scheme". Ann Surg 2007; 246(5):910.

Vollmer CM, **Callery MP**. Biliary injury following laparoscopic cholecystectomy: why still a problem? Gastroenterology 2007; 133:1039-41.

Reviews, Chapters, and Editorials (Submitted or In press)

Callery MP, Pratt WB, **Vollmer CM**. Prevention and management of pancreatic fistula. J Gstrointest Surg 2007; in press.

Books, Monographs, and Textbooks

Callery MP, section editor. In: Fischer JE, editor. Mastery of surgery, 6th edition. Philadelphia: Lippincott, Williams and Wilkens; 2007.

Clinical Communications

Callery MP, Vollmer CM. Patient Care Guidelines – Society for Surgery of the Alimentary Tract

Vollmer CM. Cystic neoplasms of the pancreas. J Gastrointest Surg 2007; 11: 1225-7.

Vollmer CM. Surgical treatment of esophageal cancer. J Gastrointest Surg 2007; 11: 1216-8.

Vollmer CM. Surgical repair of incisional hernias. J Gastrointest Surg 2007; 11: 1231-2.

Abstracts

Pratt W, **Callery MP**, **Vollmer CM.** Prediction of morbidity in high-acuity surgery: the influence of surgical performance on baseline physiology. J Am Coll Surg 2007; 204 (Supplement 3): 74A.

Moss AC, **Callery MP**, Falchuck KR. Gastroinstestinal stromal tumor of the ampulla of vater mimicking a duodenal ulcer. Clin Gastroenterol Hepatol 2007; 5(10):26A.

Rosemary Duda, MD, MPH

BASIC RESEARCH


Rosemary Duda

Identification of a marker for breast cancer detection
This study involves collecting blood samples from women with a diagnosis of breast cancer. Samples are analyzed for a nuclear matrix protein that may be linked with early detection of breast cancer.

CLINICAL RESEARCH

Women's Health Study in Accra, Ghana
This study is an assessment of the burden of communicable and non-communicable disease in a cohort of 3200 adult women who reside in Accra, Ghana.

Assessing the ideal body image for Ghanaian women and men
Obesity and the linked illnesses are highly prevalent in Accra, the capital and largest city in Ghana. General reasons for obesity include genetics, lack of exercise, and increased dietary intake. Another possible reason for obesity is culture. This study assesses the cultural ideal body image for both men and women and compares gender differences in perception of ideal body image.

Prevalence of breast cancer in Ghana
This is a first step to quantify breast cancer prevalence and the identification of risk factors for breast cancer in Ghanaian women.

Mortality in Accra, Ghana
This study assessing the all cause mortality in Accra, Ghana.

EDUCATIONAL RESEARCH

Assessment of the impact of leadership courses for academic medical faculty
This is an assessment of the impact on academic and leadership career development for faculty who have attended one of the leadership courses offered for BIDMC faculty.

LIST OF CURRENT EMPLOYEES

Marlene Johns — Administrative Assistant

LIST OF CURRENT FUNDING

"Health, poverty and place: modeling inequities in Accra Ghana using RS and GIS"
NIH, **R01HD054906-01A1**
Project Period: 2007-2012
PI: John Weeks, PhD
Co-Investigator: Rosemary B. Duda, MD, MPH

"An investigation of the clinical utility of NMP66 in breast cancer detection"
Matritech, Inc.
Project Period: 2001-2007
PI: Rosemary B. Duda, MD, MPH

"Development and evaluation of the Center for Faculty Development Leadership development course for junior faculty"
Educational Grant/ Matritech, Inc.
Project Period: 2002-2007

PI: Rosemary B. Duda, MD, MPH

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

Health: Our goal for 2007 was to finalize and publish the results of the Women's Health Study in Accra. The major paper reporting on the results is now published.

Faculty Development: We conducted a survey of all faculty assessing the impact of mentorship and gender on career advancement. The data has been analyzed and manuscript submitted for publication. A second survey, this one for New Faculty hired through HMFP, assess career goals, mentorship and leadership. It is a longitudinal study that will collect data for at least ten years.

Abstracts presented at Local, National, and International Meetings

"An assessment of a leadership development course for junior faculty". The American Association of Medical Colleges annual meeting in Washington, DC. November, 2007.

Individual Accomplishments

- Professional and Educational Leadership Role
- Commission on Cancer, American College of Surgeons
- Conference Planning Committee
- Genetics Subcommittee
- Society of Surgical Oncology
- Chair, Clinical Affairs Committee
- Recognition of Service – 10 years of serving on the ACS Commission on Cancer
- Volunteer medical service in Nicaragua
- Co-investigator on an NIH funded study to assess the burden of disease in Accra, Ghana

Invited Presentations

"A comparative analysis of malaria in Central American countries." Maria Luisa Ortiz Cooperative and Women's Center. Mulukukú, Nicaragua; June 2007.

"A career in surgical oncology." American College of Surgeons Clinical Congress Medical Student Forum 1. October 2007.

REPORT OF TEACHING

Graduate School and graduate medical courses

Role of Discovery in Medicine
Seminar Leader
First Year medical students

4th Year Comprehensive Examination OSCE
Abdominal Pain and Breast Examination
Fourth year medical students

I am also actively involved in teaching medical students and surgical residents in the operating room.

CME courses

HMS Program for Leadership Development for Physicians and Scientists

Course co-Director, Session Moderator, Discussion Leader

CFD Course: "Distinguishing yourself as an independent clinical investigator"
Course Director
Presenter: Session II: Preparing and Training for a Clinical Research Career - "Training Programs for the Clinical Investigator offered at BIDMC"

CFD 2007 Leadership Course for Junior Faculty: Preparing for a Leadership
Career in Academic Medicine"
Course Director
Lecturer: "Leadership Course Framework and Self-Assessment of Leadership Skills"
Lecturer: "Acquiring New Skills – The Principles of Leadership"

Effective Mentoring: A faculty development Course for Mentors
Course Director, Sponsored by CHADD (Consortium of Harvard Affiliated Offices and Centers for Faculty Development and Diversity)
Lecturer: "Assessing the Impact of Mentorship in Academic Medicine"

Other Teaching Contributions

4th Year Harvard Medical Student Honors Thesis Advisor

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original Articles

Bober SL, Hoke LA, **Duda RB**, Tung NM. Recommendation recall and satisfaction after attending breast/ovarian cancer risk counseling. J Genet Couns 2007 Dec; 16(6):755-62.

Duda RB, Jumah NA, Hill AG, Seffah J, Biritwum R. Assessment of the ideal body image of women in Accra, Ghana. Trop Doct 2007 Oct; 37(4):241-4.

Duda RB, Kim MP, Darko R, Adanu RM, Seffah J, Anarfi JK, Hill AG. Results of the women's health study of Accra: assessment of blood pressure in urban women. Int J Cardiol 2007 Apr 12; 117(1):115-22.

Hill AG, Darko R, Seffah J, Adanu RMK, Anarfi J, **Duda RB**. Clinical findings from the women's health study of Accra. Int J of Gyne and Ob 2007; 99(2): 150-6.

Original Articles (Submitted or In press)

Duda RB, Brodsky D, Krishnamurthy KB, Pradhan L. The impact of mentorship and gender on career goals and success in academic medicine. Arch Intern Med 2007; in press.

Duda RB, Anarfi J, Darko R, Adanu RMK, Seffah J, Hill AG. The health of the "older women" in Accra, Ghana: results of the women's health study of Accra. J Cross Cult Gerontol 2007; in press.

Duda RB. Impact of leadership development courses for junior faculty. Leadership Health Sci 2007; in press.

Jumah NA, **Duda RB**. Comparison of the perception of ideal body images of Ghanaian men and women. Afr J Health Sci 2007; in press.

Reviews, Chapters, and Editorials

Duda RB, Hill AG. Surgery in developing countries: should surgery be a component of population-based health care? ACS Bulletin 2007; 92(5):12-8.

Educational Materials

Duda RB. CFD/GME: Transitioning from training to faculty. 2007; syllabus.

Duda RB. The Center for Faculty Development course for clinical investigators. 2007; syllabus.

Duda RB. The Center for Faculty Development leadership course for junior faculty: preparing for a leadership career in academic medicine. 2007; syllabus.

Duda RB. Lo que usted debe saber sobre los exámenes de los senos: A handbook for performing self-breast examinations in Spanish. 2007; brochure.

Clinical Communications

Duda RB. "At the end of the day, did we make a difference?" AWS Communications, October 2007.

Sandra M. Gaston, PhD

BASIC RESEARCH


Sandra Gaston

My research laboratory is focused on characterizing the individual biological differences that can influence the clinical behavior of human cancers, with a major emphasis on prostate cancer. We are fortunate to have access to well-documented human clinical samples, and we have developed a number of innovative technologies that allow us to perform detailed molecular genetic analyses of these specimens without compromising patient care. These include a set of tissue print and print-phoresis technologies designed to generate spatial-molecular maps of tumor markers in needle biopsies and surgical specimens while preserving the tissue itself for diagnostic histopathology (Gaston et al. Nature Medicine 11: 95-101, 2005). Currently, with support from three different grants from the National Cancer Institute, we are utilizing our tissue print technologies to investigate the molecular genetic events that shape the behavior of prostate cancers in human patients. By using our gene expression maps as overlays to annotate the histological features of clinical specimens, we have been able to use tumors and tissues from radical prostatectomies to identify a set of molecular marker profiles that differentiate locally invasive prostate cancer from indolent tumors. We are also using tissue print gene expression maps to profile the molecular genetic events that correspond to specific prostate cancer phenotypes that can by imaged in human patients using advanced Magnetic Resonance Imaging (MRI) techniques. In addition, we are applying our tissue print techniques to the analysis of prostate needle biopsies; these are key diagnostic specimens that must be submitted in their entirety for surgical pathology and are thus not usually available for molecular marker studies. These efforts have produced several sets of new biomarkers that may ultimately be useful in the management of patients with prostate cancer (see section V, part 1-4).

The hormonal microenvironment is an important variable in the biological behavior of many types of cancer, including prostate cancer, and my laboratory has developed a set of micro-bioassays that allow us to evaluate bioavailable androgens and estrogens in complex biological fluids. In a mouse model of prostate cancer, we showed that our bioassays could detect changes in bioavailable serum androgen that occur in response to soy based dietary supplements that inhibit tumor growth, and that these are distinct from immunoassay measurements of total and free serum testosterone (Zhou et al. Prostate 53:143-153, 2002). Recently, using this same mouse model of prostate cancer, we found that soy based dietary supplements that inhibit tumor growth also produce significant changes in tumor choline metabolism. With support from the DOD Prostate Cancer Research Program, are following up on this discovery, with the goal of developing a pre-clinical model to evaluate MR spectroscopy as an *in vivo* non-invasive technique for monitoring tumor response to soy-based dietary interventions in prostate cancer patients. We anticipate that that this project may have translational applications in the design of pharmacological and dietary interventions for prostate cancer patients who want to incorporate complementary therapies into their cancer care program.

During my first four years at BIDMC, in addition to my research laboratory, I was director of the BIDMC Andrology Laboratory. Although the clinical aspect of this laboratory is outsourced, the research component remains active under my direction. Our current Andrology research efforts focus on individual differences in the susceptibility to mitochondrial toxins, as measured by the effects of these toxins on sperm mitochondrial respiration and motility. Using this approach, we have identified a set of polymorphisms in the mitochondrial ATP synthetase that may be particularly important in determining both therapeutic and toxic responses to specific inhibitors of cell respiration (see section V, part 5).

LIST OF CURRENT EMPLOYEES

Andrew Guerra	Research Technician
Jerry Trejo	Research Technician
Heather Conroe	Research Student

Joanna Jung	Research Student
Julie Meadows	Research Student
Jason E Conage-Pough	Research Student
Amy L Moore	Research Student
Sarah J Han	Research Student
Yusuf Erkul	Research Student
Catriona MacDougall	Exchange Medical Student

LIST OF CURRENT FUNDING

"Tissue print micropeels for molecular profiling of cancer"
National Institutes of Health, **R21 CA112220**
Project Period: 2005-2007
PI: Sandra M. Gaston

"New strategies for interpreting *in vivo* prostate MRI/MRS choline spectra: manipulating gene expression to enhance cancer specificity"
DOD Prostate Cancer Research Grant, **PC051144**
Project period: 2005-2007
PI: Sandra M. Gaston

"Prostate MRI and MRS: correlations with gene expression"
NCI Grant, **R21 CA116866**
Project period: 2006-2009
PI: Sandra M. Gaston

"Improving patient care for prostate cancer"
Ellison Foundation Research Grant
Project Period: 2007-2010
Co-PI: Sandra M. Gaston

"Multi-analyte assessment of PrCa Chr21 rearrangements in diagnostic biopsies"
National Institutes of Health, Early Detection Research Network
Project period: 2006-2008
PI: Sandra M. Gaston

"MicroRNAs as potential biomarkers for specific subtypes of TMPRSS2-ERG positive prostate cancer"
National Institutes of Health, Early Detection Research Network
Project Period: 2007-2009
PI: Sandra M. Gaston

"Tissue print analysis of prostate needle biopsies: gene expression profiles of 'suspicious' and 'premalignant' cores"
New England Baptist Hospital Intramural Funding
Project Period: 2006-2007
PI: Sandra M. Gaston, PhD
Co-Investigators: Gary Kearney and Michael Kearney

"Choline metabolism in prostate cancers: response to dietary soy phytochemicals"
National Institutes of Health, **R21 CA130013**
Project Period: 2007-2010
PI: Sandra M. Gaston

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

"Tissue print micropeels for the molecular profiling of prostate needle biopsies"
NCI Grant, **R33 CA123331**

Proposed Project Period: 2008-2011
PI: Sandra M. Gaston

DIVISIONAL ACCOMPLISHMENTS IN THE PAST YEAR

Research Accomplishments

With NIH and intramural research support, my laboratory has continued to advance the development of a set of novel tissue printing technologies that support the molecular analysis of human tissue specimens. Our tissue print techniques allow us to transfer a microscopic layer of cells and extracellular matrix from the surface of a fresh tissue specimen onto nitrocellulose membranes, creating a "molecular xerox" which preserves the specimen for histopathology. We have combined tissue print techniques with specific protein and RNA/DNA detection methods to generate two-dimensional maps of molecular markers in radical prostatectomy specimens, and these maps have allowed us to identify clusters of molecular markers that co-localize with sites of microscopic invasion of cancer into the prostate capsule.

Because our tissue print techniques do not damage tissue specimens, we have been able to utilize this approach to obtain molecular marker profiles from human prostate needle biopsies. Prostate needle biopsies are key diagnostic specimens that must be submitted in their entirety for surgical pathology and are thus not usually available for molecular marker analysis. Using biopsy cores obtained from radical prostatectomy specimens as model specimens, we have demonstrated that we can generate both mRNA and protein marker profiles from biopsy tissue prints while preserving the cores for standard H&E and immunohistochemical studies. We have systematically improved the efficiency of our print RNA and DNA extraction and have achieved high quality gene expression profiles on Affymetrix microarrays using RNA obtained from prints from single biopsy cores. These important technical milestones allowed us to move forward with a pilot translational research protocol in which we are using tissue print analysis to perform molecular profiling studies on diagnostic prostate needle biopsies. This biopsy protocol allows us to capture molecular markers in prostate tissues from a much broader range of patients than can be represented in conventional tissue banks that rely upon radical prostatectomy specimens. Our biopsy print RNAs represent an important new resource for biomarker development efforts currently underway in our laboratory and in the larger prostate cancer research community. The significance of this unique resource for prostate biomarker analysis was recognized by the NCI Early Detection Research Network with two research grants entitled "Multi-Analyte Assessment of PrCa Chr21 Rearrangements in Diagnostic Biopsies" and "MicroRNAs as Potential Biomarkers for Specific Subtypes of TMPRSS3-ERG Positive Prostate Cancer."

With support from General Electric Industry Sponsored Research funds, an NIH Grant and the Ellison Foundation, we have used tissue prints to produce "molecular whole mounts" of radical prostatectomy specimens that can be mapped point-to-point with structures visualized *in vivo* by magnetic resonance imaging (MRI) and magnetic resonance spectra (MRS). We have collaborated with Dr. Robert Lenkinski and other investigators in the BIDMC MRI/MRS program to profile the patterns of mRNA expression that underlie the MRI/MRS choline peak that is frequently observed in prostate cancer. The genes that regulate choline metabolism include several that have been identified as "druggable" targets for new anti-cancer compounds. Recently, we identified an animal model of prostate cancer that appears to recapitulate some of the tumor-associated changes in choline metabolism that are observed in human patients, and we have received a DOD prostate cancer research grant and an NIH grant to support the development of this animal model for the pre-clinical study of the molecular mechanisms that produce MRI/MRS visible changes in tumor choline metabolism.

We have used our tissue print "molecular whole mounts" of radical prostatectomy specimens to generate gene expression maps of the angiogenic processes in human prostate cancer that result in MRI visible tumor-associated changes in tissue perfusion, as visualized *in vivo* by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI). Currently, we are using both Affymetrix microarray and rt-PCR data to compile gene expression "signatures" of DCE-MRI positive prostate cancers. These studies are an important component of a larger effort to interpret prostate DCR-MRI images in terms of the biological and clinical sub-types of human prostate cancer.

Mitochondrial toxicity can present a significant limitation to the clinical application of new therapeutic agents, and current pre-clinical models are inadequate to efficiently screen for this adverse activity. Because the motility of mammalian spermatozoa is exquisitely sensitive to the status of the mitochondria in the sperm midpiece, we have developed a novel *in vitro* bioassay that utilizes motile spermatozoa to detect individual differences in susceptibility to drugs and toxins that inhibit mitochondrial respiration. Utilizing both clinical samples and samples from an animal model (domestic boars), we have identified individuals whose pattern of sensitivity or resistance to specific classes of mitochondrial toxins could have important clinical consequences. Currently, we are characterizing genetic polymorphisms that we have found to be associated with increased sensitivity to the drug oligomycin. We anticipate that this study will provide proof-of-principle for a new pharmacogenomic screening strategy that can be used to identify the human chromosomal and/or mitochondrial alleles that give rise to individual differences in sensitivity/resistance to specific inhibitors of mitochondrial respiration.

Individual Accomplishments

- For the fifth consecutive year, I was named to the NIH National Cancer Institute Special Emphasis Panel to review grant applications submitted to the "Innovative Technologies for the Molecular Analysis of Cancer" (IMAT) program.
- I was named an External Advisor for the City of Hope NIH fellowship training program in Urologic Oncology.
- I was appointed to the EDRN Standing Review Committee which is responsible for reviewing grant applications for EDRN Associate Member Candidates.
- I was awarded an NIH grant entitled "MicroRNAs as Potential Biomarkers for Specific Subtypes of TMPRSS2-ERG Positive Prostate Cancer" through the NCI Early Detection Research Network (EDRN).
- I was awarded an NIH grant entitled "Choline Metabolism in Prostate Cancers: Response to Dietary Soy Phytochemicals".

Invited Presentations (Local, National, and International)

"Heterogeneous Expression of TMPRSS2-ERG Gene Fusions in Human Prostate Cancer: Insights from Transcript Maps of Patient Biopsies and Radical Prostatectomy Specimens." Department of Urology: City of Hope. Duarte, CA; May 24, 2007.

"MRI-Visible Phenotypes of Human Prostate Cancer: Gene Expression Profiles of DCE-MRI Positive Tumors." American Urological Association. Anaheim, CA; May 2007.

"Tissue Print Micropeels for the Molecular Profiling of Cancer." Plenary Presentation: Principal Investigators Meeting. National Cancer Institute Program for Innovative Molecular Analysis Technologies (IMAT). July 2007.

"TMPRSS2-ERG Gene Fusions in Human Prostate Cancer: Insights from Tissue-Print Micropeel Maps of Patient Biopsies and Radical Prostatectomy Specimens." Ventana Medical Systems. Tucson, AZ; July 12, 2007.

"Tissue Print Micropeels: A Practical Approach to the Assessment of Diagnostic Prostate Needle Biopsies for Cancer Biomarkers Generated by Chromosome 21 Rearrangements." NIH Early Detection Research Network Steering Committee Meeting. Ann Arbor, MI; September 17, 2007.

Abstracts Presented at Local, National, and International Meetings

Gaston SM, **Guerra AL, Conroe H, Meadows J**, Hayek J, Latham G, **Kearney MC**, Juan-Miguel Mosquera JM, Rubin MA, **Sanda MG** and Kearney GP. Heterogeneous Expression of TMPRSS2-ERG Gene Fusions in Human Prostate Cancer: Insights from Transcript Maps of Patient Biopsies and Radical

Prostatectomy Specimens. Gordon Research Conference: New Frontiers in Cancer Detection and Diagnosis. January, 2007.

Gaston SM, **Guerra AL, Conroe H, Trejo G**, **Jung J,** Hayek J, Lenkinski RE and Kearney GP. Heterogeneous Expression of TMPRSS2-ERG Gene Fusions in Human Prostate Cancer: Insights from Transcript Maps of Patient Biopsies and Radical Prostatectomy Specimens. Proc of the Amer Assoc for Cancer Res. April, 2007.

Gaston SM, **Guerra AL, Conroe H**, **Jung J, Trejo G,** Hayek J, **Kearney MC** and Kearney GP. Development of New Translational Technologies to Resolve the Clinical Dilemma of "Suspicious" Prostate Biopsies. 4th Annual NEBH Research Symposium. June 5, 2007.

Zhou JR, **Guerra AL, Goldner D**, Lenkinski RE, Cheng LL and **Gaston SM**. New Strategies for Interpreting in Vivo Prostate Magnetic Resonance Imaging/Magnetic Resonance Spectroscopy: Manipulating Expression of Genes of Choline Metabolism to Enhance Cancer Specificity Congressionally Directed Medical Research Programs. Prostate Cancer Research Program IMPaCT Meeting. Atlanta, GA; September, 2007.

Andrew Guerra

Joanna Jung

Kearney MC, Kearney GP, **Guerra AL, Conroe H, Trejo G**, **Jung J, Bueti G**, Hayek J, Mosquera JM, **Sanda MG**, Rubin MA and **Gaston SM.** Heterogeneous Expression of TMPRSS2-ERG Gene Fusions in Human Prostate Cancers: Insights from a Prospective Prostate Biopsy Series. 76th Annual Meeting New England Section of the American Urological Association, Boston MA. September, 2007.

REPORT OF TEACHING

Harvard Medical School Courses and Research Mentorships

- HMS-The Human Body (Jules Dienstag, MD, Director), Tutor, Fall 2007.
- HMS Molecular and Cellular Basis of Medicine (Randall King, MD, PhD, Director), Tutor, Fall 2007.
- I was research mentor for Catriona MacDougall, a medical student from Cambridge University (UK) participating in the Cambridge-MIT Exchange program.
- I was a research mentor to the following students in 2007:
-

Julie Meadows	Wellesley Student
Jason E Conage-Pough	MIT Student
Amy L Moore	MIT Student
Sarah J Han	MIT Student
Yusuf Erkul	MIT Student
Heather Conroe	MIT Student

Joanna Jung Simmons Student

PLANS FOR THE COMING ACADEMIC YEAR

New Research Initiatives

- This year we are beginning two new NIH grants ""MicroRNAs as Potential Biomarkers for Specific Subtypes of TMPRSS2-ERG Positive Prostate Cancer" and beginning the second year of our NIH grant ""Choline Metabolism in Prostate Cancers: Response to Dietary Soy Phytochemicals"". These projects will allow us to extend and accelerate the development of our tissue print techniques for analysis of molecular biomarkers in prostate biopsies and to more fully characterize our animal model for pre-clinical studies of pathways that regulate MRI visible choline metabolites in prostate cancer.
- A major new effort this next year will be focused on developing tissue print biomarker protocols to support reliable, efficient detection of cancer-associated mitochondrial deletions in biopsy tissues and in micro-metastases that have colonized human bone.
- We look forward this year to several important new and/or expanded research collaborations. These include:

    - Gary Latham, PhD, Senior Scientist, Ambion, Inc. will expand his collaboration with us to evaluate newly developed Ambion technologies for RNA preparation using our tissue-print platform. One major focus will be on the incorporation of microRNA (miRNA) as well as messenger RNA (mRNA) analysis into the tissue print RNA profiles.
    - We will expand our collaboration with Mike Makrigiorgos PhD (Dana Farber Cancer Institute) to develop tissue print techniques for the analysis of tumor associated DNA amplifications and deletions.
    - Ryan Parr, PhD, Chief Scientific Officer, Genesis Genomics, will collaborate with us on both a clinical trial and a research study designed to more fully characterize a recently identified mitochondrial mutation that is common in prostate cancer. This molecular biomarker may be useful as a "follow up" test for men whose prostate biopsies are suspicious but not definitive for cancer as well as provide new insight into the changes in cellular metabolism associated with this malignancy.

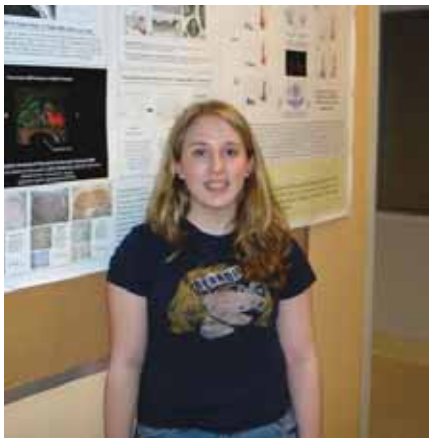
New Recruitment Activities

As both a member of the Harvard Medical School (HMS) faculty and a Visiting Scientist in the MIT Center for Biomedical Engineering, I have been able to develop a network of research students through the MIT undergraduate research program (UROP). This next year, I will continue to recruit from this highly talented pool of students.

We anticipate recruiting a postdoctoral fellow to join our tissue print based analysis of gene expression patterns associated with MRI-visible prostate cancer phenotypes.

Educational Activities

For the last seven years, I have been a member of the Teaching Faculty of Harvard Medical School. I am planning to continue to as a member of the faculty in one of the pre-clinical courses.



Heather Conroe

Julie Meadows

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Reviews, Chapters, and Editorials (Submitted or In press)

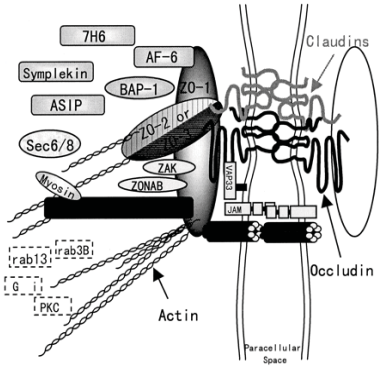
Wang F, Wang L, Briggs C, Sicinska E, **Gaston SM**, Mamon H, Kulke MH, Zamponi R, Loda M, Maher E, Ogino S, Fuchs CS, Li J, Hader C, Makrigiorgos GM. DNA degradation test predicts success in whole-genome amplification from diverse clinical samples. J Mol Diag 2007; 9(4):441-51.

Susan J. Hagen, PhD

BASIC RESEARCH

Susan Hagen

Our current NIH sponsored research projects are concerned with the regulation of gastric barrier function during health and disease, and our focus includes mechanisms that regulate tight junction organization and permeability in the stomach, gastric mucosal restitution after injury, and cell death and survival of gastric epithelial cells. Although we are particularly interested in the regulation of barrier function during *Helicobacter pylori* (HP) infection and how defects in the gastric mucosal barrier result in mucosal damage and gastric atrophy during infection, such studies are also pertinent to understanding gastric ulceration and stress-induced mucosal damage under surgical conditions and other critical illnesses including trauma and sepsis, where inflammation and hypoxia impact mucosal permeability, restitution, and epithelial cell death.



From Mitic, et al, Am J Physiol 279: G250, 2002

Inflammation-induced Defects in Tight Junction Permeability

Although the structure of tight junctions is well defined (inset), whether this generic organization is the same and how it relates to barrier properties of the gastric mucosa is unknown. In recent studies, it was shown that when occludin, one of two proteins that seal the paracellular space (inset), is knocked-out, mucosal damage occurs in the stomach and the stomach histology is identical to that seen during infection with HP. Lack of occludin affected only 2 tissues, the stomach and testis, suggesting that occludin regulates, in a unique way, the maintenance and/or development of tight junctions in these tissues. Because little is known about how occludin regulates development and/or maintenance of tight junctions at the surface of the gastric mucosa or in gastric glands, new culture models were recently developed by us to study the cell and molecular regulation of occludin in gastric surface and chief cells. How inflammation alters occludin, ZO-1, claudin, and e-cadherin localization and function, and mucosal permeability in the stomach are studies currently underway in the laboratory. We are also interested in the role of myosin light chain kinase, an enzyme that facilitates myosin contraction at the tight junction, in regulating permeability during inflammation and in facilitating the cell death of surface and chief cells.

Mechanisms that Regulate Gastric Mucosal Restitution after Injury

My laboratory is probably most well-known for studies concerning mechanisms that regulate restitution, which is rapid epithelial repair after injury, in the stomach. Our current focus concerns mechanisms by which intracellular pH is regulated and how this regulation affects restitution and subsequent repair of barrier function after injury. We recently proposed a novel idea that H^+/lactate export, via the monocarboxylate transporter-1 (MCT-1), may be essential for pH regulation during restitution by exporting lactate that is generated by glycolysis, a process we recently showed to be the main energy source for restitution. Current studies to understanding the role of MCT-1 in restitution are underway.

Heat Shock Proteins and Mucosal Protection

A new area of investigation in the laboratory is concerned with understanding pathways that regulate protection of epithelial cells against HP toxins and factors. These new studies were initiated because apoptosis of gastric epithelial cells is accelerated during HP infection and the death of gastric chief and parietal cells results in atrophic gastritis, which is the major initiating factor in the progression to gastric cancer. We recently showed that L-glutamine (Gln) protects against the death of surface cells in the presence of HP-associated ammonia (Nakamura E, AJP 2004) and, in the past year, extended these

studies to a model of HP pathogenesis in mice, using diets containing Gln. We have shown Gln-induced transcriptional regulation of heat shock proteins 70 and 25, and arginase protect against cell death and are working to elucidate how these proteins confer protection to gastric cells. These studies are done in collaboration with Dr. James G. Fox at MIT.

LIST OF CURRENT EMPLOYEES

Research Laboratory	
Songhua Zhang, MD, PhD	Research Fellow in Surgery
JiHye Seo, PhD	Research Fellow in Surgery
Core Facilities	
Microscopy-Confocal	
Lay-Hong Ang, PhD	Confocal Supervisor
Andrea Calhoun, BS	Research Assistant II (EM Core)
Histology	
Suzanne White, BS	Research Histotechnologist Supervisor
Wendy Dasgupta, BS	Research Histotechnologist
Surgical Research	
Sabrina Pinder, BS	Administrative Coordinator

Dr. Hagen with Laboratory and Core Groups
Back (from left): JiHye Seo, Susan Hagen, Suzanne White, Wendy Dasgupta.
Front (from left): Songhua Zhang, Lay-Hong Ang, Sabrina Pinder, Andrea Calhoun.

LIST OF CURRENT FUNDING

"GI mucosal barrier in health and surgical disease"
National Institutes of Health, NIDDK **5 R01 DK15681-36**
Project Period: 2003-2008
PI: Susan Hagen

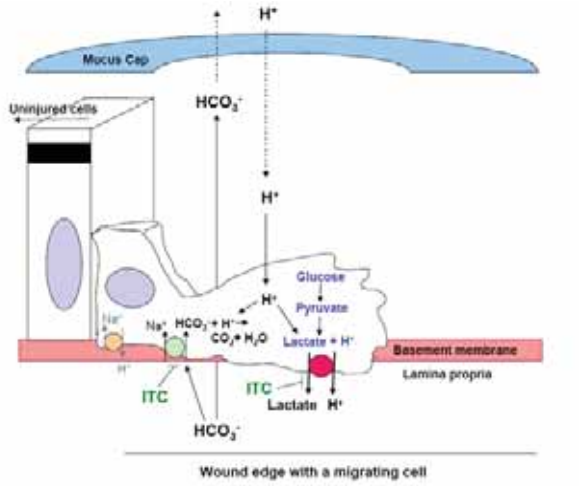
"Biology of alimentary epithelia in health and disease"
National Institutes of Health, NIDDK **P30 DK34854-12**
Harvard Digestive Diseases Center Grant
Project Period: 2005-2010
PI: Wayne Lencer, MD (Children's Hospital)

Subcontract: "Imaging Core Facility B"
Subcontract PI: Susan Hagen

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

In the past year, we finished three projects and submitted the work for publication. First, Regina Ragasa, a research assistant who spent 2 years in the lab prior to attending medical school, finished work concerning how isothiocyanate (**ITC**, below), the reactive group on stilbenes like DIDS and SITS, affects restitution and wound repair after injury. Regina found that isothiocyanates bind to the H^+/lactate co-transporter, MCT-1, in addition to the $Na^+/HCO3^-$ co-transporter and proposed that restitution is impaired because intracellular pH is affected adversely by blocking this transporter. The paper was submitted and will be the first to suggest MCT-1 plays a role in cell migration. Two abstracts from this work were accepted for presentation at DDW in May and her paper was published in the Journal of Pharmacology and Experimental Therapeutics in October (see the Bibliography, below).



from Ragasa, et al J Pharmacol Exp Ther 2007; 323(1):1-9.

Dr. Zhang finished a paper that was started by Dr. Tashima concerning the procedure for preparing isolated cultures of gastric chief cells that grow into a confluent monolayer within 3 days. Dr. Zhang extended this work to also show that chief cells divide in culture and de-differentiate into cells that contain trefoil factor (TFF2), a marker only found in spasmolytic polypeptide-containing metaplastic (SPEM) cells during HP infection. These results are important to lend insight as to how chief cells may become metaplastic during inflammatory disorders of the stomach. Dr. Zhang's work on TFF2 was also accepted for presentation at DDW in May of 2007. Work with Dr. James Fox concerning the expression of cell death and survival proteins and pathways in gastric cells was also finished and submitted for publication and an abstract on our collaborative work concerning glutamine protection during HP infection, *in vivo*, in mice was also accepted for presentation at DDW in May. We finished the paper on the later work, which is now under consideration in the Journal of Nutrition.

Administrative Accomplishments

I continued to work as Associate Director for Research in the Department of Surgery. Accomplishments this year were successful completion of, in collaboration with Dr. Per-Olof Hasselgren and with help from Kim Emswiler, the "Annual Research Report". We were also able to fill the vacant Administrative Coordinator position in the Office for Surgical Research (June of 2007) with a very capable person, Sabrina Pinder (photo at right), who was previously a Policy Department Supervisor at First American Title Insurance Company in Boston. With Sabrina's help, we published the "Funding Sources for Surgical Residents', maintained the space database for Surgery, organized seminars, and maintained HMS appointments and visas.

Sabrina Pinder

I also continued to direct the Microscopy, Histology, and

Confocal Core Facilities at BIDMC and to provide oversight and consultation for imaging experiments in the hospital and for members of the Harvard Digestive Diseases Center. Accomplishments this year were that I applied for and was awarded, by the BIDMC, funds to purchase a new Zeiss Photomicroscope for the Microscopy Core Facility. We also fully finished installation of the new Zeiss LSM510-META "live cell" confocal.

Individual Accomplishments

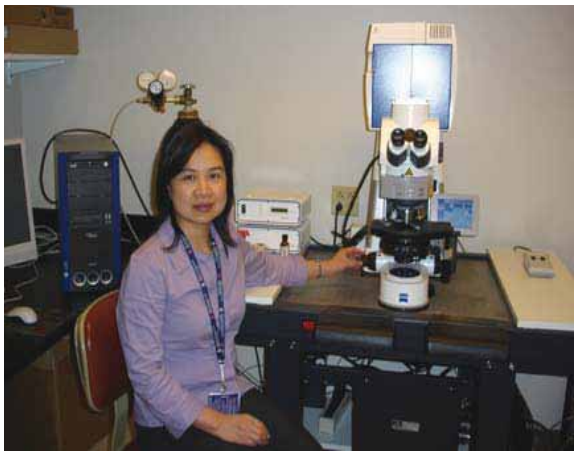
Again this year, I reviewed grant applications for the Gastrointestinal Mucosal Pathobiology (GMPB) study section, which met in February, June, and October. I am one of 12 chartered members of this study section.

I participated in reorganization of the Human Body course at HMS (IN753.0) as a member of the Planning Committee.

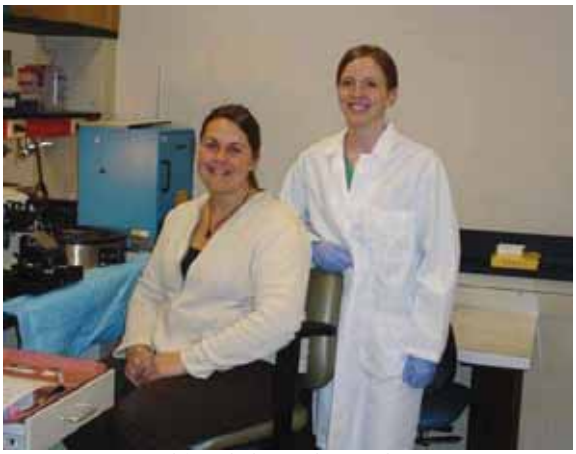
I was nominated to receive an Excellence in Mentoring Award at HMS.

I served as a panelist at the 2007 New England Science Symposium "Road to Success: Navigating Your Career".

I was nominated and then elected as a Councilor for the GI section of the American Physiological Society. This post is for the Steering Committee and will be from 2008-2011.



Lay-Hong Ang using the Zeiss Confocal System



Suzanne White (left) and Wendy Dasgupta

Invited Presentations (Local, National, and International)

Hagen SJ. "Mechanisms that regulate barrier properties of the stomach". Clowes Visiting Professor Investigator's symposium. January, 2007.

Poster Presentations at Local, National, and International Meetings

Hagen SJ, Ohtani M, Zhou J-R, Taylor NS, Rickman B, Fox JG. "Dietary glutamine supplementation reduces inflammation and hyperplasia during *Helicobacter pylori* infection in mice". This work was presented as a poster at Digestive Diseases Week and the 108th annual meeting of the American Gastroenterological Association. May, 2007.

Hayashi S, Nakamura E, Kubo Y, Suzuki M, **Hagen SJ**, Takeuchi K. "Isothiocyanate-related compounds inhibit the recovery of wounds induced in gastric epithelial cells: mediation by Trap1". This work was collaborative between my group and Professor Koji Takeuchi, Kyoto Pharmaceutical University. This

work was presented as a poster at Digestive Diseases Week and the 108th annual meeting of the American Gastroenterological Association. May, 2007.

Ragasa R, Nakamura E, Marrone LM, Yanaka S, Hayashi S, Takeuchi K, **Hagen SJ**. "Isothiocyanate blocks restitution and wound repair in the mammalian stomach by inhibiting both monocarboxylate and bicarbonate transport activity". This work was presented as a poster at Digestive Diseases Week and the 108th annual meeting of the American Gastroenterological Association. May 2007.

Ragasa R, Zhang S, Ong SH, **Hagen SJ**. "Monocarboxylate transporter-1 and sodium bicarbonate co-transport cooperate in the regulation of gastric epithelial restitution by influencing cell viability".
This work was presented as a poster at Digestive Diseases Week and the 108th annual meeting of the American Gastroenterological Association. May 2007.

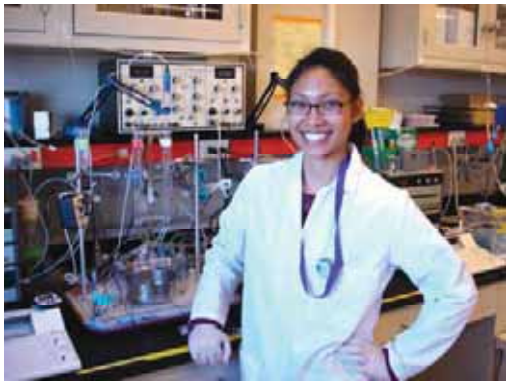
Zhang S, Tashima K, Ragasa R, Goldenring JR, **Hagen SJ**. "Isolation and culture of gastric chief cells are accompanied by proliferation and co-expression of intrinsic factor and Tff-2". This work was a collaborative effort between my group and Jim Goldenring at Vanderbilt and was presented as a poster at Digestive Diseases Week and the 108th annual meeting of the American Gastroenterological Association. May 2007.

REPORT OF TEACHING

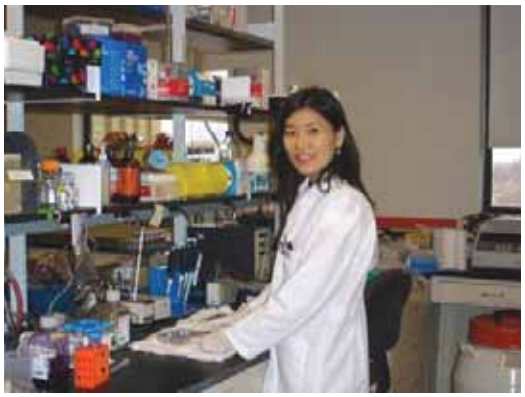
Undergraduate and Medical School Courses
I taught in the Human Body course (IN753.0) at Harvard Medical School from 10/9/2007- 12/1/2006 as co-director of the Cannon Society histology laboratory and as a tutor.

In addition to my usual responsibilities in the Human Body, this year I was responsible for staffing the histology labs, preparing the laboratory manual, and writing the curriculum for Histology.

Songhua Zhang



Regina Ragasa (Lab member until 9/07)



JiHye Seo

BIBLIOGRAPHY (JANUARY-DECEMBER 2007)

Original Articles

Ragasa R, Nakamura E, Marrone L, Yanaka S, Hayashi S, Takeuchi K, **Hagen SJ**. Isothiocyanate inhibits restitution and wound repair after injury in the stomach: *ex vivo* and *in vitro* studies. J Pharmacol Exp Ther 2007; 323(1):1-9.

Original Articles (Submitted or In press)

Kaufhold M-A, Krabbenhoft A, Song P, Engelhardt R, Riederer B, Fahrmann M, Klocker N, Beil W, Manns M, **Hagen SJ**, Seidler U. Localization, trafficking, and significance for acid secretion of parietal cell Kir4.1 and KCNQ1 K^+-channels. Gastroenterology 2007; in press.

Hagen SJ, Yang DX, Taylor J, Fox JG. Cell-specific survival and death pathways may regulate *Helicobacter pylori*-induced pathology in the mouse stomach. Am J Physiol GI Liver Physiol 2007; submitted.

Tashima K*, Zhang S*, Ragasa R, Muvaffak A, Nakamura E, **Hagen SJ**. Establishment of high resistance and low permeability cultures of chief cells from the rat stomach. Am J Physiol GI Liver Physiol 2007; submitted. *Contributed equally to the work.

Hagen SJ, Ohtani M, Zhou J-R, Blackburn GL, Taylor NS, Rickman B, Fox JG. Dietary glutamine supplementation reduces inflammation and hyperplasia during *Helicobacter pylori* infection in mice. J Nutr 2007; submitted.

Educational Materials

Hagen SJ. Histology Manual-The Human Body. Harvard Medical School, 2007.

Abstracts

Hagen SJ, Ohtani M, Zhou J-R, Taylor NS, Rickman B, [illegible]on reduces inflammation and hyperplasia during *Helicobacter pylori* infection in mice. Gastroenterology 2007; 132(4):218A.

Hayashi S, Nakamura E, Kubo Y, Suzuki M, **Hagen SJ**, Takeuchi K. Isothiocyanate-related compounds inhibit the recovery of wounds induced in gastric epithelial cells: mediation by Trap1. Gastroenterology 2007; 132(4):272A.

Ragasa R, Nakamura E, Marrone LM, Yanaka S, Hayashi S, Takeuchi K, **Hagen SJ**. Isothiocyanate blocks restitution and wound repair in the mammalian stomach by inhibiting both monocarboxylate and bicarbonate transport activity. Gastroenterology 2007; 132(4):273A.

Ragasa R, Zhang S, Ong SH, **Hagen SJ**. Monocarboxylate transporter-1 and sodium bicarbonate co-transport cooperate in the regulation of gastric epithelial restitution by influencing cell viability. Gastroenterology 2007; 132(4):271A.

Zhang S, Tashima K, Ragasa R, Goldenring JR, **Hagen SJ**. Isolation and culture of gastric chief cells are accompanied by proliferation and co-expression of intrinsic factor and Tff-2. Gastroenterology 2007; 132(4):544A.

Andrea Calhoun sitting at the JEOL 1200EX electron microscope

Per-Olof Hasselgren, MD, PhD

The research in our group is focused on mechanisms regulating the catabolic response to sepsis and injury in skeletal muscle. Sepsis and injury (and a number of other conditions as well, including cancer, AIDS, uremia, and starvation) are associated with muscle wasting (**Fig 1**), mainly reflecting ubiquitin-proteasome-dependent degradation of the myofibrillar proteins actin and myosin. This response in skeletal muscle has severe clinical consequences, including muscle weakness and fatigue, delayed ambulation with risk of thromboembolic and pulmonary complications and prolonged stay in the intensive care unit. Our research supports a model in which myofilaments are released from the sarcomere through a calcium/calpain-dependent mechanism followed by ubiquitination and degradation of actin and myosin by the 26S proteasome. The gene expression of calpains and several components of the ubiquitin-proteasome system, in particular the ubiquitin ligases atrogin-1 and MuRF1, is upregulated in atrophying muscle, supporting the concept that increased gene transcription is an integral part of muscle wasting mechanisms. Currently, the transcriptional regulation of genes in the ubiquitin-proteasome pathway is examined. In particular, the roles of the transcription factors C/EBPβ and δ and NF-kB as well as the nuclear co-factors p300 and PGC-1α and β in the regulation of atrogin-1 and MuRF1 expression are examined. In addition, the role of calcium in sepsis-induced and glucocorticoid-regulated muscle proteolysis is examined, in particular with regards to changes in store-operated calcium entry and regulation of calcium-calmodulin protein kinase II and PI3K/Akt/GSK3β signaling.

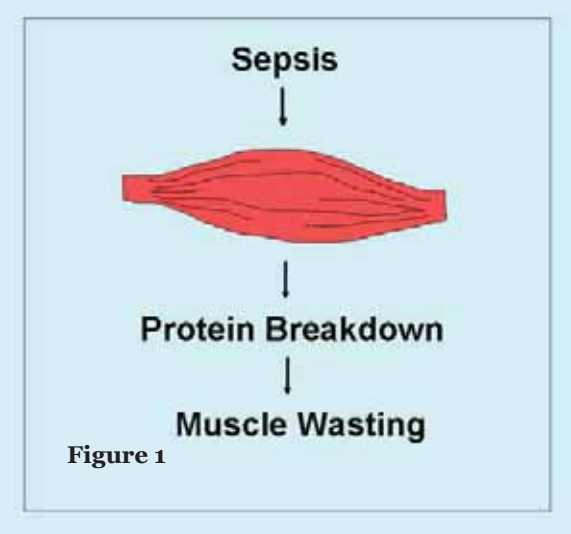


Figure 1

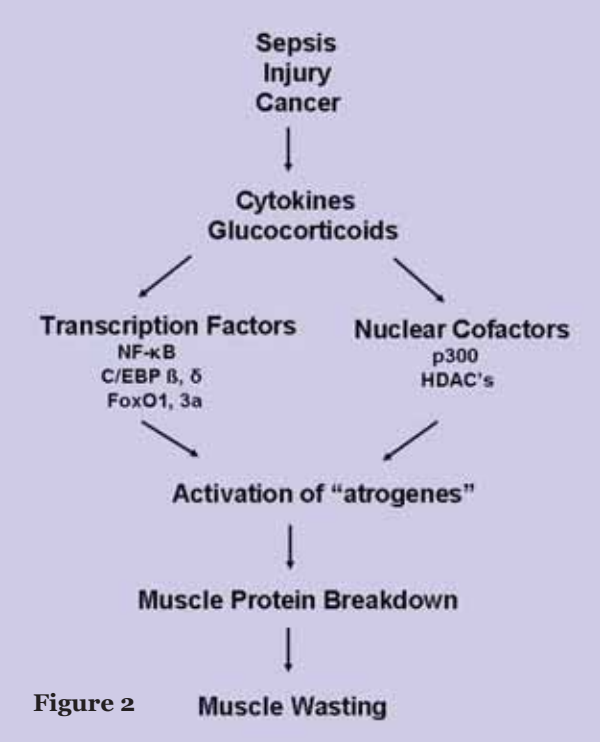


Figure 2

In recent studies we have found evidence that p300-regulated acetylation of certain transcription factors and probably other nuclear proteins as well regulates protein breakdown in catabolic muscle. Our current understanding of some of the molecular mechanisms involved in muscle wasting, in particular the role of transcription factors and nuclear co-factors, is summarized in **Fig 2**. The long-term goal of our studies is to define molecular mechanisms responsible for sepsis-induced muscle proteolysis and to define molecule(s) that can be targeted to prevent or treat muscle wasting in sepsis and other catabolic conditions.

Transcription factors involved in muscle wasting are regulated by multiple posttranslational modifications. For example, the transcription factor C/EBPβ can be activated by acetylation and phosphorylation (**Fig 3**). Indeed, recent experiments in our laboratory have provided evidence that C/EBPβ is acetylated at multiple sites in dexamethasone-treated myotubes and in the same experimental model, silencing of the histone acetyl transferase p300 blocks dexamethasone-induced protein degradation in cultured myotubes (**Fig 3 a and b**). Thus, the regulation of protein degradation in atrophying muscle is complex and factors influencing protein degradation in catabolic muscle are regulated at multiple levels.

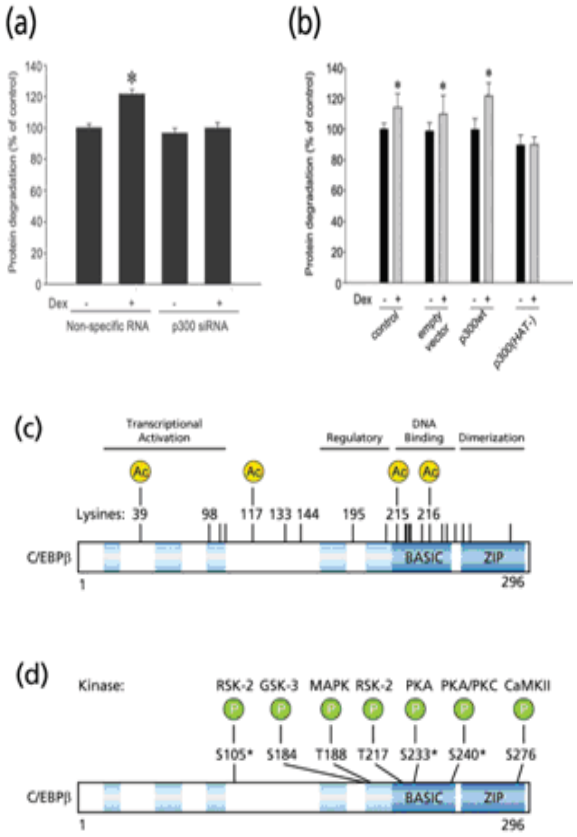


Fig 3 (**a**) Transfection of cultured L6 muscle cells with p300 siRNA prevents dexamethasone-induced protein degradation. (**b**) Transfection of cultured L6 muscle cells with a p300 plasmid mutated in its HAT activity domain prevents dexamethasone-induced protein degradation, supporting a role of p300-mediated acetylation in the catabolic response in skeletal muscle. C/EBPβ can be modified by posttranslational (**c**) acetylation and (**d**) phosphorylation at multiple sites.

from: Hasselgren PO. Ubiquitination, phosphorylation, and acetylation – triple threat in muscle wasting. J Cell Physiol 2007; 213:679-689.

List of Current Employees

Michael Menconi, PhD	Assistant Professor of Surgery
Patricia Gonnella, PhD	Assistant Professor of Surgery
Patrick O'Neal, MD	Research Fellow, Surgical Resident
Ira Smith, PhD	Research Fellow in Surgery
Nima Alamdari, PhD	Research Fellow in Surgery
Sally Gwin, BS	Administrative Coordinator

Michael Menconi and Patrick O'Neal reviewing data at the lab bench.

List of Current Funding

"C/EBP and IL-6 production in mucosa and enterocytes"
National Institutes of Health, **R01 DK-060546**
Project Period: 2003-2007
PI: Per-Olof Hasselgren

"C/EBP, Atrogin-1, and muscle wasting"
National Institutes of Health, **R01 NR-08545**
Project Period: 2004-2009
PI: Per-Olof Hasselgren

"Muscle protein turnover and amino acid uptake in sepsis"
National Institutes of Health, **R01 DK-037908**
Project Period: 2006-2011
PI: Per-Olof Hasselgren

Gastrointestinal training grant
National Institutes of Health, **T32-DK007760-07**
Trainee: Vitaliy Poylin, MD
Project Period: 2005-2007
PI: David Soybel, MD
Mentor: Per-Olof Hasselgren

Vascular surgery training grant
National Institutes of Health, **T32-HL007734-12**
Trainee: Patrick O'Neal, MD
Project Period: 2006-2008
PI: Frank W. LoGerfo, MD
Mentor: Per-Olof Hasselgren

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

"Acetylation, deacetylation, and p65 in muscle wasting"
National Institutes of Health, **R01 AR-055235**
PI: Per-Olof Hasselgren

"The role of PGC-1β in muscle wasting"
National Institutes of Health, **R03 AR-055346**
PI: Michael Menconi, PhD
Mentor: Per-Olof Hasselgren

Patricia Gonnella

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Invited Presentations

Hasselgren PO. Invited speaker, "Role of transcription factors and nuclear cofactors in muscle wasting." Round Table conference for Critical Care Medicine. Brussels, Belgium; May 2007.

Hasselgren PO. Invited speaker. "Glucocorticoids and muscle wasting." International Conference for Critical Care Medicine. Brussels, Belgium; May 2007.

Hasselgren PO. Invited speaker. "Development of muscle wasting." International Conference for Critical Care Medicine. Brussels, Belgium; May 2007.

Hasselgren PO. Invited speaker. "Transcription factors and nuclear cofactors in sepsis-induced muscle wasting." International Sepsis Forum 6th Annual Summer Colloquium. Annapolis, Maryland; June 2007.

O'Neal P. Oral presentation. "Do all patients undergoing parathyroidectomy require additional neck exploration when intraoperative PTH levels do not fall appropriately?" New England Surgical Society Annual Meeting. Burlington, VT; September 2007. 2nd prize in Residents' Presentation Contest.

Report of Teaching

Graduate School and Graduate Medical Courses
Surgical Clerkship, Medical Students 3rd year, Harvard Medical School: Endocrine Surgery – Thyroid and Parathyroid.

Nima Alamdari

Ira Smith

Bibliography (January – December 2007)

Original Articles

Evenson A, Mowschenson P, Connoly J, Wang H, Parangi S, **Hasselgren PO.** Hyalinizing trabecular adenoma – an uncommon thyroid tumor frequently misdiagnosed as papillary or medullary thyroid carcinoma. Am J Surg 2007; 193:707-12.

Fang CH, Li B, James JH, Yahya A, Kadeer N, Guo X, Xiao C, Supp DM, Kagan RJ, **Hasselgren PO,** Sheriff S. GSK-3β activity is increased in skeletal muscle after burn injury in rats. Am J Physiol 2007; 293:R1545-51.

Reilly N, **Poylin V, Menconi M,** Onderdonk A, Bengmark S, **Hasselgren PO.** Probiotics potentiate IL-6 production in IL-1β-treated Caco-2 cells through a heat shock-dependent mechanism. Am J Physiol 2007; 293:R1169-79.

Wei W, Yang H, Menconi M, Cao P, Chamberlain CE, **Hasselgren PO.** Treatment of cultured mytoubes with the proteasome inhibitor β-lactone increases the expression of the transcription factor C/EBPβ. Am J Physiol 2007; 292:C216-26.

Yang H, Wei W, Menconi M, Hasselgren PO. Dexamethasone-induced protein degradation in cultured myotubes is p300/HAT-dependent. Am J Physiol 2007; 292:R337-44.

Original Articles (Submitted or In press)

Menconi M, Gonnella P, Petkova V, Lecker SH, **Hasselgren PO.** Dexamethasone and corticosterone induce similar but not identical muscle wasting-related metabolic changes in cultured L6 and C2C12 myotubes. 2007; submitted.
O'Neal P, Poylin V, Mowschenson P, Parangi S, Horowitz G, **Hasselgren PO.** Do all patients undergoing parathyroidectomy require additional neck exploration when intraoperative PTH levels do not fall appropriately? 2007; submitted.

Poylin V, Fareed MU, O'Neal P, Alamdari N, Reilly N, Menconi M, Hasselgren PO. The NF-kB inhibitor curcumin blocks sepsis-induced muscle proteolysis. Mediat Inflam 2007; in press.

Reviews, Chapters, and Editorials

Hasselgren PO, Hubbard, WJ, Chaudry IH. Metabolic and inflammatory reposnes to trauma and infection. In: Fischer JE, editor. Mastery of surgery, 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2007; p 2-24.

Hasselgren PO. Transcription factors and nuclear cofactors in muscle wasting. In: JL Vincent, editor. Yearbook of intensive care and emergency medicine. Heidelberg: Springer-Verlag; 2007; p 229-37.

Hasselgren PO. Ubiquitination, phosphorylation, and acetylation – triple threat in muscle wasting. J Cell Physiol 2007; 213:679-89.

Menconi M, Fareed M, O'Neal P, Poylin V, Wei W, Hasselgren PO. Role of glucocorticoids in the molecular regulation of muscle wasting. Crit Care Med Suppl 2007; 35:S602-8.

Reviews, Chapters, and Editorials (Submitted or In press)

Alamdari N, O'Neal P, Menconi M, Hasselgren PO. Curcumin and muscle wasting. Nutrition 2007; submitted.

Smith I, Lecker S, **Hasselgren PO.** Calpain activity and muscle wasting in sepsis. Am J Physiol 2007; in press.

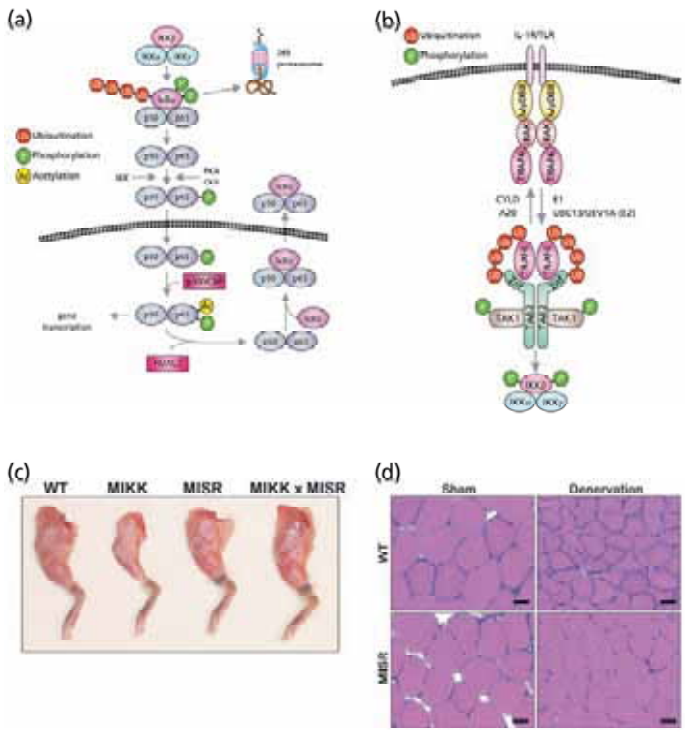
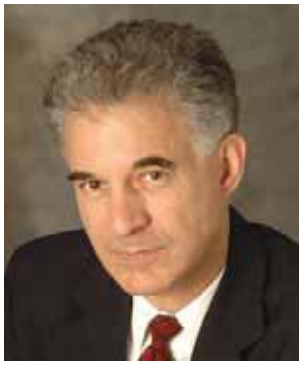


Fig 4 (**a**) and (**b**) The activity of NF-kB is regulated by multiple posttranslational modifications of IKK, IkBα, and p65. Those modifications include acetylation, phosphorylation, and ubiquitination. (**c**) Transgenic overepxression of activated IKKβ (MIKK) results in phosphorylation and degradation of IkBα, activation of NF-kB and subsequent development of muscle atrophy. (**d**) Transgenic overexpression of a dominant negative IkBα prevents NF-kB activation and MIKK-induced as well as denervation-induced muscle atrophy. Taken together, the experiments shown in this figure support the concept that transcription factors involved in muscle wasting are regualated by multiple posttranslational modifications.

Panels (a) and (b) are from Hasselgren PO: Ubiquitination, phosphorylation, and acetylation – triple threat in muscle wasting. J Cell Physiol 2007; 213:679-689.

Panels (c) and (d) are from Cai D, Frantz JD, Tawa NE, Melendez PA, Lidow HGW, Hasselgren PO, et al: IKKβ/NF-kB activation causes svere muscle wasting in mice. Cell 2004; 119: 285-298.

Carl J Hauser, MD, FACS, FCCM



Carl Hauser

My research over the past 5 years has focused on the translational biology of innate immunity. In that effort, I believe we have become one of the premier groups in the country studying neutrophil biology. Our work has mainly been devoted to studies of the regulation of calcium entry as a cellular activation signal. Current though, our work has shifted focus slightly, and we are looking less specifically at G-protein coupled receptor-linked calcium signaling and more at the composition of lipid rafts and the role of raft composition in cell signaling both in inflammation and in general.

All of our basic science interests are translational so our studies are firmly rooted in clinical care. Thus is our practice to study basic molecular events concurrently in cell systems, animal systems and human disease states where ever possible.

Basic science interests include:

1. Neutrophil signaling in critical illness.
2. Clinical inflammation biology in the ICU.
3. Chemokine biology in trauma and sepsis.
4. The biology of the peritoneum in shock and sepsis.
5. Development of treatments for critical illness based on the control of immune cell calcium entry.
6. The composition of lipid rafts and the role of raft composition in raft function.

Of special note is that we are always looking for new collaborators with whom we can study new disease models and clinical processes, and who can provide us with clinical, animal or cellular specimens where we can extend our observations as to signaling mechanisms.

Clinical research interests include:

1. Shock and resuscitation.
2. Wound biology.
3. Chest trauma.
4. Transfusion biology and surgical hemostasis.
5. Surgical infections.

List of Current Employees

Kiyoshi Itagaki, PhD	Instructor in Surgery and Laboratory Manager
Qin Zhang, MD	Research Associate
Bosena Antoniu, MS	Research Associate
Mustafa Raoof, MD	Visiting (Volunteer) Research Fellow

List of Current Funding

"Sphingosine-1-phosphate and PMN Ca^{2+} entry in trauma"
National Institutes of Health, **R01GM059179**
Project Period: 03/01/2006–02/28/2010
PI: Carl J Hauser

Bibliography (January – December 2007)

Original Articles

Caputo FJ, Magnotti LJ, **Hauser CJ**, Livingston DH. Descending necrotizing mediastinitis: unique complication of central venous catheterization. Surg Infect (Larchmt) 2007; 8(6):611-4.

Homnick A, Lavery R, Nicastro O, Livingston DH, **Hauser CJ**. Isolated thoracolumbar transverse process fractures: call physical therapy, not spine. J Trauma 2007;63(6):1292-5.

Itagaki K, Yun JK, Hengst JA, Yatani A, **Hauser CJ**, Spolarics Z, Deitch EA. Sphingosine 1-phosphate has dual functions in the regulation of endothelial cell permeability and Ca^{2+} metabolism. J Pharmacol Exp Ther 2007; 323(1):186-91.

Kannan KB, Barlos D, **Hauser CJ**. Free cholesterol alters lipid raft structure and function regulating neutrophil Ca^{2+} entry and respiratory burst: correlations with calcium channel raft trafficking. J Immunol 2007; 178(8):5253-61.

Lee C, Xu DZ, Feketeova E, Nemeth Z, Kannan KB, Haskó G, Deitch EA, **Hauser CJ**. Calcium entry inhibition during resuscitation from shock attenuates inflammatory lung injury. Shock 2007; 154-57.

Mohr AM, Sifri ZC, Horng HS, Sadek R, Savetamal A, **Hauser CJ**, Livingston DH. Use of aerosolized aminoglycosides in the treatment of Gram-negative ventilator-associated pneumonia. Surg Infect (Larchmt) 2007;8(3):349-57.

Sifri ZC, Cohen D, Ananthakrishnan P, Wang L, Kaiser VL, Mohr AM, **Hauser CJ**, Rameshwar P, Deitch EA, Livingston DH. Sex hormones affect bone marrow dysfunction after trauma and hemorrhagic shock. Crit Care Med 2007;35(3):864-9.

Original Articles (Submitted or in press)

Deitch EA, Feketeova E, Lu Q, Zaets S, Berezina TL, Machiedo GW, **Hauser CJ**, Livingston DH, Xu DZ. Resistance of the female, as opposed to the male, intestine to I/R-mediated injury is associated with increased resistance to gut-induced distant organ injury. Shock 2007; in press.

Daniel B. Jones, MD, MS, FACS
Chief, Section of Minimally Invasive Surgery
Director, Bariatric Program

Dan Jones

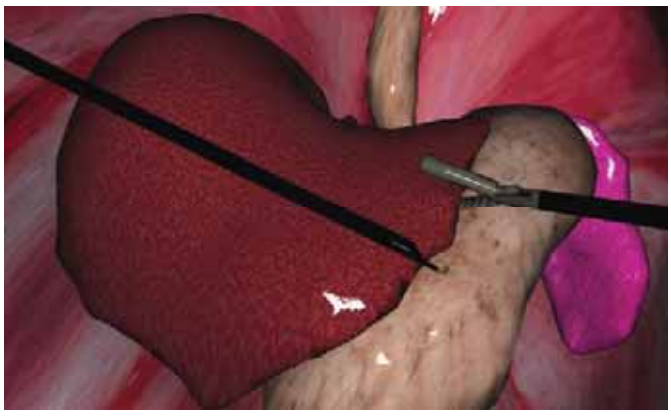
Our group integrates clinical activity and teaching into innovation and education research. We have focsed on minimally invasive surgery, bariatric surgery, and technical skill acquisition. Bench-top work last year has led to innovative endoscopic operations, better models and simulators, and a new understanding of hormonal regulation of obesity.

The Center for Minimally Invasive Surgery (CMIS) has trained medical students, residents, research fellows, clinical fellows and surgeons worldwide in advanced laparoscopic techniques. CMIS founded The Carl J Shapiro Simulation and Skills Center (www.bidmc.harvard.edu/sasc). Education research is focused on establishing a technical skills laboratory validating new teaching tools and instituting curriculums for Harvard medical students and BIDMC residents. Research assesses team simulation of the novice, expert, and seasoned surgeon in the unique mock laparoscopy endosuite.

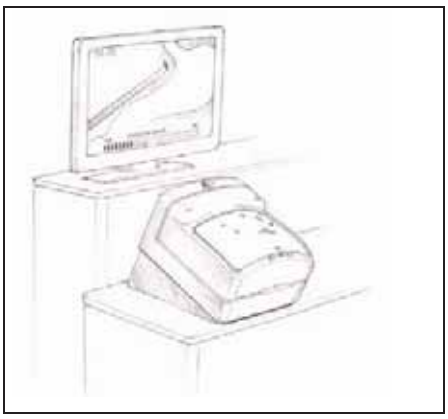
BIDMC was the first Level I Comprehensive Education Institute accredited by the American College of Surgeons in New England. In 2007, SASC crafted the ACS-APDS national Surgery Residency curriculum for basic and advanced laparoscopic skills. We also formally partnered with the Dubai Health Authority to initiate a Simulation Center in the UAE for regional training of physicians and surgeons in the Middle East region.

In collaboration with Dr. Chuttani of GI Endoscopy (Department of Medicine at BIDMC) we have developed new approaches to less invasive operations for reflux and weight loss surgery with NOTES at the Center for Minimally Invasive Surgery animal lab at HMS. Endoscopic banding techniques may achieve comparable outcomes with faster recuperation.

Collaborative efforts have also worked toward developing better simulators. With S. De, PhD at RPI we have been funded by an NIH R01 grant to create a virtual reality laparoscopic simulator for teaching the technique of the laparoscopic adjustable gastric band using virtual reality and haptic feedback (see figure below). The newly developed Point-Associated Finite Field (PAFF) approach provides users a smooth visual display and realistic touch response. PAFF provides surgeons a more realistic experience of cutting, bleeding, smoke, and tissue pressure response. Virtual laparoscopic instruments are controlled by the surgeon. Also, with Caroline Cao, PhD at Tufts University and Steven Schwaitzberg, MD at Cambridge Hospital we are assessing cognitive loading and value of haptics in task acquisition.



PAFF Virtual Simulator



Jones Lap-Band Simulator

With industry we are creating simulators for laparoscopic surgery and NOTES. Simulators allow the surgeon to practice the procedures safely (see figure above, right).

Through the Program for Obesity and Weight Loss Surgery we have strived to increase our knowledge of obesity and establish best practice guidelines for bariatric surgery. With Drs. Steven Loring and Stephanie Jones (Department of Anesthesia at BIDMC), we are investigating the use of esophageal pressure measurements as a surrogate of pleural pressure to characterize the effects of obesity on respiratory function. With the MGH Weight Loss Program, BIDMC developed a rodent model to study the laparoscopic adjustable band compared to the gastric bypass, and with Dr. Ronit Grinbaum subsequently established an animal model for the gastric sleeve procedure. Studies evaluate central gut neuroendocrine changes after surgery, specifically ghrelin, POMC pathway, and PYY 3-3. Under leadership of Dr. George Blackburn, MD, we have served on the Expert Panel on Weight Loss Surgery for the Betsy Lehman Center in 2007. At BIDMC, Bariatric Surgery efforts have studied the impact of hospital clinical care pathways for laparoscopic adjustable band and gastric bypass procedures (www.bidmc.harvard.ede/wls). With Dr. Christine Wee will are studying the patient's assessment of risk and benefit of weight loss surgery.

List of Current Employees

Alex Derevianko, MD, MA	Simulation and Skills Center Coordinator
Noel Irias	Simulation and Skills Center Coordinator
Linda Trainer, RN	Nurse Educator
Maritza Avendano	Administrator

Collaborators

Ben Schneider, MD	Surgery, Section of MIS, BIDMC
Jonathan Critchlow, MD	Surgery, Section of MIS, BIDMC
Vivian Sanchez, MD	Surgery, Section of MIS, BIDMC (Needham Campus)
Steven D. Schwaitzberg, MD	Surgery, Section of MIS, BIDMC (Cambridge Health Alliance)
George Blackburn, MD, PHD	Surgery, Section of Nutrition, BIDMC
Steven Loring, MD, PHD	Anesthesiology, BIDMC
Stephanie Jones, MD	Anesthesiology, BIDMC
Ram Chuttani, MD	Medicine, BIDMC
Christina C. Wee, MD, MPH	Medicine, BIDMC
Christos Mantzoros MD	Medicine, BIDMC
Dan Rooks, PhD	Medicine, BIDMC
Lee Kaplan, MD	Weight Loss Center, MGH
Caroline Cao, PhD	Tufts, Human Performance
Grace Zhou, PhD	Tufts, Human Performance
Suvranu De, ScD	Mechanical, Aerospace and Nuclear Engineering, Rensselaer Polytechnic Institute

MIS Fellows (BIDMC)

Limaris Barrios, MD	Surgery, MIS Clinical Fellow
James Ellsmere, MD	Medicine, GI Fellow
Ronit Grinbaum, MD	Surgery, MIS Research Fellow
Rabi Kundu, MD	Medicine, GI Fellow
Torsten Olbers, MD	MIS Research Fellow
Kinga Powers, MD, PhD	Surgery, MIS Clinical Fellow
Scott Rehrig, MD	Surgery, MIS Clinical Fellow
Shawn Tsuda, MD	Surgery, MIS Clinical Fellow

List of Current Funding

"Physically realistic virtual surgery"
NIH/NIBIB, **R01 EB005807-01**
Project Period: 2006-2010

PI: Suvranu De, PhD
Collaborator: Daniel Jones, MD

"Evaluation of endostapled anastomosis for lapararoscopic gastric bypass"
United States Surgical Industry Funding
Project Period: 2007-2008
PI: Daniel Jones, MD

"Role of haptic feedback and cognitive load in laparoscopic surgery performance"
SAGES
Project Period: 2007-2008
PI: Caroline Cao, PhD
Collaborator: Daniel Jones, MD

"Understanding how patients value bariatric surgery"
NIDDK, **R01 DK073302-01**
Project Period: 2007-2008
PI: Christina Wee, MD
Collaborator: Daniel Jones, MD

"Endoscopic gastrojejunostomy in porcine model using full thickness Plicator device"
Project period: 2007-2008
PI: Rabi Kunde, MD
Collaborator: Daniel B. Jones, MD

"AP Lap-Band"
Allergan
Project Period: 2007-2008
PI: Daniel B. Jones, MD

Applications Submitted and Pending Review/Funding

"Recognizing technical errors using teleproctoring during simulation."
CRICO/RMF
PI: Shawn Tsuda, MD
Collaborator: Daniel B. Jones, MD

"Framing family conversations after early diagnosis of iatrogenic and incidental operative findings"
CRICO/RMF
PI: Limaris Barrios, MD
Collaborator: Daniel B. Jones, MD

"N.O.T.E.S. Simulator"
NOSCAR
PI: Shawn Tsuda, MD
Collaborator: Daniel B. Jones, MD

"Development of endoscopic deployed band for treatment morbid obesity: feasibility and survival in animal model"
SAGES
PI: Shawn Tsuda, MD
Collaborator: Daniel B. Jones, MD

Research Accomplishments in the Past Year

Clinical Research Accomplishments

Patient Safety: We implemented Clinical Pathways for laparoscopic adjustable gastric band and gastric bypass in 2007.

An on-line bariatric surgery educational web site was implemented with CRICO-RMF to train surgeons, anesthesiologist and nurses.

We successfully proposed a premium incentive discount for Harvard surgeons with FLS certificate. This resulted in the Controlled Risk Insurance Company (CRICO) of Harvard's Risk Management Foundation (RMF) endorsing the *Fundamentals of Laparoscopic Surgery (FLS) Patient Safety Incentive Program* for general surgery attending physicians who perform laparoscopic surgery. The Society of American Gastrointestinal Endoscopic Surgeons (SAGES) developed the FLS program which is a comprehensive, CD-Rom based education module that includes a hands-on skills training component and assessment tool. FLS sets a bar guaranteeing a level of competence in technical and cognitive skills related to laparoscopic surgery. SASC at BIDMC serves as a training and the testing site.

MIS Fellows Research: Drs Kinga Powers and Scott Rehrig performed team simulations in the first mock operating endosuite. The scenario was selected as part of ACS-APDS national simulation curriculum for surgical residency.

Abstracts presented at Local, National, and International Meetings

Powers KA, Rehrig ST, Irias N, Albano HA, Feinstein DM, Johansson AC, Jones SB, Malinow A. Moorman DW, Pawlowski JP, **Jones DB**. Simulated laparoscopic operating room crisis: approach to enhance the surgical team performance. Surg Endosc S313, April 2007.

Ellsmere J, Kundu R, Jones DB, Pleskow D, Chuttani R. A novel percutaneous endoscopic sleeve gastroplasty (PESG) using the endoscopic fullthickness plicator. Surg Endosc S315, April 2007.

Rehrig, ST, Powers K, **Jones DB**. A single massed skills course for surgery trainees does not convey long-term performance benefit. Surg Endosc S415, April 2007.

Malinow A, **Jones DB**. Decision-making constructs in a high stakes laparoscopy simulation. Association of Surgical Education, Poster, Washington D.C., June 9, 2007.

Ellsmere J, **Jones DB**, Wells W. An office based system for accessing implanted ports. SAGES, Emerging Technology Session, Poster, Las Vegas, NV, April 21, 2007

Irias N, Hasimoto D, **Jones DB**. Development of hybrid surgical simulation devices. SAGES, Emerging Technology Session, Poster, Las Vegas, NV, April 21, 2007.

Arden D, Kim YB, **Jones DB,** Awtrey CS. Pelv-sim; a novel pelvic trainer designed to improve gynecologic laparoscopic suturing skills. SAGES Las Vegas, NV, April 21, 2007.

Zhou G, **Jones DB**, Schwaitzberg S, Cao C. Role of haptic feedback and cognitive load in surgical skill acquisition. Human Factors and Ergonomics Society, 51st Annual Meeting. Baltimore, MD, October 1, 2007.

Kundu R, Ellsmere J, **Jones DB**, Pleskow D, Chuttani R. Endoscopic gastrojejunostomy using full

thickness plications. NOCARS, Boston, MA, 2007.

Ellsmere J, Kundu R, **Jones DB**, Pleskow D, Chuttani R. Durability of percutaneous endoscopic sleeve gastroplasty (PESG) using full thickness endoscopic plications. NOCARS, Boston, MA, 2007.

Individual accomplishments

Member of the Expert Panel on Weight Loss Surgery, Betsy Lehman Center
SAGES Board of Governors
SSAT Foundation Trustee
Chair, Education Committee, SSAT
Chair, Educational Resources Committee, SAGES
Dinner Chair, Boston Surgical Society
ACS Bariatric Advisory Board
BSBC MA Bariatric Advisory Committee
ACS Committee of Accreditation Learning Centers.
The Fellowship Council Site Reviewer.
Consultant, Dubai Health Authority, UAE

Invited presentations

Local
"Medical simulation." Healthcare Immersion Course for Harvard Business School: Carl J. Shapiro Simulation and Skills Center: BIDMC. Boston, MA; January 9, 2007.

"Current surgical procedures for obesity." Obesity Day – Dietetic Intern Class. Boston, MA; January 22, 2007.

"Simulation in surgery." Information Technology in the Healthcare System of the Future: Harvard Medical School/Massachusetts Institute of Technology: Health Sciences and Technology. Boston, MA; March 22, 2007.

"Bariatric surgery." Gastroenterology and Hepatology Update: Harvard Medical School. Boston, MA; March 27, 2007.

"Percutaneous endoscopic sleeve gastroplasty (PESG) using an endoluminal plicator." American Society for Gastrointestinal Endoscopy: ASGE Learning Center. Washington DC; May 20, 2007.

"Weighing in on obesity surgery." Surgery Grand Rounds: BIDMC. Boston, MA; September 5, 2007.

"Inguinal hernia." Department of Surgery: BIDMC. Boston, MA; September 24, 2007.

"Surgical management of obesity." Pri-Med: Harvard Medical School. Boston, MA; October 12, 2007.

"Surgical approaches to the treatment of obesity." Harvard-Joslin Advances in Diabetes. Cambridge, MA; November 2, 2007.

"Developing and initiating an obesity and nutrition program in an outpatient setting." Harvard-Joslin Advances in Diabetes. Cambridge, MA; November 2, 2007.

"Recruiting faculty. Communicating when things go wrong." CRICO/RMF Surgery Summit. Cambridge, MA; November 5, 2007.

"Technical errors and ways to reduce it. Communicating when things go wrong." CRICO/RMF Surgery Summit. Cambridge, MA; November 5, 2007.

"Use of simulation for assessment of competency." Principal Investigator Seminar: BIDMC. Boston, MA; November 13, 2007.

"Framing family conversation after early diagnosis of iatrogenic injury and incidental findings." 54th Annual Meeting ACS. Boston, MA; December 8, 2007.

"A novel percutaneous endoscopic sleeve gastroplasty (PESG) using the endoscopic full thickness plicator." Video Forum: SAGES. Las Vegas, NV; 2007.

National

"Since the SAGES appropriateness conference on weight loss and surgery." Safety in Bariatric Surgery: SAGES. Las Vegas, NV; April 20, 2007.

"Simulated laparoscopic operating room crisis: approach to enhance the surgical team performance." SAGES: Scientific Session. Las Vegas, NV; April 21, 2007.

"Pelv-sim; a novel pelvic trainer designed to improve gynecologic laparoscopic suturing skills." SAGES: Scientific Session. Las Vegas, NV; April 21, 2007.

"Postoperative considerations." Fundamentals of Laparoscopic Surgery Postgraduate Course: SAGES. Las Vegas, NV; April 22, 2007.

"The evolution of surgical simulation." Simulation Postgraduate Course: SAGES. Las Vegas, NV; April 22, 2007.

"Significance of ACS education institutes." Simulation Postgraduate Course: SAGES. Las Vegas, NV; April 22, 2007.

"Endoscopic gastrojejunostomy using full thickness placations." New England Endoscopy Society. Westin, MA; May, 2007.

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"Use of simulation for intraoperative complications." Complications in the OR: Laparoscopic Surgery: American College of Surgeons. Chicago, IL; October 10, 2007.

"Technical errors and ways to reduce it." Surgery Summit: CRICO-RMF. Boston, MA; November 5, 2007.

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"Training, models and simulation." 2nd Annual International Conference on NOTES. Boston, MA; July 13, 2007.

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"Safer surgery through simulation." Rashid Hospital: Department of Health and Medical Services. Dubai, United Arab Emirates; September 11, 2007.

"Laparoscopic obesity surgery." Rashid Hospital: Department of Health and Medical Services. Dubai, United Arab Emirates; September 12, 2007.

"Use of simulation for education and assessment." International Society for Quality in Health Care (ISQua). Boston, MA; October 3, 2007.

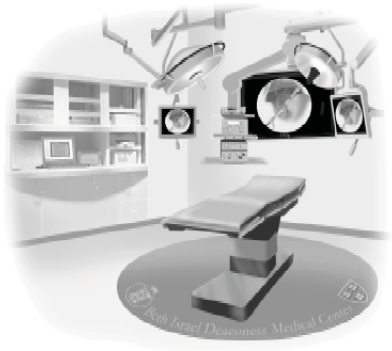
REPORT OF TEACHING

Undergraduate and medical school courses

Obesity – Bariatric Surgery, HMS III Longitudinal Learning. 4 medical students.

Graduate School and graduate medical courses
Surgical Resident Mock Oral Exams (April 7, 2006), Beth Israel Deaconess Medical Center. 6 surgery residents.
Skills Lab instructor for all surgery residents.
Course Director and Lecturer, Laparoscopic Inguinal Hernia Repair – MetroWest (Jan 5, 2007). Approximately 12 surgeons attended the course.
Course Director, Healthcare Immersion, Harvard Business School (Jan 9, 2007)

Resident Education
The Carl J Shapiro Simulation and Skills Center hosted the HUB GUN LAPAROSCOPIC FLS SKILLS competition which attracted surgery residents across the state of Massachusetts.



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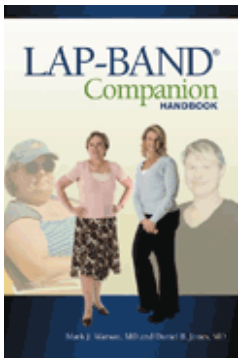

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Wolfgang G. Junger, PhD, DI

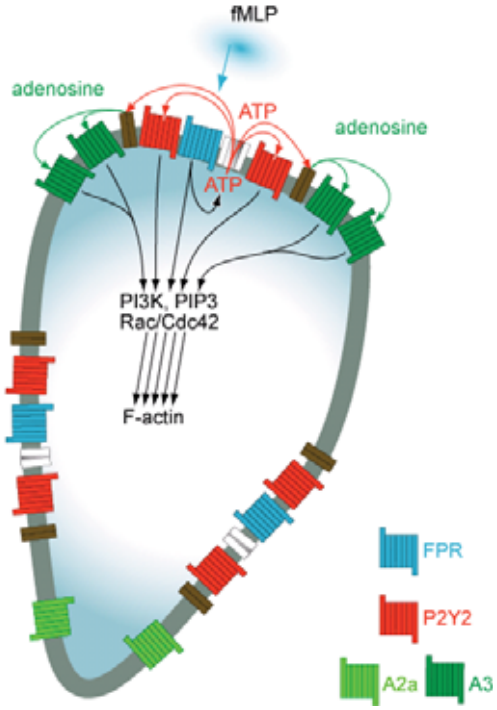
BASIC RESEARCH

Wolfgang Junger

Our research focuses on the cellular immune response in trauma and critical care patients. In healthy subjects, a delicate balance between inflammatory and anti-inflammatory signals allows the cellular immune system to recognize and destroy invading microorganisms while sparing host tissues. In trauma and critical care patients, this balance is lost: On one hand, overzealous and excessively activated phagocytes damage host tissues, causing organ damage and complications such as acute respiratory distress syndrome (ARDS) and multi-organ failure syndrome (MOFS). On the other hand, subsequent compensatory down-regulation of cellular immune responses results in immune suppression and a weakening of the patient's ability to fend off microbial invaders. As a consequence, many patients develop severe infections and sepsis. Both phenomena lead to post-traumatic complications that account for large proportion of deaths among those patients who die in the intensive care setting.

We study the molecular and cellular mechanisms associated with these complications using a wide range of techniques that include molecular techniques, cell biology, animal models, and clinical trials. Using these methods and the close interdisciplinary cooperation between physician scientists and basic researchers, we work on the design of novel therapeutic approaches to prevent immune-related complications in trauma and critical care patients.

We have discovered that extracellular osmolarity can modulate the functions of neutrophils and T lymphocytes. We found that the infusion of hypertonic resuscitation fluids in traumatized animals can modulate the inflammatory response by preventing excessive activation of neutrophils and reducing the risk of sepsis. These findings have encouraged much interest among researchers and trauma care providers in the US and abroad. Many groups were able to confirm our findings. As a consequence, hypertonic resuscitation fluids are increasingly used for the treatment of military and civilian trauma patients.



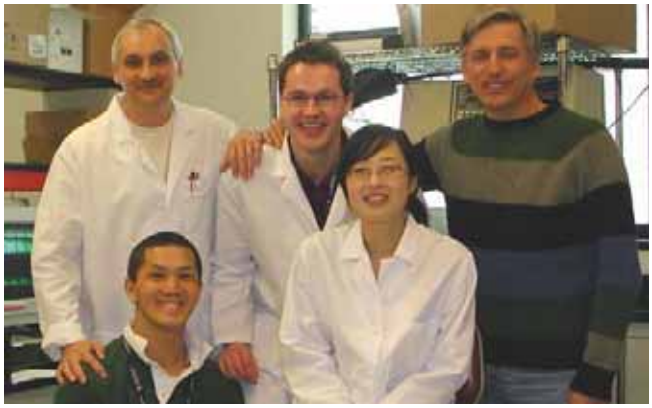
Cellular ATP released from neutrophils controls chemotaxis in a chemotactic gradient field.

In the past several years, we have investigated the cellular mechanisms by which hypertonic fluids regulate leukocyte functions. We could show that neutrophils and T lymphocytes respond to hypertonicity by releasing cellular ATP, which is converted to adenosine. We found that ATP and adenosine modulate the functions of neutrophil and T lymphocytes through autocrine feedback mechanisms that involve a large family of purinergic receptors that are expressed on the cell surface of neutrophils and T lymphocytes. In neutrophils, two types of adenosine receptors (A3 and A2a) with opposing effects on cell activation define the cellular response to hypertonic stimulation. In T lymphocytes, P2X type ATP receptors are involved in the up-regulation of T lymphocyte function by hypertonic fluids. Utilizing our knowledge of how hypertonicity affects immune cell function, we are designing novel hypertonic resuscitation fluids with improved anti-inflammatory properties.

Recently we found that cellular ATP released from migrating neutrophils is also responsible for controlling chemotaxis. ATP and adenosine that is generated by the hydrolysis of released ATP activate P2Y2 and A3 adenosine receptors. Both receptors serve essential roles by facilitating gradient sensing and

by promoting the migration of neutrophils. These findings may allow us to explore new strategies to control neutrophil-induced host tissue damage in trauma patients and in patients with other inflammatory diseases.

In addition to our work on purinergic signaling, we study the role of gamma-delta T cells in host defense. Gamma-delta T cells are a rare and little studied T lymphocyte subpopulation. We found that these cells are able to recognize and eliminate inflammatory neutrophils; thus gamma-delta T cells protect host organs such as the lungs from inflammatory tissue damage. We found that gamma-delta T lymphocytes recognize and target inflamed neutrophils by detecting heat shock protein (Hsp) 72 on the cell surface of the inflamed cells. We are currently studying ways to augment the ability of gamma-delta T lymphocytes to recognize and eliminate inflamed neutrophils from affected host tissues.



Researchers in the Junger lab gather around the HPLC system.

***Back row*: Mark Hirsh, Reinhard Pauzenberger, and Wolfgang Junger.**

***Front row*: Yoshiaki Inoue and Yu Chen.**

Clinical Research

Our basic research efforts described above have led us to the discovery of a promising novel approach that might be useful to modulate the cellular immune responses in trauma patients. In association with collaborators at the University of Washington in Seattle and at the University of Toronto, we have initiated a multi-center clinical study to test the immunomodulatory potential of hypertonic resuscitation fluids in trauma patients. The aims of this collaborative effort are to study if preclinical administration of hypertonic resuscitation fluids in trauma patients can prevent inflammation and excessive activation of neutrophils and of monocytes. Our group will focus in particular on the effects of hypertonic resuscitation on T lymphocyte activation, apoptosis, and T helper lymphocyte subset distribution patterns.

List of Current Employees

Yu Chen, MD	Instructor in Surgery
Mark I. Hirsh, MD, PhD	Lecturer on Surgery
Yoshiaki Inoue, MD, PhD	Visiting Scientist
Reinhard Pauzenberger, MD	Postdoctoral Fellow

Mark Hirsh

List of Current Funding

"Hypertonic saline and immune function"
National Institutes of Health, **R01 GM051477-09**
Project Period: 2003-2008
PI: Wolfgang G. Junger, PhD

"Hypertonic saline and neutrophil function"
National Institutes of Health, **R01 GM060475-06**
Project Period: 2006-2010
PI: Wolfgang G. Junger, PhD

Yu Chen

"Hypertonic Saline Resuscitation, gamma-delta T cell function, and post-traumatic organ failure"
Department of Defense, **W81XWH-05-1-0488**
Project Period: 2005-2009
PI: Wolfgang G. Junger, PhD


Yoshiaki Inoue

"Hypertonic modulation of inflammation"
National Institutes of Health, **R01 GM076101-01**
Project Period: 2007-2011
Subcontract PI: Wolfgang G. Junger, PhD

"Hemorrhagic shock and hemostasis"
Shock Society Novo Nordisk
Project Period: 2007-2009
PI: Yu Chen, MD


Reinhard Pauzenberger

"The UCSD/San Diego Resuscitation Research Center"
National Institutes of Health, **U01HL779080-01**
Project Period: 2004-2009
PI: David B. Hoyt, MD

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

"Autocrine regulation of chemotaxis"
National Institutes of Health
Project Period: 2008-2013
PI: Wolfgang G. Junger, PhD

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

In June of 2007, I moved my laboratory from the University of California San Diego to the Beth Israel Deaconess Medical Center where our research continues to focus on the molecular mechanisms underlying inflammatory diseases, particularly in the context of traumatic, septic, and hemorrhagic shock. In addition, we pursued a number of related research projects. For example, we studied the role of ATP release in the response of T cells to shock waves in a collaborative effort with Dr. Yu at Jilin University, China. The aim of this research is to define the immunomodulatory effects that Dr. Yu has observed in response to shock wave treatment of patients. We also studied the role of nucleotide receptors in the regulation of kidney function. This collaborative effort with UCSD researchers has elucidated how osmotically-induced ATP release and feedback through purinergic receptors regulates kidney function. Another project with collaborators at UCSD and at the Lainz Hospital in Vienna, Austria focuses on the use of hypertonic fluids to treat inflammatory bowel disease. This research effort is aimed at determining whether hypertonic manipulation can be utilized to prevent the flair-up complications associated with colitis. We further explored the role of ATP release in neutrophil function. In particular, we studied the mechanisms by which neutrophils hydrolyze released ATP to adenosine. In collaboration with Dr. Simon Robson, BIDMC Department of Medicine, we have begun to investigate the involvement of NTPDase 1 (CD39) in this process.

Accomplishments

- Nomination to serve as Editorial Board Member for the journal Shock;
- Invitation to serve as reviewer for numerous journals including Shock, Journal of Immunology, Journal of Surgical Research, Journal of Leukocyte Biology, American Journal of Physiology, FASEB Journal;
- Honored by the federal state government of Salzburg, Austria

- Interviewed by leading Austrian daily newspaper ("Der Standard") and by two magazines associated with the city government of Vienna and the federal state government of Salzburg, Austria;
- Invited to serve as reviewer for DoD grant submission;
- Invited to serve as reviewer for a NIH P50 grant application

Invited Presentations

Wolfgang G. Junger
"ATP release guides neutrophil chemotaxis." The Gordon Research Conference on Gradient Sensing & Directed Cell Migration. Ventura, CA; February 2007.

"ATP and adenosine guide neutrophil chemotaxis." The Gordon Research Conference on Phagocytes: Bryant University. Smithfield, RI; August 2007.

"ATP and adenosine receptors in the regulation of neutrophil chemotaxis." The 30th Annual Conference on Shock. Baltimore, ME; August 2007.

"Control of neutrophil migration." The Department of Surgery, Beth Israel Deaconess Medical Center. Boston, MA; August 2007.

"ATP guides neutrophil migration." Research Day, Beth Israel Deaconess Medical Center. Boston, MA; September 2007.

"Autocrine control of immune cell function." The CIMIT Forum: Massachusetts General Hospital. Boston, MA; September 2007.

"Hypertonic saline and beyond." The Principal Investigator Seminar: Department of Surgery, Beth Israel Deaconess Medical Center. Boston, MA; November 2007.

"Hypertonic saline and immune function." Department of Surgery, Harborview Medical Center. Seattle, WA; December 2007.

Yu Chen
"Regulation of neutrophil chemotaxis." The First Clinical Hospital of Jilin University. Changchun, China; September 2007.

Mark I. Hirsh
"Assessment of T lymphocyte function with flow cytometry." Department of Surgery, Harborview Medical Center. Seattle, WA; December 2007.

REPORT OF TEACHING

Undergraduate courses

- Undergraduate teaching at UCSD; taught Chem 199, Bio 199 (independent studies in Chemistry and Biology)
- Served in the Faculty Mentor Program at UCSD. I provided mentorship for Cindy Cheung (now working on PhD degree at the University of California Irvine), Uyen Kim To (now medical student at Stony Brook University School of Medicine), and Vhe Ferrari (now applying for medical school).

Graduate School and graduate medical courses

- Thesis advisor Ross Corriden (now finalizing his PhD thesis on the role of purinergic receptor signaling in neutrophil migration) at UCSD's Biomedical Science Graduate Program.

- Faculty advisor to Melanie Gephart (now graduated from medical school) and Andrew Li (plans to finalize ISP in my new lab at BIDMC). Both are medical students doing independent study projects at UCSD School of Medicine

Other Teaching Contributions

- Mentor for junior faculty members at UCSD planning and applying for research grants. The faculty members mentored were Declan McCole, PhD and Suzi Hong, PhD.
- Mentor for postdoctoral fellows and visiting scientists. The fellows mentored were Yoshiaki Inoue MD, PhD (accepted an Associate Professor position at the Department of Emergency and Disaster Medicine, Juntendo University, Urayasu Hospital, Urayasu, Ciba, Japan) and Linda Yip, PhD (accepted a postdoctoral position at Stanford).

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Inoue Y, Chen Y, Hirsh MI, Yip L, **Junger WG**. A3 and P2Y2 receptors control the recruitment of neutrophils to the lungs in a mouse model of sepsis. Shock. 2007; in press.

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Hirsh MI, Junger WG. Heat shock proteins and the resolution of inflammation by lymphocytes. In: Asea AA, De Maio A, editors. Heat shock proteins: potent mediators of inflammation and immunity. New York: Springer Verlag; 2007. p. 335-52.

Uyen Kim To (left), Linda Yip (center), and Ross Corriden (right) are some of our former coworkers and students in San Diego who could not join us at BIDMC.

John T. Mullen, MD, FACS


John Mullen

I am a co-investigator on the Melanoma SPORE grant awarded to the Dana Farber/Harvard Cancer Center, and I participate in a study funded by this grant to evaluate the effect of melanoma on immune function in the regional lymph node basin. In addition, I am proposing a novel study to be funded by this grant examining the effect of antibody blockade of the integrin (VLA-4) on the metastatic potential of melanoma cells.

I am presently developing a comprehensive, prospective clinical database of surgically-treated melanoma patients at BIDMC in order to answer important clinical questions, such as the role of sentinel lymph node biopsy in patients with thin melanomas. Furthermore, I am co-investigator of a pilot study on the use of dynamic infrared imaging (DIRI) as a noninvasive approach to the early detection of malignant melanoma. Lastly, I am conducting health services and outcomes research utilizing large, national databases to identify the significant patient and provider characteristics that predict optimal cancer surgery treatment outcomes. For example, I am studying the impact of body mass index on surgical outcomes in patients undergoing complex intra-abdominal cancer surgery utilizing the National Surgical Quality Improvement Program (NSQIP) database.

LIST OF CURRENT EMPLOYEES

Colleen Martorano Administrative Assistant

LIST OF CURRENT FUNDING

"Effect of melanoma on immune function in regional lymph nodes"
National Institutes of Health, Harvard Skin SPORE Grant **P50 CA93683-01**, Project 5
Project Period: 2007
Co-Investigator: John T. Mullen, MD

Research Accomplishments in the Past Year

Individual Accomplishments

1. Named as a reviewer for the journals Cancer and Annals of Surgical Oncology
2. Named to a Program Subcommittee for the 2008 Annual Meeting of The Society for Surgery of the Alimentary Tract (SSAT)

Invited Presentations

"Surgical management of malignant melanoma." Surgery Grand Rounds: Mount Auburn Hospital. Cambridge, MA; September 11, 2007.

REPORT OF TEACHING

Graduate School and Graduate Medical Courses
As an Assistant Program Director of the Residency Program in General Surgery at BIDMC, I assist in the organization and execution of the educational curriculum for the residents. I teach the residents informally on the ward and in the operating room and more formally with didactic lectures and mock oral exams.

I teach Harvard Medical School (HMS) students during their Third-Year Core Surgery Clerkship, informally in the clinic and in the operating room and formally with lectures on several cancer surgery

topics and mock oral examinations. I also conduct a once-weekly tutorial group for 4 - 5 HMS third-year students on the core clerkship for more individualized instruction.
I currently serve as an instructor of the Patient-Doctor II course for the second-year HMS students, and next year I will serve as the course director at BIDMC of the six-week block of Patient-Doctor II which serves as an introduction to surgery for 40+ medical students.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original articles

Chun YS, Vauthey JN, Ribero D, Donadon M, **Mullen JT**, Eng C, Madoff DC, Chang DZ, Ho L, Kopetz S, Wei SH, Curley SA, Abdalla EK. Systemic chemotherapy and two-stage hepatectomy for extensive bilateral colorectal liver metastases: perioperative safety and survival. J Gastrointest Surg 2007;11:1498-1504.

Mullen JT, Rodriguez-Bigas MA, Barcenas CH, Crane CH, Skibber JM, Feig BW. Results of surgical salvage after failed chemoradiation therapy for epidermoid carcinoma of the anal canal. Ann Surg Oncol 2007;14:478-83.

Mullen JT, Ribero D, Reddy S, Donadon M, Zorzi D, Gautam S, Abdalla EK, Curley SA, Capussotti L, Clary BM, Vauthey JN. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007; 204:854-62.

Original Articles (Submitted or in press)

Mullen JT, Vartanian TK, Atkins MB. Melanoma complicating treatment with natalizumab for multiple sclerosis. N Engl J Med 2007; in press.

Negin B, Panka D, Wang W, Siddiqui M, **Tawa N**, **Mullen J**, Tahan S, Mandato L, Polivy A, Mier J, Atkins M. Effect of melanoma on immune function in the regional lymph node basin. Clin Cancer Res 2007; in press.

Division of Plastic and Reconstructive Surgery

Sumner Slavin, MD — **Chief, Division of Plastic and Reconstructive Surgery**
Associate Professor of Surgery

Division Members

Loren J. Borud, MD	**Instructor in Surgery**
Geoffrey Brahmer, MDiv	**Education, Research and Residency Coordinator**
Linda Dicenzo, RN	**Nurse Manager**
Bernard T. Lee, MD	**Instructor in Surgery**
Samuel J. Lin, MD	**Instructor in Surgery**
Adam M. Tobias, MD	**Instructor in Surgery**
Joseph Upton, MD	**Associate Clinical Professor of Surgery**
Eran Bar-Meir, MD	2007/08 Aesthetic & Reconstructive Breast Surgery Fellow
Stephanie A. Caterson, MD	2006/08 Aesthetic & Reconstructive Breast Surgery Fellow
Sharon Fox, BA	HMS Medical Student Doris Duke Clinical Fellow (2006 / 07)
Robert Goldwyn, MD	Professor of Surgery (retired from surgical practice)

Kristen Rezak, MD	Clinical Fellow in Surgery-Body Contouring
Amir Taghinia, MD	Clinical Fellow in Surgery-Hand and Microsurgery
Janet Yueh, BSc	HMS Medical Student Doris Duke Clinical Fellow (2007 / 08)

Sumner A. Slavin, MD
Plastic Surgery Research Center

BASIC RESEARCH

The Division of Plastic Surgery focused on two primary basic research projects in 2007:

1. Perforator Identification Using Near-Infrared Imaging (NIR) and the
2. Cortical Neuroplasticity and Perforator Breast Reconstruction Research Projects (Translational)

Perforator Identification Using Near-Infrared Imaging (NIR): Techniques were developed by out group to localize perforating vessels for use in reconstructive surgery. Utilizing a real time, light emitting diode (LED)-based imaging system to exploit invisible near-infrared (NIR) light, this procedure assesses the physiology of tissue while also providing simultaneous color video imaging of the surgical field. The perforating vessels are assessed with NIR fluorescence angiography using indocyanine green (ICG), a FDA-approved NIR fluorophore. This permits patient-specific planning, image-guided creation, and intraoperative assessment without the need for lasers or ionizing radiation. This research is conducted on pigs by Bernard Lee MD, in collaboration with John Fragioni MD, PhD, who oversee the research effort.

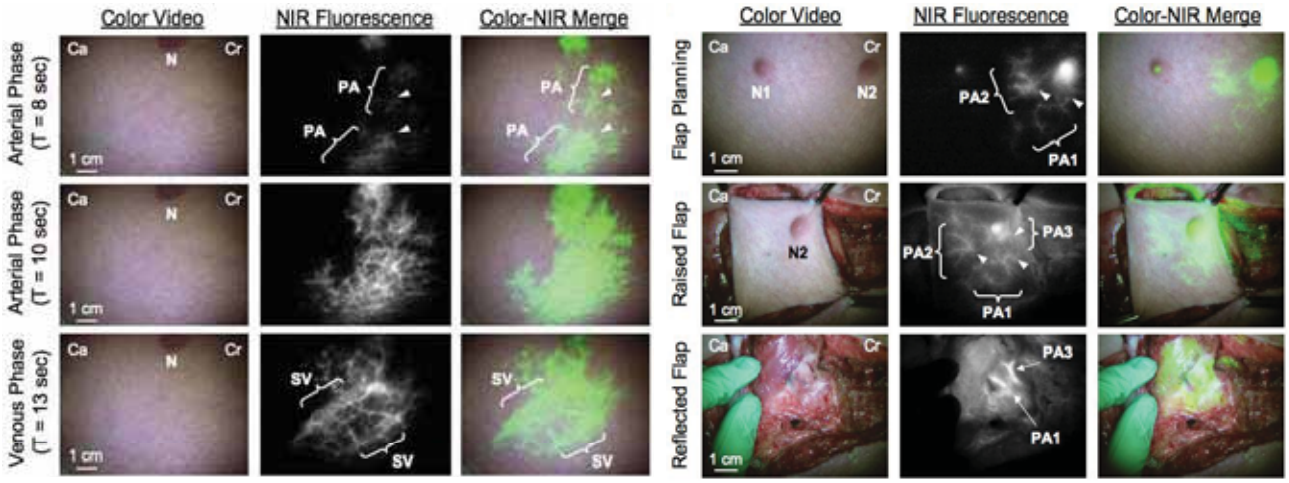


Figure 1(left) Dynamic NIR fluorescent contrast for flap design: ICG distribution and clearance during early arterial phase (T = 8 sec; top row), late arterial phase (T = 10 sec; middle row), and venous phase (T = 13 sec; bottom row). Ca: Caudal, Cr: Cranial, N: Nipple, PA: Perforating artery, SV: Superficial vein.

Figure 2(right) Identification of the perforating arteries *in vivo*. ICG (0.08 mg/kg; 0.1 mmol/kg; 2.5 mg total) was injected intravenously for flap planning (top row). Perforating arteries (PA1 and PA2; PA3 not shown) were identified around a nipple (N2) 12 sec post-injection. Arrowheads identify the origin of each PA. After raising the flap, all three PAs were identified by re-injection of ICG (middle row). Two vascular pedicles, including PA1 and PA3 (bottow row; arrows), are shown at the underside of the flap. Images shown include color video (left), NIR fluorescence (middle), and a pseudo-colored (lime green) merged image of the two (right). Ca: Caudal, Cr: Cranial.

Cortical Neuroplasticity Project: Cortical neuroplasticity has long been thought to contribute to the success of surgery involving peripheral neuromuscular grafts. We are attempting to quantitatively test the hypothesis that primary plasticity of the motor cortex is responsible for the gain of function seen in patients who have undergone procedures in plastic surgery pertaining to peripheral nerve, with current focus on facial reanimation. Patients have been analyzed using functional MRI (fMRI), with preliminary results suggesting that cortical neuroplasticity is involved in the gain of function associated with facial reanimation. Understanding the ways in which such plasticity occurs, as well as the distance over which it

can occur in motor cortex, may help us to understand the capabilities and boundaries of peripheral nerve surgery. Results suggest that manipulation of peripheral nerves may have a significant effect on the function of the central nervous system.

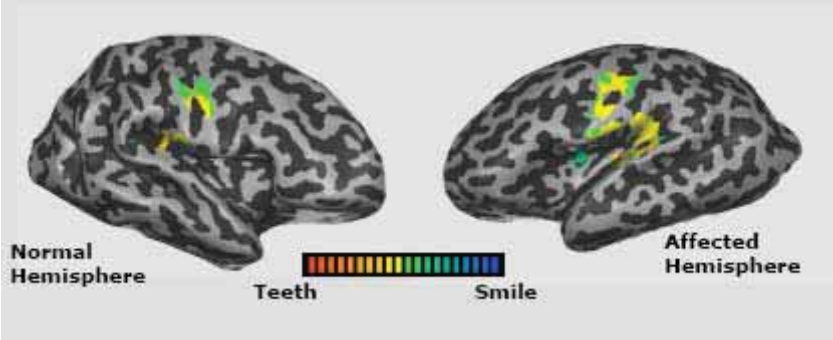
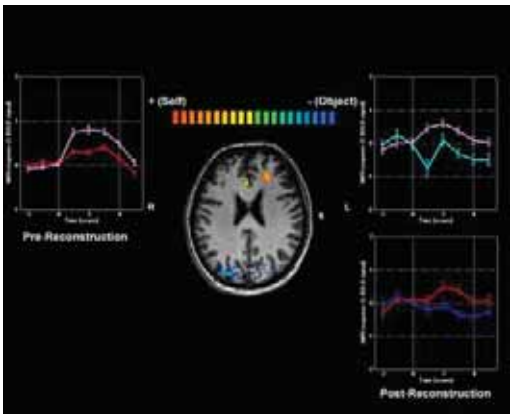


Figure #3 fMRI image from an adult patient with a congenital, unilateral facial paralysis who underwent facial reanimation surgery at BIDMC. Activity for teeth clenching is compared to smiling.

Perforator Breast Reconstruction Project. The project assesses the impact of breast reconstruction, following mastectomy, on improving the psychology and quality of life of patients. Functional MRI is utilized changes in areas of self-recognition following breast reconstruction. Nine patients with breast cancer have been studied. Four patients had a mastectomy without reconstruction, while four patients had a mastectomy and reconstruction with autologous tissue. A single patient had a mastectomy with delayed reconstruction with autologous tissue. Each patient had one unaffected breast, allowing for an internal control. After analyzing the results, it was concluded that patients who choose breast reconstruction with autologous tissue demonstrate self-recognition of the reconstructed breast. In addition, self-perception of the reconstruction may be a mechanism by which these procedures improve patient quality of life.



The Translational Research Projects were made possible by the **Doris Duke Clinical Research Fellowship at Harvard Medical School** (awarded to **Sharon E. Fox**, HMS '08), who spent a year in the Division of Plastic Surgery (2006/07). Sharon Fox developed the protocol, patient base, fMRI procedures, and project analysis for the Translational FMRI Projects. Mentors included **Drs. Bernard Lee, Robert Goldwyn, Adam Tobias, Sumner Slavin, Joseph Upton,** and **Mr. Geoffrey Brahmer**.

Figure 4 (left) Perception of the body as "self" following mastectomy and breast reconstruction.

CLINICAL RESEARCH

The Division of Plastic Surgery focused on following clinical research areas in 2007:

1) Lymphedema. The lymphedema clinic, under the direction of Drs. Sumner Slavin and Loren Borud, serves as a focal point for much needed residency and medical student education in the area of the diagnosis and treatment of lymphedema. Attending, resident, and medical student involvement has led to clinical papers and presentations at regional, national, and international meetings. In 2007, Dr. Arin Greene, a plastic surgery faculty surgeon from Children's Hospital, has joined the team as a faculty

attendings With Dr. Greene's strong interest in both basic and clinical research on lymphedema, the Division hopes to develop research collaborations on lymphedema with other key researchers within the Harvard system.

Lymphedema Researcher, Mauricio Contretras, MD, also prepared a grant submission, "Temporal Gene Expression in the Pathogenesis of Chronic Secondary Lymphedema," an RO1 Grant application in response to PA-04-071. The grant was submitted in June, 2007, and is being resumitted on January 23, 2008. The specific aims of the grant are as follows:

A) Create a new lymphedema canine model that replicates the secondary lymphedema found in the clinical setting, to asses the pathological progression of this disease from the acute (1-3 months) to the chronic phase (6-12 months) in the same model (never done before).
B) Identify gene expression in lymphedematous versus normal tissues in the developing acute and chronic secondary lymphedema from skin and subcutaneous tissue of our canine model. Using Lasser CaptureMicrodissection (LCM), RNA extraction and amplification, and gene-chip microarrays.
C) Assess the contribution of specific target genes to the pathophysiology of secondary lymphedema at different stages of the disease. Identify and characterize mechanisms by which these genes are regulated and organized.

2) Massive Weight Loss / Body Contouring. In 2007, the Ethicon Corporation funded a year-long body contouring fellowship at the BIDMC. This is the first such fellowship in the New England area and one of the select few throughout the United States. **Dr. Kristen Rezak**, the first body contouring fellow in the program, started her fellowship in August. For the last several years, **Dr. Loren Borud**'s major clinical focus has been body contouring surgery following massive weight loss (MWL). He has developed a nationally and internationally recognized program in MWL body contouring surgery, also publishing over a dozen reports on clinical research in body contouring and in lymphatic research. Current research projects include:

A) Authoring a definitive surgical atlas of MWL body contouring surgery (in press for 2008).
B) Conducting research on the lymphatics and their implication for body contouring surgery.
C) Researching ultrasonic liposuction and its application to body contouring surgery in MWL patients and in patients with antiretroviral fat redistribution syndrome.
D) Developing new ways to improve wound closure in body contouring surgery.
E) Developing, refining and assessing techniques for autologous breast and buttock augmentation in body contouring.
F) Conducting research on the application of large volume fat grafting in the buttock, breast, and face.

An ongoing database of patients undergoing body contouring following massive weight loss is an ongoing aspect of the research.

3) Peter Jay Sharp Program for Aesthetic & Reconstructive Breast Surgery. The BIDMC has become a regional center for women seeking the DIEP (Deep Inferior Epigastric Perforator Flap), SIEA (Superficial Inferior Epigastric Artery Flap) and SGAP (Superior Gluteal Artery Perforator Flap) options for reconstructive breast surgery. In August of 2007, **Dr. Samuel Lin**, a plastic surgeon and board certified otorhinolaryngologist, joined the Division as a faculty member with experience in reconstructive microsurgery and perforator flap techniques. The program also completed its first year of a funded fellowship program, also accepting its second aesthetic and reconstructive breast surgery fellow, Dr. Eran Bar-Meir, a plastic surgeon from Israel.

In 2007, Drs. Adam Tobias and Bernard Lee performed more than 100 perforator flap breast reconstructive procedures. This surgical experience led to the development of an Intraoperative Pathway to further standardize care, increase efficiency, reduce morbidity, as well as optimally utilize staff in the operating room.

Janet Yueh, a Doris Duke Fellow from Harvard Medical School (HMS IV), developed a study to evaluate the DIEP flap program. Working closely with Drs. Tobias and Lee, the multi-pronged assessment attempts to:

A) Analyze the breast reconstruction rate and referral patterns before and after the development of a DIEP flap program.
B) Compare the clinical outcomes of the different types of breast reconstruction. In particular, we will compare the complication rates among the DIEP, TRAM, latissimus, and implant procedures.
C) Survey patients to assess satisfaction among the DIEP, TRAM, latissimus, and implant procedures.

In addition to the research goals stated above**,** Ms. Yueh has started to investigate the inpatient hospital cost of a DIEP flap, comparing it to the average reimbursement offered by Medicare and other insurance providers. A proposal has been created for the ICD-9-CM Coordination and Maintenance Meeting to advocate new ICD-9 Procedure Codes to distinguish the various types of breast reconstruction available after mastectomy. The study has the potential to affect the Medicare reimbursement rates throughout the United States.

This Outcomes Research Project was made possible by the Doris Duke Clinical Research Fellowship, Harvard Medical School (awarded to Janet H. Yueh, HMS '09), who is a clinical research fellow in the Division of Plastic Surgery (2007/08). Janet Yueh developed the protocol, patient base, patient satisfaction survey and project analysis.

LIST OF CURRENT EMPLOYEES

Loren J. Borud, MD	Instructor in Surgery
Geoffrey Brahmer, MDiv	Education, Research and Residency Coordinator
Linda Dicenzo, RN	Nurse Manager
Bernard T. Lee, MD	Instructor in Surgery
Samuel J. Lin, MD	Instructor in Surgery
Adam M. Tobias, MD	Instructor in Surgery
Joseph Upton, MD	Associate Clinical Professor of Surgery

Other Active Members of the Divisional Research team

Eran Bar-Meir, MD	2007/08 Aesthetic & Reconstructive Breast Surgery Fellow
Stephanie A. Caterson, MD	2006/08 Aesthetic & Reconstructive Breast Surgery Fellow
Mauricio Contreras, MD	Assistant Professor of Surgery at HMS
Sharon Fox, BA	HMS Medical Student Doris Duke Clinical Fellow (2006 / 07)
Robert Goldwyn, MD	Professor of Surgery (retired from surgical practice)
Kristen Rezak, MD	Clinical Fellow in Surgery-Body Contouring
Amir Taghinia, MD	Clinical Fellow in Surgery-Hand and Microsurgery
Janet Yueh, BSc	HMS Medical Student Doris Duke Clinical Fellow (2007 / 08)

LIST OF CURRENT FUNDING

"Peter Jay Sharp program for aesthetic and reconstructive breast surgery"
Peter Jay Sharp Foundation
Project Period: 2005-2008
Principal Investigator: Josef E. Fischer / Sumner A. Slavin

"Body contouring fellowship"
Ethicon Foundation
Project Period: 2007-2009
Principal Investigator: Loren J. Borud

"Perforator identification using near-infrared imaging (NIR)"
NIH, **R01 EB005805-01A1**
Project Period: 2006-2010
Principal Investigator: John Frangioni
Co-Investigator: Bernard T. Lee

"Doris Duke fellowship"
Harvard Medical School
Project Period: 2007-2008
Recipient: Janet Yueh
Mentors: Drs. Bernard Lee, Sumner Slavin, Robert Goldwyn, Geoffrey Brahmer

APPLICATIONS SUBMITTED AND PENDING REVIEW / FUNDING

"Temporal gene expression in the pathogenesis of chronic secondary lymphedema"
NIH/NHLBI: **RO1 HL PA-04-071**
Project Period: 2008-2013
Principal Investigator: Mauricio A. Contreras
Co-Investigator: Sumner A. Slavin

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

Research efforts in the Division of Plastic Surgery have led to a host of presentations, papers, and other scholarly activities at the local, regional, national and international areas. In all of our research, we have invited and incorporated the participation of medical students, residents, and fellows. We have also sought, where possible, to collaborate with colleagues and other researchers, both locally and internationally. For instance, the Cortical Neuroplasticity Research Project initiated by Doris Duke Fellow, Sharon Fox, was a collaboration between a young HMS researcher, a senior Plastic Surgeon, Dr. Joseph Upton, and Functional fMRI Researchers from Boston University Center for Biomedical Imaging and the Computational Neuroimage Analysis Lab at Hanyang University in South Korean. The project created a dialogue between plastic surgeons and fMRI researchers both locally and internationally. It resulted in some new understandings of the brain and led to papers, presentations, and invitations to share the information with others, including a special awarded oral presentation by Sharon Fox at Harvard Medical School 2007 Soma Weiss Research Day. Finally, this collaborative experience helped direct Ms. Fox (HMS IV) to seek out a PHD in biomedical imaging at MIT / Harvard, where she will integrate her knowledge of both imaging and medicine.

In this current academic year, Janet Yueh, another Doris Duke Fellow, started a clinical research project assessing programmatic outcomes of the DIEP flap program. Through her investigative efforts, she learned about disparities in funding mechanisms for the hospital in the medicare reimbursements for DIEP flap breast reconstructions. Her insight led to collaborative efforts, and further investigation with senior level surgical clinicians and administrators at the BIDMC, ICD-9 coders, national policy advocates, and senior clinicians in the field. From a simple question concerning DIEP flaps, and the funding of DIEP Flaps within the hospital, a process has now ensued both within the hospital and beyond. Currently, a hospital task-force has been formed to study the issue and to take it to a national task-force in Baltimore. As part of this process, and in collaboration with others, Ms. Yueh learns about her own talents as a clinician, and investigator. She also learns how the world of medicine and patient care impacts and is impacted by policy, funding, governmental and insurance protocols.

These two brief examples reveal, perhaps, one of our greatest accomplishments as a Division: our ongoing ability and commitment to work with residents, medical students, and researchers and to mentor them to be future leaders in surgery, medical education, and research. This collaborative model extends

to all of our work, including our ongoing fellowship programs: body contouring, aesthetic and reconstructive breast surgery, and hand/microsurgery fellowships.

Abstracts Presented at Local, National, and International Meetings

Caterson SA, Tobias A, **Slavin S**, Lee B. Fat necrosis after autologous breast reconstruction: a classification system and treatment algorithm. American Association of Plastic Surgeons. Coeur D'Alene, ID, May 2007.

Caterson SA, Lau F, Tobias AM, **Slavin S**, Lee BT. Deep inferior epigastric perforator flap learning curve: a single institution's experience in developing a perforator breast reconstruction program. New England Society of Plastic and Reconstructive Surgeons. Newport, RI, June 2007.

Caterson SA, Tobias AM, **Slavin S**, Lee BT. Fat Necrosis after autologous breast reconstruction: a classification system and treatment algorithm. New England Society of Plastic and Reconstructive Surgeons. Newport, RI, June 2007.

Fox SE, Koo B-B, Kwei SK, Amedi A, Kim J-M, and Upton J. Cortical adaptation following gracilis muscle transfer for congenital unilateral palsy of the facial nerve: an fMRI study. Presentation at Harvard Medical Soma Weiss Day. April 2007.

Liao EC, Taghinia AH, Nguyen LP, Yueh JH, May JW Jr., Orgill DP. Incidence of hematoma complication with heparin venous thrombosis prophylaxis after TRAM flap breast reconstruction. Presented at the 86th annual meeting of the American Association of Plastic Surgeons, May 2007.

Taghinia AH, Liao EC, May JW Jr. Randomized controlled trials in plastic surgery: a twenty-year review of reporting standards, methodological quality, and impact. Presented at the 86th annual meeting of the American Association of Plastic Surgeons. May 2007.

Taghinia AH, Bar-Meir E, Schlenker JD, Upton J. Unusual radial polydactyly in the deficient hand – 'special thumbs'. Presented at the 86th annual meeting of the American Association of Plastic Surgeons, May 2007.

Individual Accomplishments

Loren Borud

- Established, directed, and obtained funding for the Body Contouring Fellowship at the BIDMC.
- Inducted into the Maliniac Circle, American Society of Plastic Surgeons.
- Chosen for the Pathway to Leadership Program (only 20 are chosen nationwide), American Society of Plastic Surgeons.
- Performed Massive Weight Loss – Body Contouring Surgery in India, (the first, or one of the earliest such surgeries in India).
- Spent year writing and preparing the Body Contouring Atlas.

Geoffrey Brahmer

- Presented a talk on the holocaust, "In the Eye of the Storm: 6 Photographers in the Nazi Era," at the Yad Vashem, Holocaust Museum, Jerusalem, the Boston Public Library, and the General Surgery Grand Rounds, BIDMC Department of Surgery.
- Awarded oral presentation of research at Harvard Medical School 2007 Soma Weiss Research Day.

Bernard Lee

- Served as the primary academic mentor of the Doris Duke Fellow, 2007-08. In this position, Dr. Lee also provided oversight of the DIEP Flap Outcomes Study.
- Lead faculty investigator of the Translational f(MRI) study for perforator breast reconstruction project.

- Served as a primary academic and clinical mentor to the Peter Jay Sharp Aesthetic & Reconstructive Breast Surgery Fellows.
- Faculty / Mentor Advisor for Harvard Medical School, Holmes Society.
- Served as the current editor, **Encyclopedia of Flaps, 3rd edition**, Strauch B, Vasconez L, Hall-Findlay E, Lee BT, Editors**.**
- Served as Associate Editor of the Journal of Reconstructive Microsurgery**.**
- Primary surgical investigator, Peforator Identification Using Near-Infrared Imaging (NIR)
- Member, National Inservice Examination Committee, American Society of Plastic Surgeons / Plastic Surgery Educational Foundation.

Samuel Lin

- Started as Plastic Surgery Faculty Member, BIDMC, August 2007.
- Awarded the 2007 ASAPS Tiffany Award for Annual Scientific Presentation, American Association of Plastic Surgeons.

Sumner Slavin

- Provided directorship, oversight, and mentoring for all of the organizational educational, and research activities of the Division, including division administration, faculty training and development, as well as the research and clinical efforts of medical students, residents, and fellows.
- Served as Scientific Chairman and Conference Director, Plastic Surgery at the Red Sea: An International Symposium, Eilat, Israel, 2007**.**
- Invited Visiting Professor, Lahey Clinic, December, 2007**.**
- Served as Chairman, Executive Board, Harvard Plastic Surgery Residency Program.
- Invited to be presenter at 8 national and international meetings and gave 15 lectures.
- Served as an Associate Editor for the British Journal of Plastic Surgery and as a member of the Breast Committee, American Society of Plastic Surgeons.

Adam Tobias

- Served as the Director of the Peter Jay Sharp Program for Aesthetic and Reconstructive Breast Surgery. In this position, he was actively involved in all aspects and phases of the program including: funding, program organization and development, staffing, public relations, recruitment and mentoring of the breast surgery fellow, development of clinical and intraoperative pathways, and the ongoing education of residents and medical students.
- Invited panelist and moderator at the Annual Meeting of the Northeastern Society of Plastic Surgeons, October 3-6, 2007, Bermuda.

Joseph Upton

- Served as the Director of the Hand/Microsurgery Fellowship Program. In this position, he was in charge of all of the aspects of the program, including administration, fellowship recruitment and mentoring, and research activities. He also worked closely with Dr. Charles Day, in the integration of the plastic surgery and orthopedic surgery hand fellowships.
- Presented the Leonard R. Rubin Best Paper in Ghent, Belgium, American Association of Plastic Surgeons, May, 2007.

Invited Presentations

Loren Borud

"Breast augmentation in the massive weight loss patient." Body Contouring After Massive Weight Loss Symposium. Dallas, Texas; March 2007.

"Lymphatic considerations in post bariatric body contouring surgery." American Society of Aesthetic Plastic Surgeons. New York, New York; April 2007.

"Lymphatic anatomy and massive weight loss body contouring." Plastic Surgery Division Rounds. April 2007.

"Post-bariatric body contouring." Middle East Medical Assembly. Beirut, Lebanon; May 2007.

"Lymphedema." Division of Plastic Surgery Grand Rounds, American University of Beirut. Beirut, Lebanon; May 2007.

"Diagnosis and treatment of lymphedema." Association of Plastic Surgeons of India. Pune, India; December 2007.

"Body contouring after massive weight loss." Association of Plastic Surgeons of India. Pune, India; December 2007.

"Autologous fat transfer to the breast and buttock." Association of Plastic Surgeons of India. Pune, India; December 2007.

Symposium panelist: Body Contouring after Massive Weight Loss Symposium. Dallas, Texas; March 2007.

Symposium panelist: Ancillary procedures panel. Body Contouring After Massive Weight Loss Symposium. Dallas, Texas; March 2007.

Panel member: "Problem cases in MWL body contouring." Annual Meeting of the American Society of Aesthetic Plastic Surgeons, New York, New York; April 2007.

Geoffrey Brahmer
"In the Eye of the Storm: 6 Photographers in the Nazi Era."
Division Rounds, Division of Plastic Surgery, BIDMC. Boston, MA; January 2007.
Grand Rounds, Department of Surgery, BIDMC. Boston, MA; January 2007.
Yad Vashem, Holocaust Museum. Jerusalem; March 2007.
Conservative Jewish Yeshiva. Jerusalem; March 2007.
Bethlehem Hebrew Congregation: Tisha B'Av. Bethlehem, NH; July 2007.
Boston Public Library. Boston, MA; October 2007.

Stephanie A. Caterson
"My research in breast surgery." BIDMC: Plastic Surgery Division Rounds. Boston, MA; May 2007.

Bernard T. Lee
"Wound closure options for diabetic foot ulcers." Beth Israel Deaconess Medical Center: Division of Podiatry Grand Rounds. Boston, MA; January 2007.

Samuel J. Lin
"Eyelid reconstruction." Plastic Surgery Division Rounds: BIDMC. Boston, MA; November 2007.

Sumner A. Slavin
"Advances in oncoplastic surgery." Miami Cancer Meeting. Miami, FL; February 2007.

"Advances in oncoplastic reconstruction of breast conservation deformities." International Symposium on Plastic Surgery. Eilat, Israel; March 2007.

"Breast complications." Visiting Professor: Lahey Clinic. Boston, MA; December 2007.

"Breast reconstructive paradigms." Visiting Professor: Lahey Clinic. Boston, MA; December 2007.

"Management of lymphedema." Miami Cancer Meeting. Miami, FL; February 2007.

"Office safety and plastic surgery." Visiting Professor: Lahey Clinic. Boston, MA; December 2007.

"Options for prophylactic mastectomy." Miami Cancer Meeting. Miami, FL; February 2007.

"Complications of breast surgery." New York Regional Society of Plastic Surgeons Meeting: New York Academy of Medicine. New York, NY; May 2007.

"Lymphedema: new treatment options." University of Connecticut Medical Center, Combined Grand Rounds, Department of Surgery and Department of Orthopedic Surgery. Hartford, CT; May 2007.

"Lymphedema: treatment options for today." Visiting Professor: Lahey Clinic. Boston, MA; December 2007.

"Lowering the high riding nipples." Experts Meeting in Breast Reconstruction and Breast Plastic Surgery. Rheinfelden, Germany; September 2007.

"New techniques in breast reconstruction." Experts Meeting in Breast Reconstruction and Breast Plastic Surgery. Rheinfelden, Germany; September 2007.

"Plastic surgery in the office setting – is it safe?" Invited Faculty: Harvard Medical School, Continuing Medical Education Course. Boston, MA; September 2007.

"Cosmetic surgery in the office – is it safe?" Annual Meeting: Northeastern Society of Plastic Surgeons. Bermuda; October 2007.

"Complications following augmentation mammoplasty." Annual Meeting: Northeastern Society of Plastic Surgeons. Bermuda; October 2007.

Joseph Upton
"Scapular flap for facial recontouring." American Society for Reconstructive Microsurgery; January 2007.

"Infantile digital fibromatosis: an unusual complication following correction of syndactyly." New England Society of Plastic and Reconstructive Surgeons. Newport, RI; June 2007.

"The use of alloderm as a protective barrier in surgery for recurrent CTS." New England Society of Plastic and Reconstructive Surgeons. Newport, RI; June 2007.

"Replacing the mandible and reconstruction after skull base ablation." AO Craniomaxillofacial Course.

"Diagnosis and management of congenital and acquired vascular disorders of the upper extremity." 62nd ASSH Annual Meeting. Seattle, WA; September 2007.

"Microsurgical reconstruction of the immature skeleton." ASSH Annual Meeting. Seattle, WA; September 2007.

"Congenital hand abnormalities." ASSH Annual Meeting. Seattle, WA; September 2007.

REPORT OF TEACHING

Undergraduate and Medical School Courses

1. Medical students were introduced to the diagnosis, treatment, and management of lymphedema at the monthly clinic.
2. The Division of Plastic Surgery was active in teaching student clerkships and 4th year medical students for HMS course, SU514M.1. In 2007, we had 13 students clerks rotate through the

Division. Each student spent 1 month in the Division. We had hosted 4 international medical students who were on observational rotations.

3. The Division was part of the Dept. of Surgery's elective rotation for 2-week rotations of Harvard Medical Students, HMS III's. In 2007, we helped mentor 9 students. In addition to mentoring ongoing students, the Division sponsored 3-hour wound healing and suturing training seminars for each group of rotating students assigned to the BIDMC. This one-half day seminar takes place quarterly, about 4 times a year.
4. Sponsored 2 Doris Duke Clinical Fellows from HMS. The Division was the recipient of Doris Duke Fellows from HMS for 2006/2007 (Sharon Fox) and 2007/08 (Janet Yueh).

Graduate School and Graduate Medical Courses

1. Drs. Slavin and Borud introduced surgical interns and plastic surgery residents to the special challenges and approaches in clinically treating patients with lymphedema. Residents / medical students are now involved in writing papers/abstracts for papers and presentations.
2. Drs. Tobias and Lee introduced surgical interns and plastic surgery residents to the special challenges and approaches in microsurgery and working with perforator flaps. Residents, a breast surgery fellow and medical students are now involved in writing papers/abstracts for papers and presentations.
3. Drs. Slavin mentored 5 demonstrations and training sessions in the use of plastic surgery fillers for both aesthetic and reconstructive purposes.
4. Drs. Slavin, Borud, Lee, Tobias, and Upton all participated in the Core Curriculum and Journal Club of the Combined Harvard Plastic Surgery Residency Program.
5. In 2007, the Division helped mentor 24 interns (General Surgeons and EMEDS), 2 podiatry residents, and 16 plastic surgery residents. We also sponsored 3 fellows: aesthetic and reconstructive breast surgery, body contouring, and hand/microsurgery.

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DIVISION OF PODIATRY

John Giurini, DPM — **Chief, Division of Podiatry**
Associate Clinical Professor of Surgery

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Aristidis Veves, MD, DSc	**Associate Professor of Surgery**
Christina Lima, BA	Research Coordinator
Lydia Longoria, BA	Research Coordinator
Rachel Cloutier	Research Coordinator

Aristidis Veves, MD
Division of Podiatry
Joslin-Beth Israel Deaconess Foot Center and Microcirculation Lab

Basic Research

Aristidis Veves

Regarding basic research, my main interest lies in studying the effect of diabetes and peripheral neuropathy on wound healing and angiogenesis. I am currently the PI of a Juvenile Diabetes Research Foundation (JDRF) research grant that aims to develop new animal models for the study of wound healing in diabetes. This work is being conducted with Drs. Frank LoGerfo and Leena Pradhan from the Division of Vascular Surgery.

Clinical Research

My main research interest is the vascular reactivity of micro- and macro-circulation. During the last few years, I developed the Microcirculation Lab, which tests the microvasculature in a non-invasive way. The Microcirculation Lab is also equipped with an ultrasound apparatus that enables evaluation of endothelial function in the brachial artery. Our research has been mainly funded by grants from the NIH, American Diabetes Association and the Juvenile Diabetes Research Foundation. In addition, we conduct investigator-initiated studies that are funded by the pharmaceutical industry.

I am interested in the relationship between functional changes in the vascular reactivity and structural changes of the skin. Other interests include the effect of c-nociceptive fiber dysfunction of wound healing and the diabetes-related impairment of angiogenesis.

My Laboratory is also collaborating with small biotech companies. This collaboration has resulted in funding from the NIH, either in the form of SBIR or SBTT grants. The main aim of these collaborations is to develop new techniques that can improve our diagnostic abilities or develop new therapeutic interventions that will treat long-term diabetic complications.

My group is also interested in the etiology of diabetic foot problems and the pathophysiology of wound healing in diabetes. We are currently conducting a larger prospective study that will evaluate the role of microvascular dysfunction in foot ulceration and wound healing failure.

In collaboration with the department of Radiology, we employ a 3 Tesla (3T) magnetic resonance scanner that can access metabolic activity through measurements of the concentrations and reaction rates of the high-energy phosphorus cellular compounds in humans by employing magnetic resonance imaging and spectroscopy methods. The main advantage of this technique is that it can give a direct non-invasive assessment of muscle metabolism. As a first step, we evaluate the effect of diabetes and its complications on the leg blood flow and metabolic function. In addition, in collaboration with Roy Freeman, MD, examines the natural history of the progression of peripheral neuropathy in diabetic patients.

Finally, I am collaborating very closely with Dr. Atul Malhotra, MD from the Harvard Center on Sleep Neurobiology and Sleep Apnea to examine the effects of sleep apnea on vascular reactivity. I currently serve as co-mentor in two fellows who work with Dr. Malhotra.

List of Current Employees

Christina Lima, BA	Research Coordinator
Lydia Longoria, BA	Research Coordinator
Rachel Cloutier	Research Coordinator

The Microcirculation Lab Research Team

List of Current Funding

"Natural history of small fiber diabetic neuropathy"
NIH, **1 R01 NS-046710-01**
Project Period: 2005-2010
PI: Aristidis Veves

"Restoring diabetic tactile sense using mechanical noise"
NIH, **2 R44 DK-060295-02**
Project Period: 2005-2007
PI: Jason D. Harry
Collaborator: Dr. Aristidis Veves

"Role of neuropeptides in wound healing"
Juvenile Diabetes Research Foundation, **JRDF 5-2005-1006**
Project Period: 2007-2008
PI: Aristidis Veves

"Ambulatory foot temperature in diabetic neuropathy"
NIH, **1 R21 DK-071178-01**
Project Period: 2005-2007
PI: Seward Rutkove
Co-Investigator: Aristidis Veves

"Sleep apnea and obesity: cardiovascular risk assessment"
NIH, **1 R01 HL073146-01**
Project Period: 2005-2008
PI: Atul Malhotra
Co-Investigator: Aristidis Veves

"Impaired wound healing in diabetic foot ulceration"
NIH, **1R01DK-076937-01**
Project Period: 2006-2011
PI: Aristidis Veves

"Metabolic MRI of diabetic lower extremity disease"
NIH, **1R01 DK071569-01A1**
Project Period: 2006-2011
PI: Robert L. Greenman
Co-PI: Aristidis Veves

"A 12-week, double-blind, randomized, placebo controlled study to evaluate the effects of Vildagliptin on vascular and endothelial function in patients with type 2 diabetes and subjects at risk of type 2 diabetes"
Novartis Pharma Inc, **LAF237 2369**
Project Period : 2006-2008
PI : Aristidis Veves

"The effect of BioChemics cream 2007-01 in diabetic wound healing"
Biochemics Inc
Project Period: 2008-2009
PI: Aristidis Veves

APPLICATIONS SUBMITTED AND PENDING REVIEW/APPROVAL

"Role of talactoferrin in inflammation and wound healing"
NIH, **1R42 AI-072904-01**
Project Period: 2007-2008
PI: Aristidis Veves

"Diabetic neuropathy, vascular disease and muscle function"
NIH, **1RO1-**
Project Period: 2008-2013
PI: Aristidis Veves

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

During the last academic year, we continued an investigator-initiated clinical study that was related to vascular dysfunction in diabetes and were funded by Novartis Pharma, Inc. We also continued a 5-year NIH grant that will investigate the natural history of peripheral neuropathy, a 3-year NIH grant studying the vascular changes in foot ulceration, and an innovative research grant from Juvenile Diabetes Foundation. I also participated as co-investigator in two NIH-funded studies.

During the past year, we also initiated a 4-year R01 that will study wound healing in diabetic patients. I was awarded a JDRF Innovative grant that will study the effects of neuropeptides on wound healing. Biochemics Inc. will fund a study that investigates the effects of the Biochemics cream 2007-01 in wound healing. Finally, I am the PI in a new single center clinical trial that was funded by Novartis and examines the effects of a DPP-4 inhibitor (vildagliptin) on vascular function.

Individual Accomplishments

As a member of the Medical Science Review Committee of the Juvenile Diabetes Research Foundation International, I participated in the spring and fall grant reviews.

I was invited to review grants for the American Diabetes Association. I started reviewing grants during the spring review in April 2003 and continued by participation in 2007.

I was a member of the NHLBI Mentored Patient Oriented Research Career Development Award Panel for K23, K24 and K25 applications and R13 Conference Grants, and an ad hoc member for the CNNT panel, the ZRG1 MOSS-C (12) M ACTS Small Business Special Emphasis Panel, and the ZRG1 BDCN-J 03 Member Conflict: Brain Disorders and Clinical Neuroscience panel.

I continue to serve as an Associate Editor for the journal Wounds: A Compendium of Clinical Research and Practice (2000-).

I was a member of the ad hoc subcommittees of Integrated Physiology, specifically of the Obesity and Lower Extremity section, which assisted in the development of the 2008 Scientific Sessions program of the American Diabetes Association.

I was asked to act as a peer reviewer for the journals Diabetes, Diabetologia, Diabetes Care, Diabetic Medicine, Wound Repair and Regeneration, Wounds, and the New England Journal of Medicine.

Invited Presentations

"The interaction between neuropathy and microvascular abnormalities in wound healing in diabetes." Pennington Scientific Symposium: Diabetes Complications. Baton Rouge, LA; January 2007.

"Wound healing in diabetes: role of neuropathy & microcirculation." New York University Hospital Medical Grand Rounds. New York City, NY; March 2007.

"Endothelial function in diabetes: from pathophysiology to management." New York University Hospital Medical Residents Rounds. New York City, NY; March 2007.

"Wound healing in diabetes: interaction between neuropathy and vascular disease." NIDDK Workshop, "Advances toward measuring diabetic retinopathy and neuropathy: from the bench to the clinic and back again." Baltimore, MD; April 2007.

REPORT OF TEACHING

In the past year, I participated as co-mentor in the applications of Drs. Susie Yim, MD (NRSA and CITP application), Shilpa Rahangdale, MD, (King Foundation), Christopher H. Gibbons. MD (K23 application) and Leena Pradhan, PhD (Juvenile Diabetes Research Foundation). The applications are currently in the review process.

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Original Articles

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O'Neill MS, **Veves A**, Sarnat JA, Zanobetti A, Gold DR, Economides PA, Horton ES, Schwartz J. Air pollution and inflammation in Type 2 diabetes: A mechanism for susceptibility. Int J Occup Med Environ Health 2007; 64:373-9.

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Reviews, Chapters, and Editorials

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Reviews, Chapters, and Editorials (in press)

Veves A, Malik RA, Backonja M. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis and treatment options. Pain Med 2007; in press.

Abstracts

Dinh T, Panasyuk S, Jiang C, Freeman J, Panasyuk AA, Nerney M, Lew R, Brand D, Lima C, Giurini JM, Lyons TE, Khaodhiar L, **Veves A**. The use of medical hyperspectral imaging (MHSI) to evaluate microcirculatory changes in diabetic foot ulcers and predict clinical outcomes. Diabetes 2007; 55 (Suppl 1):106A.

DIVISION OF TRANSPLANTATION

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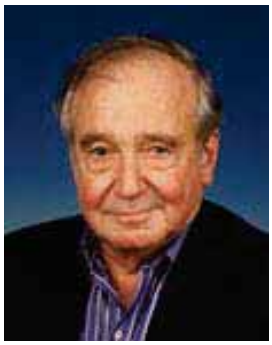
Karen Ho, PhD	Research Fellow in Surgery
Yan Lu, MD	Research Fellow in Surgery
Nidhi Jain, PhD	Research Assistant in Surgery
Brunilda Ramos-Perez	Administrative Coordinator

Fritz H. Bach, MD

Basic Research


Fritz Bach

My group focuses on the effects of heme oxygenase-1 (HO-1) and two of the products of HO-1 degradation of heme in models of shock, transplantation and vascular injury. We are particularly interested in cell signal transduction and have focused on the mitogen activated protein kinases (MAPK) and other signaling molecules in particular this year.

We studied the effects of biliverdin/bilirubin in ischemia-reperfusion injury (IRI) in models of the small intestinal and liver transplantation as well as in intimal hyperplasia following balloon injury. Most have begun a study of the signaling events consequent to biliverdin administration in LPS stimulated macrophages. Biliverdin acted to ameliorate the undesirable consequences of decreased function and tissue injury in IRI likely based on its potent anti-inflammatory properties. Interestingly, biliverdin did not achieve these results in the same manner as carbon monoxide (CO), another agent we tested in the small bowel transplantation model even though both agents prevented bowel dysfunction and cell damage. Biliverdin suppressed the expression of the adhesion molecules and markedly reduced the infiltration of host leukocytes into the bowel, something that CO did not do. This is in concert with our findings that bilirubin suppressed adhesion molecules on cultured endothelial cells stimulated with TNF-α while CO did not.

The studies on the suppression of smooth muscle cell (SMC) proliferation following balloon injury provided further evidence that the beneficial effects of biliverdin/bilirubin are mediated by pathways different from the effects of CO. Both biliverdin/bilirubin and CO suppressed SMC proliferation *in vitro* and intimal hyperplasia *in vivo,* however, the signaling molecules that effected these changes were different for CO and biliverdin. Even though both molecules involved modulation of p38 MAPK, biliverdin suppressed p38 while CO stimulated p38. We hypothesize that this is due to the differential modulation of p38α and p38β by CO and biliverdin. As a part of the study with biliverdin and intimal hyperplasia, we studied the downstream signaling molecules involved in those effects. Interestingly, biliverdin modulated the phosphorylation of Rb leading to hyperphosphorylation of that molecule and consequent suppression of action of transcription factors such as YY1 that are needed for SMC proliferation. This again was different from the effects of CO.

We extensively studied the effects of expressing HO-1 in a model of tolerance induced by DST. The conclusions from that study showed that not only did induction of HO-1 increase the efficacy of DST stimulated tolerance, but blocking of HO-1 eliminated the tolerance-inducing effects of DST. This finding suggests that HO-1 may be a critical molecule that is needed for T regulatory mediated tolerance, something we are testing further. Also in that study, we confirmed the earlier findings of the previous years that HO-1 expression leads to antigen induced cell death (AICD). However, in this case we showed additionally that HO-1 expression did not lead to the death of T regulatory cells, although exact quantitation of those effects must still be accomplished.

List of Current Employees

Hongjun Wang, PhD	Instructor in Surgery
Michael Thomas, MD	Research Fellow in Surgery
Fredy Rocuts, MD	Research Fellow in Surgery
Eva Czismadia	Research Technician
Xinyu Zhang,	Research Technician
Julienne Carty	Research Assistant II

List of Current Funding

"Heme oxygenase-1: protection against chronic rejection"
NIH, **5RO1 HL077721-03**

Project Period: 2006-2009
PI: Fritz Bach

DIVISIONAL ACCOMPLISHMENTS IN THE PAST YEAR

Patent disclosures
I have continuing involvement in the litigation of several patent applications for the use of carbon monoxide as a therapeutic.

I have taken over the funding and execution of a patent on the use of biliverdin/bilirubin and other molecules of the HO-1 system (except CO).

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Chin BY, Jiang G, Wegiel B, Wang HJ, Macdonald T, Zhang XC, Gallo D, Cszimadia E, **Bach FH**, Lee PJ, Otterbein LE. Hypoxia-inducible factor 1alpha stabilization by carbon monoxide results in cytoprotective preconditioning. Proc Natl Acad Sci U S A 2007; 104 (12): 5109-14.

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Haschemi A, Wagner O, Marculescu R, Wegiel B, Robson SC, Gagliani N, Gallo D, Chen JF, **Bach FH**, Otterbein LE. Toll-like receptor 4 suppression leads to islet allograft survival. FASEB J 2007; 21(11):2840-8.

Lee SS, Gao W, Mazzola S, Thomas MN, Csizmadia E, Otterbein LE, **Bach FH**, Wang H. Heme oxygenase-1, carbon monoxide, and bilirubin induce tolerance in recipients toward islet allografts by modulating T regulatory cells. FASEB J 2007; 21(13):3450-7.

Ollinger R, Yamashita K, Bilban M, Erat A, Kogler P, Thomas M, Csizmadia E, Usheva A, Margreiter R, **Bach FH**. Bilirubin and biliverdin treatment of atherosclerotic diseases. Cell Cycle. 2007; 6(1):39-43.

Ramlawi B, Scott JR, Feng J, Mieno S, Raman KG, Gallo D, Csizmadia E, Yoke Chin B, **Bach FH**, Otterbein LE, Sellke FW. Inhaled carbon monoxide prevents graft-induced intimal hyperplasia in swine. J Surg Res 2007; 138 (1):121-7.

Original Articles (Submitted or in press)

Ollinger R, Thomas M, Kogler P, Hermann M, Weiss H, Mark W, Bilban M, Troppmair J, **Bach FH**, Margreiter R. Blockade of p38 MAPK inhibits chronic allograft vasculopathy. Transplantation 2007; in press.

Reviews, Chapters, and Editorials

Ollinger R, Wang H, Yamashita K, Wegiel B, Thomas M, Margreiter R, **Bach FH**. Therapeutic applications of bilirubin and biliverdin in transplantation. Antioxid Redox Signal 2007; 9(12): 2175-85.

Soares MP, **Bach FH**. Heme oxygenase-1 in organ transplantation. Front Biosci 2007; 12:4932-45.

Douglas W. Hanto, MD, PhD

Basic research

My current laboratory research is focused on the ability of carbon monoxide (CO) at low concentrations to be protective in rodent and large animal models of ischemia-reperfusion injury and delayed graft function, allograft rejection and survival, and in hepatic regeneration. The goal of these studies is to perform critical experiments that will allow CO to be studied in human clinical trials of organ donation and transplantation, chronic allograft nephropathy, and hepatic resection and transplantation. CO is a product of HO-1 action on heme and has potent anti-inflammatory, anti-apoptotic, and anti-proliferative effects. It is of great interest that the CO effects are observed with intermittent exposure e.g. 1 hour per day. We believe that CO will be effective in abrogating the ischemia/reperfusion injury (IRI) associated with organ procurement, preservation, and reperfusion. In a rat kidney allograft model we have shown that inhaled CO confers protection against chronic allograft nephropathy. We have also developed and validated a model of delayed graft function (DGF) in pig kidney allografts and have shown that CO decreased the severity of DGF and resulted in earlier recovery of kidney function. We are examining whether treatment of donor and/or recipient with CO is optimal in blocking IRI and DDF, as well as determining the optimal dose, duration, and interval. We are also examining the effects of CO on hepatic regeneration in a rodent hepatic resection model and in a model of hepatic ischemia. This work is being done in collaboration with Dr. Leo Otterbein in our division.

Clinical Research

We are engaged in a number of prospective and retrospective clinical studies involving transplantation (kidney, liver, pancreas, and islet), dialysis access, and nontransplant hepatobiliary surgery. We have had a longstanding interest in the development of malignancies after transplantation, particularly post-transplant lymphoproliferative diseases (PTLD), and also in the risk of transmission of malignancy to recipients from donors with cancer. We have also been interested in antibody mediated rejection in kidney and liver allograft recipients and the development of therapeutic strategies to permit ABO incompatible transplants and transplants in highly sensitized patients. With the introduction of several new immunosuppressive drugs over the past several years, we are examining changes in immunosuppressive protocols to minimize the side-effects of chronic corticosteroid and calcineurin inhibitor toxicity. The ability to safely transplant HIV+ patients is another significant focus of our clinical research activities as part of a multi-center NIH sponsored trial. We are co-investigators in an NIH/NIAID Clinical Trials in Organ Transplantation study of novel immunosuppressive protocols. We are beginning a clinical study in liver transplant recipients using transcriptional profiling to analyze the allograft response in patients that are likely to have predictive value for post-transplant liver function and risk of rejection, with the ultimate goal of being able to individualize the degree of immunosuppression. There are many other ongoing clinical studies.

List of Current Funding

"Solid organ transplantation in HIV: Multi-site study"
NIH/NIAID, **5U01-AI052748-05**
Project Period: 2004-2009
PI: Peter G. Stock (University of California San Francisco)
Site Principal Investigator: Douglas Hanto

"Clinical trials in organ transplantation"
NIH/NIAID, **5U01-AI63623-04**
Project Period: 2004-2009
PI: Mohamed H. Sayegh (Brigham and Women's Hospital, Boston)
Site Principal Investigator: Douglas Hanto

"A prospective, open-label, multi-center randomized trial of the efficacy and safety of long term calcineurin inhibitor free maintenance regimen with mycophenolate mofetil and sirolimus in recipients of an orthotopic liver transplant"

Roche Laboratories
Project Period: 2005-2008
Co-Investigator: Douglas Hanto

"Open label, prospective, randomized controlled, multi-center study assessing fixed dose vs concentration controlled cell cept regiments for patients following a single organ renal transplantation in combination full dose and reduced dose calcineurin inhibitors"
Roche Laboratories.
Project Period: 2005-2008
Co-Investigator: Douglas Hanto

"Belatacept evaluation of nephroprotection and efficacy as first-line immunosuppresion trial-extended criteria donors"
Bristol-Myers Squibb
Project Period: 2005-2008
Co-Investigator: Douglas Hanto

"Novel calcineurin inhibitor for *de novo* renal transplant recipients"
Isotechnika
Project Period: 2006-2008
Co-Investigator: Douglas Hanto

"Inhaled CO in kidney transplantation in swine."
iNO Therapeutics
Project Period: 2006-2008
Co-Principal Investigator: Douglas Hanto

"Renal ischemia reperfusion injury in rats"
iNO Therapeutics.
Project Period: 2006-2008
Co-Investigator: Douglas Hanto

"Randomized double-blind study to assess the efficacy and safety of prophylactic use of mariavir versus oral gancyclovir for the prevention of cytomegalovirus disease in recipients of orthotopic liver transplants"
ViroPharma
Project Period: 2007-2010
Co-Investigator: Douglas Hanto

"A 12-month open-label randomized multi-center sequential cohort dose-finding study to evaluate the efficacy, safety, and tolerability of oral AEB071 versus tacrolimus in combination with Myfortic, Simulect, and Corticosteroids in de novo adult renal transplants"
Novartis
Project Period: 2007-2010
Co-Investigator: Douglas Hanto

REPORT OF TEACHING

Undergraduate and Medical School Courses

This year, as I have done since 2001, I participated in the Core Clerkship in Surgery and in the Transplant Elective as an attending Surgeon for Harvard Medical School Students. I also participated as a Faculty Member in "Introduction to the Abdominal Exam, which was on November 19, 2007, and held for 2nd-year HMS students.

Invited Presentations

"Organ donation and transplantation: the good, the bad, and the ugly." Grand Rounds: Lowell General Hospital. Lowell, MA; March 7, 2007.

"The intersection of patients' needs, economics, and ethics in organ donation and transplantation." Keynote speaker at the MIT Hippocratic Society Conference, Massachusetts Institute of Technology, Cambridge, MA; March 10, 2007.

"Transplant update." Grand Rounds: MetroWest, Leonard Morse Hospital. Natick, MA; April 23, 2007.

"Update: kidney, liver, and pancreas transplantation." Grand Rounds: Saint Vincent Hospital. Worcester, MA; May 17, 2007.

"Surgical considerations in the management of portal hypertension." Invited speaker at the American College of Surgeons 93rd Annual Clinical Congress. New Orleans, LA; October 8, 2007.

"Transplant immunosuppression 2007: the ongoing search for improvement." University of Minnesota, Minneapolis, MN; October 18, 2007.

"Treatment options for hepatocellular carcinoma." Grand Rounds: Baystate Medical Center. Springfield, MA; October 25, 2007.

Invited speaker. "Pancreas transplantation." Joslin Diabetes Center: Advances in Diabetes 2007. Boston, MA; November 3, 2007.

"Current status of organ transplantation and future trends." Harvard Medical International and Wockhart Hospitals CME. Mumbai, India; November 12, 2007.

"Current status of organ transplantation and future trends." Harvard Medical International and Wockhart Hospitals CME. Bangalore, India; November 15, 2007.

"When to say no to transplantation." Transplant Conference: Baystate Medical Center. Springfield, MA; November 27, 2007.

Abstracts Presented at Local, National, and International Meetings

Ho KJ, Owens CD, Johnson S, Khwaja K, Pavlakis M, Mandelbrot D, Saidi RF, Ko D, Malek S, Tullius S, Whiting J, **Hanto DW**, Karp SJ. Sustained donor hypotension and long times to death during DCD kidney procurement correlate with increased rates of DGF and worse long term renal function. Presented at the American Society of Transplant Surgeons State of the Art Winter Symposium, 2007. Marco Island, FL. January 12-14.

Rogers C, Bain B, Johnson S, Wong M, Stablein D, Stock P, Frasetto L, **Hanto D,** Roland M. Renal sparing effects of rapamycin in HIV+ transplant recipients. Presented at the American Transplant Congress, 2007. San Francisco, CA. May 5-9.

Rogers C, Johnson S, Gribbons M, Khwaja K, Karp S, Egbuna O, Mandelbrot D, Pavlakis M, **Hanto D,** Curry M. Timing of sirolimus conversion influences recovery of renal function in liver transplant recipients. Presented at the American Transplant Congress, 2007. San Francisco, CA. May 5-9.

Yoon M, Konduru B, Gallo DJ, Otterbein LE, **Hanto DW.** Carbon monoxide prevents rejection and delayed graft function following kidney transplantation in rats and pigs. Presented at the American Transplant Congress, 2007. San Francisco, CA. May 5-9.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original Articles

Hanto DW. Ethical challenges posed by the solicitation of deceased and living organ donors. N Engl J Med 2007; 356:1062-6.

Johnson SR, Alexopolous S, Curry M, **Hanto DW**. Primary nonfunction (PNF) in the MELD era: an SRTR database analysis. Am J Transplant 2007; 7:1003-9.

Kauffman HM, Cherikh WS, McBride MA, Cheng Y, **Hanto DW**. Deceased donors with a past history of malignancy: an OPTN/UNOS Update. Transplantation 2007; 84:272-4.

Mandelbrot DA, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, Khwaja K, **Hanto DW,** Rodrigue JR. The medical evaluation of living kidney donors: a survey of US transplant centers. Am J Transplant 2007; 7:2333-43.

Rodrigue JR, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, Khwaja K, **Hanto DW,** Mandelbrot DA. Evaluating living kidney donors: relationship types, psychosocial criteria, and consent processes at transplant programs in the United States. Am J Transplant 2007; 7:2326-32.

Wray CJ, Lowy AM, Matthews JB, James LE, Choe KA, **Hanto DW**, Ahmad SA. Intraoperative margin re-resection for colorectal metastases. J Surg Ed 2007; 64:150-7.

Reviews, Chapters and Editorials

Hanto DW. Autogenous arteriovenous hemodialysis access. Commentary. In: Fischer JE, editor. Mastery of Surgery, 5th edition. Philadelphia: Lippincott, Williams and Wilkins: 2007; p 2263.

Hanto DW, Johnson SR. Liver transplantation. In: Fischer JE, editor. Mastery of Surgery, 5th edition. Philadelphia: Lippincott, Williams and Wilkins: 2007; p 1196-1211.

Pavlakis M, **Hanto D**, Mandelbrot D. "Do we know enough to mandate testing of living donors?" Letter. Am J Transplant 2007; 7: 1.

Seth J. Karp, MD


Seth Karp

Basic Research

Basic research in the laboratory is concerned with the molecular basis for liver development and regeneration. Ultimately we would like to apply this knowledge to produce liver tissue substitutes, enhance liver regeneration, and understand liver cancer.

Multiple projects are ongoing in the laboratory. We performed a screen for genes involved in liver regeneration and development. This demonstrated that regeneration and development are distinct process, and that at a molecular level, liver regeneration is best thought of as hepatocyte hyperplasia. We also discovered a class of inhibitory molecules that are down regulated during regeneration, loss of which enhances liver regeneration. We are currently analyzing these genes using liver specific knockout technology we have produced, as well as n AAV-8 vector to introduce genes, also which we helped develop.

The second project seeks to determine lineage commitments in the developing and regenerating liver. We believe understanding which cells give rise to which cells in vivo will suggest a strategy for recapitulating liver organogenesis in vitro. Using transgenic mice that express an inducible recombinase in the liver and a target construct that fluoresces when the recombinase is activated, we are able to heritably mark liver cells in a temporally-restricted manner. Following the cells and their progeny is then possible. Combining this approach with 2/3 hepatectomy and other models of liver damage we can determine how the liver is repopulated.

We have also initiated a collaborative project with a group from MIT led by Ionnas Yannas trying to use defined scaffolds to encourage normal liver regeneration in fibrotic liver.

Clinical Research

Clinical research is concerned with predictors of graft survival from donation after cardiac death organs (DCD).We reviewed the database of the New England Organ Bank and determined factors that predict function after DCD transplantation.

List of current Employees

Nicole Nesbit	Research Technician
Karen Ho, MD	Surgical Resident/Research Fellow

List of Current Funding

"The role of activin signaling in liver growth and regeneration"
National Institutes of Health, **5 K08 DK064648**
Project Period: 2003-2008
PI: Seth J. Karp

"Lineage analysis in the developing and regenerating liver"
American Society for Transplant Surgery Faculty Development Award
Project Period: 2005-2007
PI: Seth J. Karp

Applications Submitted and Pending Review/Funding

"BMP signaling in the regenerating liver"
NIH R01
PI: Seth J. Karp, MD

Research Accomplishments over the Past Year

We performed a screen for genes involved in liver regeneration and development. This demonstrated that regeneration and development are distinct process, and that at the molecular level, liver regeneration is best thought of as hepatocyte hyperplasia. We also discovered a class of inhibitory molecules that are down-regulated during regeneration, loss of which enhances liver regeneration.

Abstracts Presented at Local, National, and International Meetings

Outcomes after DCD liver and kidney transplantation ASTS winter symposium

Invited Presentations

"Negotiation." ASTS fellows symposium; 2007.

Patent Disclosures

Karp SJ, Garfein E, Frangione J, Onishi S. Compositions and methods for locating an internal bleeding site

Karp SJ, Garfein E, Frangione J, Onishi S Method and product for locating an internal bleeding site.

Bibliography (January – December 2007)

Original articles

Mandelbrot DA, Pavlakis M, Danovitch GM, Johnson SR, **Karp SJ**, Khwaja K, Hanto DW, Rodrigue JR. The medical evaluation of living kidney donors: a survey of US transplant centers.
Am J Transplant 2007; 7(10):2333-43.

Nadig SN, Bratton CF, **Karp SJ**. Marginal donors in liver transplantation: expanding the donor pool. J Surg Educ 2007; 64(1):46-50.

Otu HH, Naxerova K, Ho K, Can H, Nesbitt N, Libermann TA, **Karp SJ**. Restoration of liver mass after injury requires proliferative and not embryonic transcriptional patterns. J Biol Chem 2007; 282(15):11197-204.

Rodrigue JR, Pavlakis M, Danovitch GM, Johnson SR, **Karp SJ**, Khwaja K, Hanto DW, Mandelbrot DA. Evaluating living kidney donors: relationship types, psychosocial criteria, and consent processes at US transplant programs. Am J Transplant 2007; 7(10):2326-32.

Maria Koulmanda MSc, PhD
Transplant Research Center

BASIC RESEARCH


Maria Koulmanda

I trained with Professor Thomas Mandel at the Walter and Eliza Hall Institute, Melbourne, and then became a faculty member in his lab. We demonstrated that fetal mouse, pig, and human islets are far more resilient than conventional islets and expand after transplantation. Using our pioneering high-oxygen fetal pancreas organ culture technique, we discovered that fetal endocrine tissues selectively survive, thereby dramatically reducing inflammation and immunogenicity.

In 1995, while writing my PhD dissertation part-time, I was recruited as an Overseas Research Associate by Professor David White of Cambridge University, UK. Using the transgenic pig-to-monkey model, we demonstrated that hyperacute rejection, the barrier that prevents xenogeneic organ transplants, is not a barrier to islet transplants. In 1998 I was recruited by Dr. Hugh Auchincloss to establish non-human primate and NOD mouse core programs for the Juvenile Diabetes Foundation (JDF) Center for Islet Transplantation at Harvard Medical School. In collaboration with Dr. Terry Strom, we achieved remarkable prolongation (ca. 300 days) of allogeneic monkey islets following a short course of novel co-stimulatory based therapy. Indeed, the grafts failed due to non-immune related islet loss that also destroyed a similarly sized autologous pancreas. We subsequently tested the effect of short-term treatment with IL-2.Ig mutant antagonist type IL-15.Ig plus sirolimus in the monkey islet allograft and new-onset Type 1 (T1) diabetes mellitus (DM) NOD models. In treated monkey recipients, long-term drug free graft survival, a cardinal achievement in this extremely difficult model, is routine. In the new-onset T1DM NOD model this regimen restores normoglycemia, immune tolerance to islets, and abolishes a previously unrecognized inflammatory state that impairs insulin signaling, thereby causing insulin resistance. This regimen has been approved for a funded clinical trial in T1DM.

Next we hypothesized that agents that tilt the balance of pro- to anti-inflammatory molecules toward an anti-inflammatory state would prove similarly effective in these models. Hence, new-onset T1DM mice were treated short-term with alpha-1-anti-trypsin (AAT), an acute phase reactant. Although this agent does not directly act upon T cells, AAT promotes rapid restoration of normoglycemia and islet cell tolerance in the NOD model. In fact, the remnant islet cell mass rapidly tripled in size in the AAT-treated mice. In AAT-treated monkey islet allograft recipients, insulin levels rise substantially ca. 30 days post-transplantation. In contrast, insulin levels insidiously decrease in other islet (even autologous) transplant models. While this work is not yet published, the Immune Tolerance Network has approved an AAT clinical trial in new-onset T1DM. As hypoxic- and ischemic-reperfusion type injuries lead to amplified expression of pro-inflammatory cytokines in human transplants, these findings open new opportunities for clinical application of inflammation-altering cytoprotective strategies. Going forward I am concentrating on the study of allogeneic and xenogeneic (both fetal and conventional) islet transplants placed into cynomolgus monkey recipients. I will pay particular attention to the study of novel anti-inflammatory (cytoprotective) strategies as a means to enable immune tolerance and nurture resilient ("cytoprotected") islets as a means to cure T1DM in new-onset diabetics or in recipients of islet transplants.

LIST OF CURRENT EMPLOYEES

Andi Qipo, MD	Research Fellow in Surgery
Zhigan, Fan MD, PhD	Research Fellow in Surgery
Dusan Hanidziar, MD	Research Fellow in Surgery
Derek Liu, PhD	Research Fellow in Surgery
Sayed K. Hasan, MD	Research Fellow in Surgery
Singh Gurbakhish MD	Research Fellow in Surgery
Rita Gottschalk	Lab manager

List of Current Funding

"Tolerance induction for primate islet transplantation"
National Institutes of Health, **NIAID UO1 AI151706-01**
Project Period: 2002-2008
PI: Maria Koulmanda

"Thoracic allograft tolerance in non-human primates"
National Institutes of Health, **NIAID U19 AI066705-01**
Project Period: 2005-2010
PI: Joren Madsen
Collaborator: Maria Koulmanda

"JDRF center for diabetes research: human islet transplantation"
Juvenile Diabetes Research Foundation
Project Period: 2006-2010
Pilot study "New strategy of tolerance induction using DC's.
PI: Maria Koulmanda

"To test the new Aralast-NP on the role of inflammation and autoimmunity in the NOD mouse"
Baxter Healthcare Corporation
Project Period: 2007-2008
PI: Maria Koulmanda

"To test the effect of anti-α vB6 mAb on syngeneic and allogeneic skin"
Stromedix
Project Period: 2007-2008
PI: Maria Koulmanda

"New strategy to induce islet allograft tolerance"
Juvenile Diabetes Foundation, **1-2007-52**
Project Period: 2007-2010
PI: Maria Koulmanda

"On the role of regulatory T cells in transplantation"
National Institutes of Health, **PO1 AI041521**
Project Period: 2007-2012
PI: Terry Strom
Collaborator: Maria Koulmanda

"Inflammation and T cell memory: inter-related barriers to allograft tolerance"
National Institutes of Health, **1-U19 DK080652**
Project Period: 2007-2012
PI: Maria Koulmanda

Research Accomplishments in the Past Year

My biggest accomplishment of 2007 was preparing and publishing a paper in a high impact journal (PNAS). The **Abstract** for this work is below.

In NOD mice with overt new onset type 1- diabetes mellitus (T1DM), short term treatment with the "Power Mix" regimen [rapamycin plus agonist IL-2- and antagonist-type, mutant IL-15-related Ig fusion proteins (IL-2/Fc and mIL-15/Fc)] abolishes immunologic destruction of the islet beta cells and restores both euglycemia and immune tolerance to beta cells. To our surprise, increases in the mass of insulin producing beta cells or circulating insulin levels were not linked to the restoration of euglycemia. Instead, the restoration of euglycemia was linked to relief from an unforeseen inflammatory state in fat and muscle tissues that impair the ability of these tissues respond to insulin. Consequently, restoration of immune

tolerance enables the immune protected residual beta cell mass to maintain normoglycemia following resolution of the insulin resistant state. Both restoration of T cell tolerance to beta cells and relief from the adverse metabolic effects of an inflammatory state in insulin sensitive tissues appear essential for permanent restoration of normoglycemia in this informative model of T1DM. Power Mix, a regimen with both tolerance inducing and select anti-inflammatory properties, may represent a proto-type for therapies able to restore euglycemia and self-tolerance in this difficult setting.

Invited Presentations

"Is ablation of insulitis and restoration of T cell tolerance necessary but insufficient to cure T1DM?" Transplant Conference: Beth Israel Deaconess Medical Center. Boston, MA; February 20, 2007.
"The pathogenic role of inflammation in autoimmune diabetes model." Updates in Surgical Research: Department of Surgery: Beth Israel Deaconess Medical Center. Boston, MA; September 24, 2007.

"Tolerance induction in cytomologys monkeys." NIH Primate workshop. Bethesda, MD; November 2007.
"New strategy of tolerance induction in non-human primates." Austin Research Institute. Melbourne, Australia; December 2007.

Abstracts presented at Local, National, and International Meetings

M. Koulmanda, L. Hoffman, A. Qipo, H. Shi, Z. Fan, J.F. Flier, T.B. Strom. Aralast or anti-TNF-α. treatment prevents autoimmune destruction of islet grafts in nonobese diabetic (NOD) mice. American Association of Immunologists Annual Meeting, Miami, FL. May, 2007.

M. Koulmanda, L. Hoffman, A. Qipo, H. Shi, Z. Fan, J.F. Flier, T.B. Strom. Aralast or anti-TNF-α. treatment prevents autoimmune destruction of islet grafts in nonobese diabetic (NOD) mice. American Transplant Congress, San Francisco, CA. May, 2007.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original articles

Koulmanda M, Budo E, Bonner-Weir S, Qipo A, Putheti P, Degauque N, Shi H, Fan Z, Flier JS, Auchincloss H Jr, Zheng XX, Strom TB. Modification of adverse inflammation is required to cure new onset type 1 diabetic hosts. Proc Natl Acad Sci USA 2007;104(32):13074-9.

Anthony P. (Tony) Monaco, MD
Takashi Maki, MD, PhD
Transplant Research Center and the Transplantation and Cellular Immunology Laboratory


Tony Monaco

BASIC RESEARCH

Induction of tolerance to allografts
The major goal of this project is to study the allograft tolerance induced by donor bone marrow cell infusion combined with immunosuppression by polyclonal anti-T cell antibody (ALS) and rapamycin in a mouse skin allograft model and a nonhuman primate kidney transplantation model.

Treatment of overtly diabetic NOD mice
The major goals of this project are to study the effectiveness of ALS and FTY720 in preventing and curing autoimmune diabetes in NOD mice, a mouse model of type 1 diabetes. We also study the effectiveness of allogeneic islet transplantation under the tolerance induction protocol using donor bone marrow infusion to treat autoimmune diabetes.

LIST OF CURRENT EMPLOYEES

Takahiro Torii, MD Postdoctoral Fellow

LIST OF CURRENT FUNDING

"Induction of unresponsiveness to allografts"
NIH R56, **AI014551**
Project period: 2007-2008
Principal Investigator: Anthony P. Monaco

"Induction of tolerance to allografts in non-human primates" (RFA, Non-human Primate Immune Tolerance Cooperative Study Group)
Project period: 2002-2008
Principal Investigator: Anthony P. Monaco
Co-Principal Investigator: Takashi Maki

"Mechanistic study of CCR5 antagonist in allogeneic kidney transplantation in cynomolgus monkeys"
Ono Pharmaceutical Co.
Project period: 2007-2008
Principal Investigator: Takashi Maki

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

Tolerance induction in sensitized mice"
National Institutes of Health, 1RO1 **AI076375-01**
Principal Investigator: Takashi Maki

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Abstract Reviewer (T. Maki) for the "Tolerance/Immune Deviation" section of the American Transplant Congress.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original Articles

Gautum A, Fischer SA, Yango AF, Gohh RY, Morrissey PE, **Monaco AP**. Suppression of cell-mediated immunity by a donor-transmitted lymphocytic choriomeningitis virus in a kidney transplant recipient. Transpl Infect Dis 2007 Dec; 9 (4): 339-42.

Kroemer A, Vu MD, Xiao X, Gao W, Minamimura K, Chen M, **Maki T**, Li XC. OX40 controls functionally different T cell subsets and their resistance to deletion therapy. J Immunol 2007; 179: 5584-91.

Original Articles (Submitted or In press)

Maki T, Carville A, Stillman I, Sato K, Kodaka T, Minamimura K, Ogawa N, Kanamoto A, Gottschalk R, **Monaco AP**, Marr-Belvin A, Westmoreland S, Sehgal P. SV40 infection associated with rituximab treatment after kindney transplanation in non-human primates. Transplantation 2007; in press.

Reviews, Chapters, and Editorials

Monaco AP, Morris PJ. Editorial comment: a role for alloimmune response mediators in tolerance induction? Transplantation 2007;84:S1-2.

Monaco AP. Is there a rational solution to the kidney shortage? Med Health R I. 2007;90(3):89-90.

Monaco AP. Reducing the financial disincentives to living kidney donation: will compensation help the way it is supposed to? Nat Clin Pract Nephrol 2007;3(3):132-3.

Morris PJ, **Monaco AP**, Mulligan J. Instant electronic access to randomized controlled trials (RCT). Transplantation 2007 Oct; 84(8):939.

Leo E. Otterbein

Leo Otterbein

My group focuses primarily on the gas molecule carbon monoxide (CO) and the potent therapeutic effects it has when used at low concentrations in models of shock, transplantation and vascular injury. This work stems from the study of heme oxygenase-1 (HO-1), also a focus of the laboratory, as this inducible enzyme, which has been labeled a protective gene that generates CO as a product during the catalysis of heme. This year we have added the investigations of asecond product of HO-1 activity, biliverdin (BV) and more specifically biliverdin reductase (BVR) that converts BV to bilirubin (BR). BV has been shown to exert potent protective effects in a number of *in vitro* and *in vivo* models with the assumption that it is the powerful anti-oxidant effects that underlie the mechanism of action. We tested the hypothesis that BVR can act as a receptor and, in addition to converting BV to BR, initiates, via the binding of BV, a signaling cascade through PI3K and Akt activation. Moreover, that this occurs because BVR, in part, is localized on the external surface of cells. **Figure 1** shows total internal reflective fluorescence (TIRF) data depicting cell-surface BVR on macrophages. This work has been accepted by the Journal of Clinical Investigation.

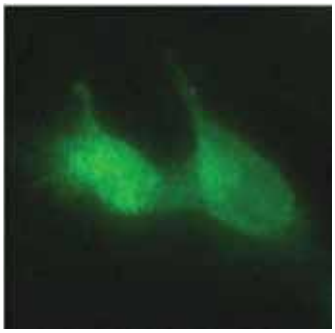


Figure 1

Results from a comprehensive gene microarray in CO-exposed macrophages revealed the candidate target gene Egr-1 is driven by activation of PPARγ. While PPARγ was essential in the protection afforded by CO, it occurred after 3-4 hr of exposure. Due to the rapid increase (<5 minutes) in reactive oxygen species, and that CO targets heme-containing proteins, we hypothesized that hypoxia-inducible factor-1a (HIF1-α) would be a likely target. Rapid stabilization of HIF1-α significantly precedes expression of PPARγ. We show that CO, via HIF1-α increases expression of TGF-β (**Figure 1**) in macrophages and in the lung and protects against ischemia/reperfusion injury. Our focus this year is to apply this information in a live bacterial sepsis model where preliminary data suggests that CO can act therapeutically to both prevent the sequelae of shock and augment bacterial killing via increased production of ROS and reactive nitrogen species arising from inducible nitric oxide synthase. CO was unable to kill bacteria in cells deficient in iNOS (**Figure 2**).

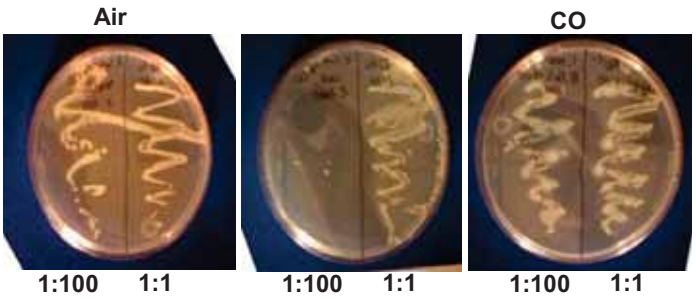


Figure 2

In a collaborative effort with Dr. Simon Robson, Department of Medicine at BIDMC, we demonstrated that the anti-inflammatory effects of adenosine in macrophages occur in part by increasing the expression of HO-1. The endogenous CO generated via HO-1 in turn upregulates the selective expression of the A2a adenosine receptor that drives the anti-inflammatory response. These effects were lost in A2a deficient macrophages. These data exemplify the close and complex interrelationship between these protective genes and their products.

Ongoing studies in models of vascular injury related to both arteriosclerosis arising that leads to chronic rejection as well as balloon angioplasty have elucidated that CO augments vascular repair via select targeting of calcium channels which lead subsequently to downstream activation of Akt and NO generation via eNOS.

<u>Preclincial research –large animal model of kidney transplantation</u>
A large animal study was continued this year in preparation for a clinical trial for CO in organ transplantation to prevent early loss of function and ultimately chronic rejection. The hope is that CO can

be used to increase the donor pool and permit the use of extended criteria donors. In collaboration with Doug Hanto, we developed a model of delayed graft function (DGF) following kidney transplantation in swine, which is primarily due to ischemia/reperfusion injury. We are now testing the ability of CO, now known as Covox to prevent DGF when administered only to recipients. Our data suggests that intraoperative administration of CO to the recipient through the ventilator as a one-time exposure, reduces DGF. Continued experiments are underway to optimize dose ranging and the cellular and molecular target(s) of CO.

LIST OF CURRENT EMPLOYEES

Beek Yoke Chin, PhD	Instructor in Surgery
Martin Bilban, PhD	Instructor in Surgery
Barbara Wegiel, PhD	Research Fellow in Surgery
Kyoichiro Maeshima, PhD	Research Fellow in Surgery
Chiara Attanasio, PhD	Research Fellow in Surgery
David Gallo	Research Associate in Surgery
Theresa MacDonald	Research Technician
Arvand Haschemi	Graduate Student
Eva Czismadia	Research Technician

LIST OF CURRENT FUNDING

"Carbon monoxide to prevent circulatory collapse"
NIH, **7 R01 HL076167-02**
Project period : 2004-2008
PI: Leo E. Otterbein

"Investigations of mechanisms of action of carbon monoxide as an anti-inflammatory and anti-proliferative agent in vascular disorders"
Linde Gas Therapeutics
Project Period: 2004-2007
PI: Leo E. Otterbein

"Carbon monoxide to prevent ischemia reperfusion injury in rodents"
iNO Therapeutics
Project Period: 2006-2008
PI: Leo E. Otterbein

"Carbon monoxide to prevent kidney delayed graft function"
iNO Therapeutics
Project Period: 2006-2008
PI: Leo E. Otterbein

"Heme oxygenase-1: protection against chronic rejection"
NIH **1R01HL077721-02**
Project Period: 2006-2009
PI: Fritz H. Bach, MD
Collaborator: Leo E. Otterbein, PhD

"Macrophage gene expression in mucosal inflammation"
NIH, **2R01DK054452-06**
Project Period: 2006-2011
PI: Scott Plevy, MD
Collaborator: Leo E. Otterbein, PhD

Applications Submitted and Pending Review/Funding

"Carbon monoxide creates tolerance in airway inflammation via modulation of dendritic cells"
Sandler Program for Asthma Research
Project Period: 2008-2009
P.I. Leo E. Otterbein

"Carbon monoxide promotes vascular repair"
NIH RO1
Project Period: 2008-2012
PI: Leo E. Otterbein

"Carbon monoxide as a therapy for septic shock"
NIH RO1
Project Period: 2008-2012
PI: Leo E. Otterbein

Research Accomplishments in the Past Year

Research Accomplishments

I am a part of the training grant that was submitted by the division and am actively collaborating with new colleagues towards integrating my research interests with theirs and have begun sketching out potential program grants. We are the point-lab for all preclinical research including device testing for inhaled CO, which entered phase II clinical trials the second half of 2007 based in large part on our findings in the pig kidney transplant model. We have a contract to continue development of CO in a pig model of kidney transplantation in swine exploring mechanism of action using gene chip technology. Cell Cycle commissioned a review article on the role of HO-1/CO on cellular proliferation.

Patent Disclosures

I have continuing involvement in the litigation of nine patent applications for the use of carbon monoxide as a therapeutic. The first patent was granted conditional approval titled. *"Carbon monoxide improves outcomes in tissue and organ transplants and suppresses apoptosis."*

Individual Accomplishments

I remain a member of the American Heart Association study sections for the Northeast affiliate. This is a continued commitment. I am also a member of the NIH study section Special Emphasis Panel/Scientific Review Group for KO2, K23 and KO8 awards. This committee meets three times a year for grant review. This is an ongoing commitment that began in 2004. We were given media coverage through a worldwide press release describing our PNAS paper demonstrating the mechanism by which carbon monoxide initiates cellular signaling events. This work was highlighted in the HMS Focus magazine.

Report of Teaching

Barbara Wegiel in my laboratory was awarded a commendation from the center for vascular biology research and presented her work at the yearly meeting at HMS. My laboratory was an integral part of abstracts presented at the American College of Surgeons, the Society of Thoracic Surgeons and the American Thoracic Society and the American Society for Cell & Molecular Biology. These abstracts have been submitted as manuscripts. I am currently serving as a first year medical school tutor for the Human Body curriculum which encompasses anatomy and histology.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original Articles

Chin BY, Jiang G, Wegiel B, Wang HJ, Macdonald T, Zhang XC, Gallo D, Cszimadia E, Bach FH, Lee PJ, **Otterbein LE**. Hypoxia-inducible factor 1alpha stabilization by carbon monoxide results in cytoprotective preconditioning. Proc Natl Acad Sci USA 2007; 104(12):5109-14.

Goldberg A, Parolini M, Chin BY, Czismadia E, **Otterbein LE**, Bach FH, Wang H. Toll-like receptor 4 suppression leads to islet allograft survival. FASEB J 2007; 21(11): 2840-8.

Haschemi A, Wagner O, Marculescu R, Wegiel B, Robson SC, Gagliani N, Gallo D, Chen JF, Bach FH, **Otterbein LE**. Cross-regulation of carbon monoxide and the adenosine A2a receptor in macrophages. J Immunol 2007; 178:5921-9.

Lee SS, Gao W, Mazzola S, Thomas MN, Csizmadia E, **Otterbein LE**, Bach FH, Wang H. Heme oxygenase-1, carbon monoxide, and bilirubin induce tolerance in recipients toward islet allografts by modulating T regulatory cells. FASEB J 2007; 21(13):3450-7.

Ramlawi B, Scott JR, Feng J, Mieno S, Raman KG, Gallo D, Csizmadia E, Yoke Chin B, Bach FH, **Otterbein LE**, Sellke FW. Inhaled carbon monoxide prevents graft-induced intimal hyperplasia in swine. J Surg Res 2007;138(1):121-7.

Zuckerbraun BS, Chin BY, Bilban M, de Costa d'Avila J, Rao J, Billiar TR, **Otterbein LE.** Carbon monoxide signals via inhibition of cytochrome c oxidase and generation of mitochondrial reactive oxygen species. FASEB J 2007; 21:1099-106.

Original Articles (Submitted or in press)

Bilban M, Haschemi A, Wegiel B, Chin BY, Wagner O, **Otterbein LE.** Heme oxygenase and carbon monoxide initiate homeostatic signaling. J Mol Med 2007; in press.

Feghali-Bostwick CA, Gadgil AS, **Otterbein LE**, Pilewski JM, Stoner MW, Csizmadia E, Zhang Y, Sciurba FC, Duncan SR. Auto-antibodies in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007; in press.

Reviews, Chapters, and Editorials

Scott JR, Chin BY, Bilban M, **Otterbein LE.** Restoring homeostasis: is heme oxygenase-1 ready for the clinic? Trends Pharmacol Sci 2007; 28:200-5.

Terry B Strom, MD
Transplantation Research Center

Basic Research

Terry Strom

The focus of the highly interactive Strom and Koulmanda laboratories is immune tolerance, with the goal to create immune tolerance in the clinic. To work toward this goal, we attempt to define the precise nature of immune tolerance and of immunoregulatory T cells at the molecular and cellular levels. Transplant tolerance is obtained when the functional supremacy of donor reactive immunoregulatory T cells is obtained and remains dominant following the cessation of immunosuppression. A distinctive cell surface phenotype for immunoregulatory T cells has been discerned. This molecular signature consists of two ectoenzymes that catalyze the formation of adenosine, an immunoregulatory substance, which contributes importantly to immunoregulatory T cell function. These laboratories place strong emphasis in the development of innovative biotherapeutics. Our first effort to use mAbs and cytokine related fusion proteins directed against activated, but not resting, T cells directly led to the development of anti-CD25 mAbs for use in transplantation and autoimmunity. More recently, novel biotherapeutic proteins developed and tested within our lab have shown great promise in the murine model of type1 diabetes and difficult mouse and non-human primate models of islet and cardiac transplantation. As a direct result of these efforts, we have obtained valuable information concerning the role of certain T cell growth factors, T cell immunoglobulin mucin domain proteins (Tim) and acute phase reactants on T cell apoptosis, and on the differing vulnerabilities of regulatory, transplant protective and cytopathic-transplant destructive T cells to therapy. Other work has given insight as to the effect of certain therapies on inhibition or promotion of activation-induced T cell death, an event that is crucial for tolerance induction.

List of Current Employees

Xiang C Li, MD, PhD	Associate Professor of Medicine
Xin Xian Zheng, PhD	Assistant Professor of Medicine
Wenda Gao, PhD	Instructor in Medicine
Gulcin Demirci, MD, PhD	Instructor in Medicine
James Kenny, PhD	Staff Scientist in Medicine
Nasim Kassam, BSc, MD	Sr. Research Associate in Medicine
Xiaobo Zhang, MD	Sr. Research Associate in Medicine
Prabhakar Putheti, PhD	Research Fellow in Medicine
Savithri Balasubramanian, PhD	Research Fellow in Medicine
Gabor Bodonyi-Kovacs, MD, PhD	Research Fellow in Medicine
Karoline Edtinger, PhD	Research Fellow in Medicine
Tetsuo Kodaka, MD	Research Fellow in Medicine
Alexander Kroemer, MD	Research Fellow in Medicine
Sarada Kuchibhotla, PhD	Research Fellow in Medicine
Thomas B. Thornley, PhD	Research Fellow in Medicine
Xiang Xiao, PhD	Research Fellow in Medicine
Dong Zhang, PhD	Research Fellow in Medicine
Wensheng Zhang, MD, PhD	Research Fellow in Medicine
Qiang Zhou, MD, PhD	Research Fellow in Medicine
Karen Ho, PhD	Research Fellow in Surgery
Yan Lu, MD	Research Fellow in Surgery
Nidhi Jain, PhD	Research Assistant in Surgery
Brunilda Ramos-Perez	Administrative Coordinator

List of Current Funding

"B7 co-stimulatory blockade in pediatric transplantation"
NIH, **5U01AI055801-02**
Project Period: 2003-2008
Program Project Director: William Harmon, M.D.
Principal Investigator: Terry Strom

"Novel therapies of chronic allograft dysfunction (CTOT)"
NIH, **UO1 06362**
Project Period: 2004-2009
Principal Investigator: Terry B. Strom

"Molecular profiling and immunomodulatory intervention (CTOT)"
NIH, **U01 AI063589**
Project Period: 2004-2009
Principal Investigator: Terry B. Strom

"Cardiac allograft tolerance in non-human primates"
NIH, **U01 AI066705-01**
Project Period: 2005-2010
Principal investigator: Terry B. Strom

"Human islet transplantation at BIDMC"
Juvenile Diabetes Research Fund (JDRF), **7-2005-1329**
Project Period: 2006-2011
Principal Investigator: Terry B. Strom

"Costimulation and cytokines in tolerance"
NIH, **PO1AI41521**
Project Period: 2007-2012
Principal Investigator: Terry B. Strom

Applications Submitted and Pending Review/Funding

"Inflammation and T cell memory: inter-related barriers to allograft tolerance"
NIH, **1U19DK080652-01**
Project Period: 2007-2012
Principal Investigator: Terry B. Strom

Research Accomplishments in the Past Year

Research Progress

The basic biology governing the commitment of naïve or activated to distinctive T cell subset phenotypes has been explored in detail, with new insights provided concerning the reciprocal commitment to tissue protective Foxp3+ regulatory cells or to virulent tissue injuring Th17 T cells. The critical role of certain pro- and anti-inflammatory cytokines upon T cell lineage commitments, pancreatic islet cell viability/expansion and insulin signaling has also fostered a healthy respect for and means to overcome the confounding role of adverse inflammation upon tolerance induction and important role for promoting the resilience of tissues under confound immune and inflammatory attack. Two new novel therapeutic regimens, power mix and the use of alpha1 anti-trypsin, an acute phase reactant protein, are slated for clinical trial in humans with new onset diabetes and islet transplantation, as a result of preliminary funding support from the NIH and JDRF funded Immune Tolerance Network. Finally the Strom lab probes mouse, non-human primate and human tissue samples for biomarkers associated with adverse or

tolerance inducing immunity. Through identification of molecular signatures (biomarkers), the potential for precise guidance of therapy in the clinic can hopefully be enhanced.

Xiang Xiao and Terry Strom discussing results in the laboratory.

Abstracts presented at Local, National and International Meetings

Degauque N, Mariat C, Kenny J, Sanchez-Fueyo A, Alexopoulos SP, Kuchroo V, Zheng XX, **Strom TB**. Regulation of T-cell immunoglobulin and mucin domain proteins. Presented at the American Transplant Congress in San Francisco, CA. May, 2007.

Dwyer KM, Deaglio S, Crikis S, Gao W, Enjyoji K, **Strom TB**, Cowan PJ, d'Apice AJF, Robson SC. Salutary roles of CD39 in transplantation. Presented at the American Transplant Congress in San Francisco, CA. May, 2007.

Individual Accomplishments

Dr. Strom received the Homer Smith Award for career-long excellence in research from the American Society of Nephrology.

Dr. Strom had the privilege of speaking at national and international meetings and was able to expand his research grant portfolio.

Invited Presentations

"Strategies to alter the balance between alloreactive and Treg cells." American Transplant Congress. San Francisco, CA. May, 2007.

"Antibodies, fusion proteins and peptides and potential new therapeutic targets for use in transplantation." Joint Conference – CTS-IPITA-IXA. Minneapolis, MN. September, 2007.

"The adverse effects of subtle inflammation on renal transplant outcomes." Distinguished Lecturer for the Billingham Lectureship in Transplant Immunology. Vanderbilt University Medical Center, Nashville, TN. October, 2007.

Strom TB, Homer W. Lecture: Taming T Cells. American Society of Nephrology. November, 2007.

REPORT OF TEACHING

Lecture at the Pasteur Institute, Harvard Medical School. "Training T Cells to be well-behaved." Boston, MA. February, 2007.

Lecture on "Allergy/Immunology." Brigham and Women's Hospital Conference, Boston, MA. October, 2007.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original articles

Deaglio S, Dwyer KM, Gao W, Friedman D, Usheva A, Erat A, Chen JF, Enjyoji K, Linden J, Oukka M, Kuchroo VK, **Strom TB**, Robson SC. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. J Exp Med 2007; 204: 1257-65.

Gao W, Lu Y, El Essawy B, Oukka M, Kuchroo VK, **Strom TB**. Contrasting effects of cyclosporine and rapamycin in de novo generation of alloantigen-specific regulatory T cells. Am J Transplant 2007; 7:1722-32.

Korn T, Bettelli E, Gao W, Awasthi A, Jäger A, **Strom TB**, Oukka M, Kuchroo VK. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature 2007; 448: 484-87.

Korn T, Reddy J, Gao W, Bettelli E, Awasthi A, Petersen TR, Backstrom BT, Sobel RA, Wucherpfennig KW, **Strom TB**, Oukka M, Kuchroo VK. Myelin-specific regulatory T cells accumulate in the CNS but fail to control autoimmune inflammation. Nat Med 2007; 13:423-31.

Koulmanda M, Budo E, Bonner-Weir S, Qipo A, Putheti R, Degauque N, Shi H, Fan Z, Flier JS, Auchincloss H, Zheng XX, **Strom TB**. Modification of adverse inflammation is required to cure new-onset type 1 diabetic hosts. Proc Natl Acad Sci USA 2007;104: 13074-79.

Koyama I, Nadazdin O, Boskovic S, Ochiai T, Smith RN, Sykes M, Sogawa H, Murakami T, **Strom TB**, Colvin RB, Sachs DH, Benichou G, Cosimi AB, Kawai T. Depletion of CD8 memory T cells for induction of tolerance of a previously transplanted kidney allograft. Am J Transplant 2007; 7: 1055-61.

Sanchez-Fueyo A, Domenig CM, Mariat C, Alexopoulos S, Zheng XX, **Strom TB**. Influence of direct and indirect allorecognition pathways on CD4(+)CD25(+) regulatory T-cell function in transplantation. Transpl Int 2007; 20: 534-41.

Xiao S, Najafian N, Reddy J, Albin M, Zhu C, Jensen E, Imitola J, Korn T, Anderson AC, Zhang Z, Gutierrez C, Moll T, Sobel RA, Umetsu DT, Yagita H, Akiba H, **Strom TB**, Sayegh MH, Dekruyff RH, Khoury SJ, Kuchroo VK. Differential engagement of Tim-1 during activation can positively or negatively costimulates T cell expansion and effector function. J Exp Med 2007;204:1691-1702.

Zhong M, Gao W, Degauque N, Bai C, Lu Y, Kenny J, Oukka M, **Strom TB**, Rothstein TL. Reciprocal generation of Th1/Th17 and Treg cells by B1 and B2 B cells. Eur J Immunol 2007; 37: 2400-4.

Reviews, Chapters, and Editorials

Degauque N, Mariat C, Kenny J, Sanchez-Fueyo A, Alexopoulos SP, Kuchroo V, Zheng XX, **Strom TB**. Regulation of T-cell immunoglobulin and mucin domain proteins. Transplantation 2007; 84 (1 Suppl):S12-16.

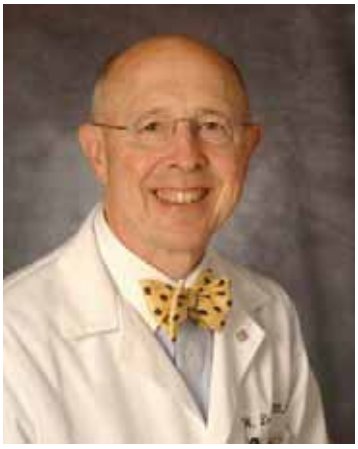
Dwyer KM, Deaglio S, Gao W, Friedman D, **Strom TB**, Robson SC. CD39 and control of cellular immune response. Purinergic Signalling 2007; 3:171-80.

Strom TB. Homer W. Lecture: taming T cells. J Am Soc Nephrol 2007; 18 (11):2824-32.

Reviews, Chapters, and Editorials (Submitted or In press)

Dwyer KM, Deaglio S, Crikis S, Gao W, Enjyoji K, **Strom Tb**, Cowan PJ, d'Apice AJF, Robson SC. Salutary roles of CD39 in transplantation. Transplantation Rev 2007; in press.

DIVISION OF UROLOGY



William DeWolf, MD — **Chief, Division of Urology**
Professor of Surgery

The Division of Urology has a wide-ranging research interest that incorporates both clinical and basic topics. The program touches on many aspects of this specialty including reproduction, stem cell biology, tumor markers, virology (AIDS), neurology and clinical outcomes analysis. The urology laboratory community involves two PhD research scientists and several students from Harvard and MIT assigned to rotations thru our laboratories. Funding is continually growing and currently involves several NIH and DOD grants as well as private funding. Much of the Clinical Research is based on work from the new Continence Center focusing on aspects of neurology, as well as our busy oncology practice. We have established a database incorporating a single surgeon series of radical prostatectomies from the decade of the 1990's involving about 500 cases. This has been used to complete a series of manuscripts that now number five with more submitted. Our Division is heavily involved in NIH outcomes research directed towards various quality of life issues and hopefully will expand to both malignant and non malignant diseases. Finally we have an active animal lab directed at various technical aspects of minimally invasive urologic surgery. The research work in Urology is presented at a wide range of meetings including the AUA, AACR, and FASAB meetings. In addition as noted, in the following descriptions, the research work is published in a broad range of journals.

Division Members

Solomon Berg, MD	**Assistant Clinical Professor of Surgery**
Paul A. Church, MD	**Assistant Clinical Professor of Surgery**
Anurag (Andy) Das, MD	**Assistant Professor of Surgery**
Robert C. Eyre, MD	**Associate Professor of Surgery**
Gary Kearney, MD	**Assistant Clinical Professor of Surgery**
Michael Kearney, MD	**Instructor in Surgery**

Ann A. Kiessling, PhD	**Associate Professor of Surgery**
Jeffrey Shaman, PhD	Research Fellow in Surgery
Anil Purohit	Medical Student
Bryan Desmarais	Laboratory Technician
Stephen Lazarou, MD	**Clinical Instructor in Surgery**
Abraham Morgentaler, MD	**Assocate Clinical Professor of Surgery**
Brian Saltzman, MD	**Associate Clinical Professor of Surgery**
Ned Saltzman, MD	**Clinical Instructor in Surgery**
Martin Sanda, MD	**Associate Professor of Surgery**
Simo Arredouani, PhD	**Instructor in Surgery**
Geraldine Bueti, BA	Research Assistant I
Donna Cote, RN	Administrative Assistant
Bin Lu, PhD	Postdoctoral Fellow
Wen Yue, BS, MSci	Research Assistant II
Amber Solivan, BA, MPH	Clinical Research Coordinator
Anu Kaul, BA	Research Assistant I
William (Mike) Schopperle, PhD	**Instructor in Surgery**
Andrew Wagner, MD	**Assistant Professor of Surgery**

Mohamed (Simo) Arredouani, PhD

Basic research


Simo Arredouani

My research activities aim at unraveling novel mechanisms of immune tolerance to prostate tumor antigens, and at breaking such tolerance for the benefit of immunotherapy for prostate cancer (PCa). To this aim, I am using the TRAMP transgenic mice that spontaneously develop PCa and present a degree of tolerance to antigens that can be manipulated through various interventions. Circumventing immune tolerance through eliciting and strengthening cytotoxic lymphocytes or interfering with the rise of regulatory T cells is attempeted through manipulating the inhibitory mechanisms that prevent CTLs from proliferating in response to tumor antigens, and also through triggering events that would prevent regulatory T lymphocytes from rising. The latter includes interference with the conversion of CD4 lymphocytes to $CD4^+CD25^+Foxp3^+$ T lymphocytes and skewing Treg phenotype toward a nonsuppressive phenotype. To carry out this project we have generated a TRAMP-GFP-Foxp3 hybrid mouse that will facilitate tracking and characterization of regulatory T cells both *in vitro* and *in vivo*.

Another focus of my research is prostate cancer immunotherapy. This interest sparked from data from our and other groups which suggest that immunization with a single prostate cancer TAA can generate an efficient anti-tumor response in preclinical studies and clinical trials. We propose extending the realm of prostate cancer immunotherapy by using transgenic mice, that express human HLA, to optimize strategies for inducing human HLA-restricted T cell responses to ERG and other TAA's identified by unbiased, genome-wide array studies of clinical prostate tumor samples. Novel tumor-associated antigen (TAA) identified through genome-wide array analyses, including ERG (a transcription factor overexpressed in PCa as a result of the TMPTSS2:ERG fusion) and other prostate cancer-specific TAA's, represent novel targets for prostate cancer immunotherapy. By a stepwise approach of screening epitope targets by HLA-A2.1 binding studies, immunization of human HLA-A2.1 transgenic mice to identify immunogenic peptides, and active and passive immunotherapy in mouse models (including probasin-ERG transgenic mice) to determine which of these peptides provide the most suitable targets for effective, human HLA-restricted, anti-tumor immunity in vivo. Coupling the targeting of such novel TAA with modulation of Tim pathways, to overcome T cell tolerance, is a rational avenue toward inducing effective, prostate cancer-specific immune responses. These studies will lead to clinical trials of new strategies for prostate cancer immunotherapy.

List of Current Employees

Anubhav Kaul, BS	Research Assistant II
Wen Yue, MS	Research Assistant II

List of Current Funding

"Targeting novel prostate tumor antigens for cancer immunotherapy"
National Institutes of Health
NCI/DF-HCC Prostate SPORE Career Development Award
Project Period: 2007-2009
PI: Mohamed Simo Arredouani, PhD

Research Accomplishments in the past year

Research Progress

We completed in silico analyses that validated ERG and identified 57 other novel, prostate cancer-restricted, TAA for prostate cancer immunotherapy, 17 of which we ascertained as showing prostate cancer-associated expression by Q-RTPCR of SPORE tissue bank specimens. We performed in silico analyses identifying putative HLA-A2.1-restricted epitopes of ERG. We then screened these candidate epitopes for binding affinity

to human HLA-A2.1 in vitro. Epitopes with high affinity were then evaluated for their human HLA-A2.1-restricted immunosusceptibility in vivo by immunization of human HLA transgenic mice (HHD mice), that showed the ability to induce ERG-specific cytotoxic T lymphocytes as measured by ELISPOT. We identified three ERG-derived epitopes that proved to be immunogenic in HHD mice. Cytotoxic lymphocytes elicited by these peptides are currently tested in a an adoptive transfer/tumor xenograft mouse model where CTL are elicited in HHD mice, expanded in vitro, and then adoptively transferred into SCID mice bearing human prostate tumors. A similar approach was utilized to identify sim2s antigen and sim2s-derived, HLA-A2.1-restricted epitopes which are being tested for immonogenicity in HHD mice at present. We will also test the potential of targeting Tim proteins on lymphocytes and dendritic cells as a strategy for circumventing immune tolerance in the context of these novel, prostate cancer-specific TAA epitopes. The results of these projects will have implications for the design of clinical immunotherapy trials targeting novel prostate TAA epitopes.

Using The TRAMP-GFP-Foxp3 hybrid mouse, we have shown elevated occurrence of regulatory T lymphocytes in the prostate draining lymph nodes from tumor-bearing mice. In addition, CD4 and CD8 T cells from tumor-bearing mice, but not from tumor-free mice, exhibit increased sensitivity to the effects of TGF-beta, as demonstrated by their elevated rate of conversion to the Treg phenotype. The latter observation triggered our interest in dissecting the gene expression profile of activated lymph node T lymphocytes from both groups of mice in the presence and absence of TGF-beta. The results of this analysis would allow identification of key molecules that are responsible for the switching process of T cells to Treg cells, and might lead to new and better ways to dampen the rise of Tregs in cancer.

Individual Accomplishments

Active Membership in the American Association for Cancer Research, the American Association for Immunologists, and the Dana-Farber/Harvard Cancer Center.

Invited Presentations

"Targeting CTL Responses to Prostate Cancer Antigens." Dana Farber/Harvard Cancer Center: Cancer Immunology Seminar Series. Boston, MA; June 7, 2007.

"Targeting Immune Responses to Novel Prostate Tumor Antigens for Cancer Therapy." BIDMC Forum for Prostate Cancer Translational Research Proposals, Boston, MA; July 11, 2007.

REPORT OF TEACHING

Director, Harvard Urology and Prostate Cancer Research Seminar Series
Conference #: 2541, Harvard Medical School In-Hospital Conference System

Immunology lecturer, Just-a-Start Corporation, Cambridge, MA. 11-29-2007.

Mentor, Eighth Annual Explorations Program, Sponsored by Harvard Medical School
Mentored 4 students and one teacher from Boston Middle Schools. 10-30-2007.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original articles

Arredouani MS, Franco F, Imrich A, Fedulov A, Lu X, Perkins D, Soininen R, Tryggvason K, Shapiro SD, Kobzik L. Scavenger receptors SR-AI/II and MARCO limit pulmonary dendritic cell migration and allergic airway inflammation. J Immunol 2007;178(9):5912-20.

Dahl M, Bauer AK, **Arredouani M**, Soininen R, Tryggvason K, Kleeberger SR, Kobzik L. Protection against inhaled oxidants through scavenging of oxidized lipids by macrophage receptors MARCO and SR-AI/II. J Clin Invest 2007;117(3):757-64.

Lim RH, **Arredouani MS**, Fedulov A, Kobzik L, Hubeau C. Maternal allergic contact dermatitis causes increased asthma risk in offspring. Respir Res 2007;8:56.

Limmon GV, **Arredouani M**, McCann KL, Corn Minor RA, Kobzik L, Imani F. Scavenger receptor class-A is a novel cell surface receptor for double-stranded RNA. FASEB J 2007;22(1):159-67.

Original articles (in press)

Neeley YC, **Arredouani SM**, Hollenbeck B, Eng MH, Rubin MA, Sanda MG. Partially circumventing peripheral tolerance for oncogene-specific prostate cancer therapy. The Prostate 2007; in press.

Tseng-Rogenski SS, **Arredouani MS**, Escara-Wilke JF, Neeley YC, Imperiale MJ, Sanda MG. A safety-modified SV40 tag developed for human cancer immunotherapy. Drug Design Dev Ther 2007; in press.

William C. DeWolf, MD
Mike Schopperle, PhD

BASIC RESEARCH

Mike Schopperle

Our basic science research focuses on studying and characterizing unique and specific human cancer stem cell molecules with the goal to further understand and define the molecular make-up of a of human cancer stem cell, to determine the molecular differences between cancer stem cells and normal cells, and to identify potential cancer stem cell molecules that may be targets for novel treatments for human cancers. Our model to carry out these studies is embryonal carcinoma, in the form of established human cancer stem cell lines derived from human germ cell tumors. Embryonal carcinoma cells are the malignant version of human embryonic stem cells derived from human embryos and embryonal carcinoma cells are true pluripotent cancer stem cells, which can be induced to differentiate into non-stem cell cancer cells. Thus, embryanal carcinoma is an excellent model for studying unique molecules expressed by human cancer stem cells and also to study their function as both cancer stem cells and their differentiated non stem-cell cancer cells.

Using this model, we have discovered a novel cancer stem cell marker in embryonal carcinoma called podocalyxin. Podocalyxin is a cell surface protein with very limited expression in human cells: it is expressed in subsets of blood cells and functions as an cell adhesion protein to allow blood cells to migrate into surrounding tissue (the spread of cancer within patients is thought to use similar mechanisms), and podocalyxin is expressed in kidney podocyte cells where it functions as a specific scaffolding protein to form large multi-protein complexes. Our identification of podocaxylin in human cancer stem cells was the first report of podocalyin in either human cancer or human stem cells, but since this discovery, numerous laboratories have discovered podocalyixn in many human cancers including breast and prostate cancers. In fact, these studies have also shown that podocalyxin is a marker for an aggressive phenotypic behavior of cancer cells. Podocalyxin has also been identified as highly expressed in embryonic stem cells further confirming the close relationship of embryonal carcinoma with embryonic stem cells.

Our continued studies of podocalyin have shown that it is the molecular carrier of the TRA antigens; TRA markers have been widely used for decades within the stem cell community to study human stem cells. The TRA markers have also been identified as potential blood markers for testis cancers. With the identification of podocalyxin as the carrier of the TRA molecules, studies can now be done to further the initial findings of the TRA antigens in human cancers and stem cells. We published our work in the journal *Stem Cells* in January of 2007 (please refer to the specific reference in our Bibliography).

Our current studies on podocalyixn are now focused in two directions; the first direction is to determine the function of podocalyin in human cancer stem cells by identifying other molecules in cancer stem cells that interact with podocalyin. We have identified six true podocalyxin-interacting proteins including a glucose transporter – the molecules responsible for suppling energy (glucose) to all cells. We are now characterizing the glucose transporter-podocalyxin complex and we are excited at the prospect of identifying the first interaction between a glucose transporter and a cell adhesion protein. Indeed, in almost all human cancers, glucose transporters are highly over-expressed, but very little is known about the underlining molecular mechanisms that drive this process. The second direction with our studies of podocalyin is more clinically oriented; we are exploring the expression of podocalyxin in human blood samples from patients with prostate and other cancers to determine podocalyin's role as a potential blood cancer marker.

Clinical Research

Clinical Research is quite active and deals with diagnostic urologic oncology, sexual rehabilitation and qualitative analysis of urologic teaching.

List of Current Funding

Intramural funding
Urology Division
Beth Israel Deaconess Medical Center

Applications Submitted/Pending Approval

"Function of podocalyxin in human cancer stem cells"
NIH, R21 Cancer and Cancer Stem Cells
PI: William Schopperle
Co-Investigator: William DeWolf

Divisional Accomplishments in the past year

Individual Accomplishments

William DeWolf, MD
AUA Program Committee for Basic Research: Prostate Cancer
Member of Medical Advisory Board, Boston Prostate Cancer Walk
Co- investigator, NIH CA 011391
Member, Editorial and Advisory Board of Perspectives on Prostate Disease
Editorial Board-Harvard Men's Health Watch
Expert panelist, Bladder Cancer, New England Section AUA Meeting, Boston
Moderator Session on Bladder Cancer: Basic Research, National AUA Meeting, Atlanta

Report of Teaching

Undergraduate and Medical School Courses

William DeWolf, MD
Undergraduate Research Opportunities Program: This is an MIT-based teaching program in which 3-5 undergraduates rotate through our laboratory on 6-12 month basis science projects and gain experience in biological research. This is particularly important because it is the only undergraduate course with opportunity to view surgical operations as part of the curriculum. Additional medical school teaching includes SU518M.1 which is a general course in urologic science for medical students. The course includes a 1 month rotation on the urology service and involves clinical and didactic experience relating to urologic disease.

Urological Oncology Fellowship

Currently Dr. Ignacio San Francisco (Santiago, Chile) is spending 4 months with us completing work on our prostate cancer active surveillance program and other clinical projects.

Bibliography (January – December 2007)

Original Articles

Schopperle W, **DeWolf WC**. The TRA-1-60 and TRA-1-81 human pluripotent stem cell markers are expressed on podpcalyxin in embryonal carcinoma. Stem Cell 2007; 25:723-30.

Original Articles (in press)

Adey G, Pedrosa I, Rofsky N, Sanda M, **DeWolf WC.** Lower limits of detection using magnetic resonance imaging for solid components in cystic renal. Urology 2007; in press.

Kerfoot BP, **DeWolf WC**, Masser BA, Church PA, Federamn DD. Spaced education improves the retention of clinical knowledge by medical students; a randomized controlled trial. Med Edu 2007; in press.

Pedrosa I, Sun MR, Spencer M, Genega EM, Olumi A, **DeWolf WC**, Rofsky, NM. MR imaging of renal masses: correlation with findings at surgery pathology. Radiographic 2007; in press.

Pedrosa I, Chou M, NGO L, Baroni R, Galaburda L, Genega EM, **DeWolf WC**, Rofsky NM. MR classification of malignant renal masses with pathologic correlation. Europ Radiol 2007; in press.

Zhang X, Zhang L, Vang H, Huang X, Out H, Liberman T, **DeWolf WC**, Khosravi-Far R, Olumi A. C-FOS as a propoptosa agent in TRAIL induced apoptosis in prostate cancer. Cancer Res 2007; in press.

Reviews, Chapters, and Editorials

DeWolf WC. Cytoreductive nephrectomy in the elderly patient: The MD Anderson Cancer Center experience. J Urol 2007; 177:860-1.

DeWolf WC, Hu J. Radical nephrectomy for renal carcinoma. In: Fischer JE, editor. Mastery of surgery, 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2007. p 1688-1702.

Reviews, Chapters, and Editorials (in press)

DeWolf WC. Short term morbidity of primary retrtroperitoneal lymph node dissection (RPLND) in a contemporary group of patients. J Urol 2007; in press.

Olumi A, **DeWolf WC**. Basic science training for the urologist oncologist. Urologic Oncol 2007; in press.

Abstracts

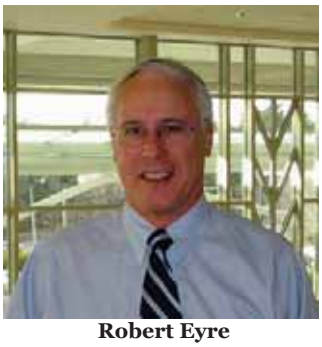
Wagner A, LaRosa SA, **DeWolf WC**, Kaplan I. Initial clinical experience with radiosurgical ablation of primary renal tumors using cyberknife: a pilot study. J Urol 2007; 177:211A.

Zhang X, Yang H, Liang Z, Xu H, Hasan O, Liberman T, Khosravi-Far R, **DeWolf W**, Olumi A. c-FOS promotes TRAIL-Induced apoptosis by repressing C FLIP(L). J Urol 2007; 177:222A.

Ann A. Kiessling, PhD
Robert C. Eyre, MD
Paul Church, MD

Ann Kiessling

The long-term goals of our research are to understand gene expression in genitourinary tract tissues and embryos. Studies of HIV infection in male GU tract tissues began over 20 years ago with the first measurements of viral burden in seminal plasma from men with AIDS. The immune privilege of most male GU tract tissues led to the hypothesis that semen- producing organs could be an isolated sanctuary of HIV disease. Originally controversial, this concept is now broadly accepted. The work on HIV infection in semen was recognized as a Prize Paper by the American Society for Reproductive Medicine at their annual meeting in 2007.



Robert Eyre

The work on HIV has lead to studies of specific immunologic features of prostate, seminal vesicles and epididymis. Results to date suggest that the role of the prostate in immune-protection of spermatozoa relates to the disease predisposition of the prostate, including bacterial infections and cancer. In addition, the unique population of tissue-specific macrophages in seminal vesicles and epididymis that play a role in their normal development and function, may also serve as hosts for HIV infection. If so, they may be important life-long reservoirs of infection, difficult to penetrate by anti-retroviral drugs. We extended this work to studies of bacteria present in semen and discovered that, as predicted, the most prevalent bacterial species detected by molecular biology are difficult to culture organisms, particularly gram positive anaerobic cocci.

Jeffrey Shaman and Ann Kiessling

More recent studies are extending the molecular biologic detection of bacteria to interstitial cystitis, a chronic, debilitating disease of unknown etiology for both men and women. Patients undergoing cystoscopy to diagnose/stage their disease may elect to submit a biopsy for bacterial assay. This approach will provide valuable, new information about treatment options for this group of patients.

Bryan Desmarais

We have also taken advantage of recent reports that adult testis of mice contain a population of stem cells that can be expanded as pluripotent stem cells in culture. Our prior experience with testis research includes studies of germ cell populations, both in mice and humans. Preliminary studies suggest well known methods of perturbing male germ cell populations may increase the number of stem cells that can be expanded in culture. A testis source of pluripotent stem cells holds great patient-specific therapeutic potential.

Current focus:

1) Genetic and phylogenetic analyses of HIV genes cloned from paired specimens of blood and semen contributed by study subjects in a five-year longitudinal study design. We created a public database: **http://www.lrb.med.harvard.edu** in which we have compiled all the published HIV*env* sequences from semen, including our own. We have included HIV*env* sequences from paired blood


Paul Church and Jeffrey Shaman

specimens when available. This is the first public database of its kind and is providing background for understanding the most significant HIV host cells in semen producing organs, as well as for the design of vaccines targeting semen transmitted disease. To date, we have sequenced and analyzed approximately 1300 clones of HIV genes including those containing Envelope, Protease, and Reverse Transcriptase. The genetic analyses have illustrated unique clustering patterns of HIV quasispecies isolated from paired blood and semen specimens from long term study subjects. These findings support and extend the concept, proposed by this laboratory over 20 years ago, that semen producing organs are a sequestered focus of HIV infection, separate from blood. Importantly, several study subjects have demonstrated the appearance of therapy resistance-conferring mutations in semen before they appear in blood.

More recent analyses of HIV envelope genes have revealed compartmentalization of syncytium-inducing virus species (utilize chemokine receptor CXCR4) and non-syncytium-inducing virus species (utilize chemokine receptor CCR5). This confirms and extends reports that HIV variants which utilize CCR5 receptors are the sexually transmitted virus species. As infection progresses, blood HIV variants mutate to express envelopes that preferentially bind to CXCR4 rather than CCR5. This switch in virus tropism is due to point mutations at one or two amino acid residues (S306R or E320K,R) in the V3 loop of HIV*env*, and marks a turning point in disease progression due to increased levels of infection and loss of CD4+ lymphocytes incorporated into lymph node syncytia.

The switch in virus tropism was formerly attributed to a high error rate in the virus reverse transcriptase, but more recent studies have revealed that a family of deaminases, CEM15 (APOBEC3G) function as an innate cellular defense mechanism against retroviral infection. CEM15 deaminates cytosine in the nascent DNA strand synthesized by viral reverse transcriptase during the process of infection. The resulting uracil residue triggers destruction of the nascent DNA strand by intracellular DNAses. If, however, the nascent DNA is not destroyed, the positive strand has an adenosine substitution for the guanosine residue that formerly paired with the cytosine. To determine if such mutations influence disease progression, we have analyzed two subsets of our HIV sequence data: 53 unique sequences of the V3 loop of Gp120 from a long-term non-progressor and 82 unique sequences of protease from a man who developed therapy resistance at 32 months of treatment. The logistics of archiving and analyzing a growing data set of gene sequences have necessitated the development of a custom laboratory database, which has been recently completed in MySQL. We use the database as the starting point for sequence analyses and evolution.

(2) Immunology of male GU tract tissues with emphasis on bacterial infection in the prostate, seminal vesicles, epididymis and bladder. Understanding immune controls in these tissues will provide important insights into not only sexually transmitted diseases, but also specific gland pathologies, such as prostatitis, prostate cancer and interstitial cystitis.

Several lines of evidence from this laboratory indicate the prostate is immunosuppressed. This characteristic could play an important role in prostate diseases, such as prostatitis and prostate cancer. We have previously reported that prostatitis may drive HIV disease by promoting the development of therapy resistance mutations. For these reasons, we explored the bacterial species present in prostatic tissues. We used PCR amplification of bacterial ribosomal gene sequences, followed by sequencing the PCR products and identification through GenBank searches. The work began with semen specimens from two cohorts of patients, one group undergoing fertility assessment, and another group undergoing vasectomy. Pre-and post-vasectomy specimens allowed the comparison of specimens with and without contribution from the epididymis. We have developed a reference library of bacterial DNA sequences amplifiable from laboratory reagents, a problem known to haunt this line of investigation. To date, we have amassed a total library of

approximately 200 rDNA gene sequences which have been submitted to GenBank and recently published in Fertility and Sterility.

(3) Endogenous retrovirus expression in male urogenital tract tissues. The human genome contains more retrovirus-related sequences (45%) than the mouse genome (37%). The first human retrovirus identified was an endogenous retrovirus expressed by placental cells – *in vivo* and *in vitro*. The physiologic significance of the human endogenous retrovirus repertoire is poorly understood, but there is a growing awareness of the mobility of genomic elements and their role in cancer. A full-length human endogenous retrovirus (HERV-L) appears to be currently active in the human genome. The mouse counterpart, MERV-L, also appears to be active in the mouse genome, and is a likely candidate for the highly epididymal specific retrovirus expression described by his laboratory over a decade ago.

For this reason, we have surveyed a library of male mouse tissue RNAs for expression of MERV-L. We extended this work to endogenous retrovirus expression in human testis and epididymis. The importance of this line of investigation was emphasized in 2006 when an infectious form of HERV(K) was isolated at Rockefeller University. This family of viruses appears to also be controlled by the CEM15 family of deaminases. We have taken advantage of recent advances in characterizing expression of retroelements to design strategies to characterize expression in all male GU tract tissues, work proposed to the NSF in our current grant applications.

(4) Pluripotent stem cells from adult mouse testis. It had long been assumed that spermatogoonia could give rise to cultured cell lines restricted to germ cell derivatives, and that such cells were most easily isolated from pre-pubertal testis. In early 2007 it was reported that with the right growth factors, pluripotent stem cell lines could be derived from adult mouse testis. Our previous experience perturbing testis populations with the alkylating agent, busulfan, suggested that the rebound from such treatment might further enrich adult testis for stem cells, and, with Dr. Jeffrey Shaman, we have initiated a search for pluripotent stem cells in tissue sections and in cultured cells from seminiferous tubules. This work was submitted as a grant application to NIH for consideration.

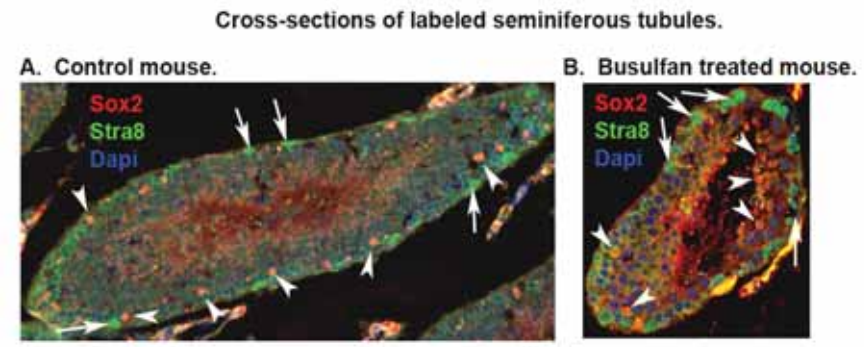


Figure 1. Cross-sections of fixed seminiferous tubules from (A) untreated mice and (B) mice treated with busulfan four weeks prior to fixation. (A) Sox2 (red; arrowheads) is a pluripotency marker and labels small cells at the basal lamina of untreated tubules. Stra8 (green; arrows) is a spermatogonial stem cell specific marker that labels distinct cells at the basal lamina. (B) Sox2 (red; arrowheads) is expressed in cells at the basal lamina and also towards the lumen in tubules from treated mice. Stra8 (green; arrows) is detected in basally located cells.

List of Current Employees

Jeffrey Shaman, PhD	Postdoctoral Fellow
Anil Purohit	Medical Student
Bryan Desmarais	Laboratory Technician

List of Current Funding

Urologic Research Fund - Provides support for the male GU tissue studies not included in the NIH funded project

Applications Submitted and Pending Review/Funding

"Retro element expression in male genital tissues"
Submitted to the National Science Foundation

"Detection and identification of bacteria in bladder biopsies from interstitial cystitis patients"
Interstitial Cystitis Foundation

"Pluripotent stem cells from adult mouse testis"
Submitted to the National Institutes of Health

Divisional Accomplishments over the Past Year

Research accomplishments

We have completed the studies of bacteria in semen and the manuscript is available "On-Line" ahead of publication. This represents the first comprehensive characterization of bacteria in semen and revealed that most specimens are negative for abundant bacteria, and a surprising preponderance of gram positive anaerobic cocci in positive specimens. We continue to characterize bacteria in prostate tissues using the same techniques.

The longitudinal genetic and phylogenetic analyses of HIV genes is now nearly complete for 9 study subjects. The results to date indicate that male GU tract organs are a clinically important reservoir of HIV disease in men, including those on therapy. To establish tissue specific reservoirs of disease, we continuing to work on a collaboration with Southwest Biomedical Research Foundation to analyze tissue biopsies from HIV-infected chimpanzees.

We have completed a survey of male mouse genital tract RNAs and DNAs for presence and expression of the endogenous retrovirus, MERV-L. This work was published in 2007 and formed the basis for the human studies leading to grant applications that will be submitted in 2008.

We have conducted pilot studies to characterize endogenous retrovirus expression in human testis and epididymis. These studies were not possible for many years because of the complexity and redundancy of the repertoire of endogenous retroviruses in the human genome. We have taken advantage of recent developments in organizing human genome information and designing PCR primers to amplify specific families of endogenous RVs. The goal is to determine tissue specific expression, and whether or not there are associated disease changes. Our work in this area was featured at a British Andrology Society meeting in Leeds, England, and has appeared in proceedings from that meeting.

Individual accomplishments

Dr. Kiessling continues to serve on the Research Standards Working Group for the California Institute for Regenerative Medicine, 2005-2011. She was asked to chair the Pre-Clinical Research Standards Subcommittee.

Dr. Kiessling continues to serve on the Stem Cell Advisory Committee for the State of Connecticut and also serves on its Ethics Subcommittee. The duties of the Advisory Committee include review and priority assignment of the grant applications which were awarded in early 2007, the first such awards in the U.S.

Dr. Kiessling was appointed to the Harvard University Embryonic Stem Cell Research Oversight Committee by Vice Provost Steve Hyman. She also serves on the ESCROs of Children's Hospital and the Joslin Diabetes Center.

Dr. Kiessling was appointed a contributing editor to ChemTracts In Brief.

Dr. Eyre continued in 2007 as a member of the American Urologic Association Investment Board.

Dr. Eyre was President of the New England Section of the American Urologic Association.

Dr. Eyre was listed in "Boston's Top Doctors" by Boston Magazine, 2007, and Best Doctors in America, 2007.

Abstracts presented at Local, National, and International Meetings

Kearnan M, Fitzgerald L, Yin H, **Kiessling AA.** Nevirapine regulation of gene expression by mouse parthenote stem cells derived without a feeder layer. Presented at the International Society for Stem Cell Research. Cairns, Australia; June 2007.

Kiessling AA, Desmarais B, Yin H, Kearnan M, **Eyre R**, Winig P. Assisted reproduction with sperm from HIV-infected men. Presented at the Annual Meeting of the American Society for Reproductive Medicine. Washington DC; October 2007.
Note: This work was chosen as the "Prize Paper" for the Society for Assisted Reproductive Technology.

REPORT OF TEACHING

Undergraduate and medical school courses

Paul Church and Robert Eyre
Surgical Core Clerkship Lecture Series, Second Year and Third Year.
Clerkship, Second Year, and Third Year.
They gave multiple lectures to the medical students rotating through the Surgical Core.
Dr. Eyre was also Director, Senior Surgical Residency Rotation at Faulkner Hospital.

Ann Kiessling
Lecture on sexually transmitted diseases and human sexuality, Department of Biology, Brandeis University

Invited presentations (local, national, and international)

Ann Kiessling

"Semen is infected with HIV from multiple reservoirs variably controlled by therapy." Boston IVF. Waltham, MA; March 2007.

"The latest on stem cell research." A Day of Hope for Diabetes: Eisenhower Medical Center. March 2007.

"Human pluripotent stem cells: new data in regenerative medicine." Alexandra Hospital. Athens, Greece; March 2007.

"AIDS and assisted reproduction: medical milestones." National Symposium for the Advancement of Women in Science: Harvard University. Cambridge, MA; April 2007.

"Stem cells: myths, facts and how state legislation can help Massachusetts be a national leader." Legislative Briefing: Massachusetts State House. Boston, MA; June 2007.

"Nevirapine regulation of gene expression by mouse parthenote stem cells derived without a feeder layer." Jackson Laboratory. Bar Harbor, Maine; July 2007.

"Embryonic stem cells: the science, ethics and the role of government." Phillips Academy. Andover, MA; September 2007.

"Assisted reproduction and sexually transmitted viruses." University of Connecticut Health Center. Hartford, CT; September 2007.

"Embryonic stem cells: the science, ethics and the role of government." Bedford Rotary Club. Bedford, MA; October 2007.

"Assisted reproduction with sperm from HIV-infected men." American Society for Reproductive Medicine, Washington DC; October 2007.

"Assisted reproductive technology and sexually transmitted disease." BIDMC Reproductive Endocrinology Conference. Boston, MA; December 2007.

Robert Eyre

"Urinary diversion – indications, techniques and complications." NE Region Wound, Ostomy and Continence: Nurses Association. Boston, MA; October 2007.

BIBLIOGRAPHY (JANUARY – DECEMBER 2007)

Original Articles (in press)

Kiessling AA, Desmarais B, Yin HZ, Loverde J, **Eyre RC**. Detection and identification of bacterial DNA in semen. Fertil Steril 2007; in press.

Proceedings of Meetings

RC Crowell, **AA Kiessling**. Endogenous retrovirus expression in testis and epididymis. Biochem Soc Trans 2007; 35(Pt3): 629-33.

Reviews, Chapters, and Editorials

Adey GS, **Eyre RC**. Complications of urinary diversions. In: Loughlin KR, editor. Complications of urologic surgery and practice: diagnosis, prevention and management. New York: Informa Healthcare; 2007. p. 163-68.

Books, Monographs, and Textbooks

AA Kiessling, S Andersen. Human embryonic stem cells. 2nd ed. Sudbury: Jones and Bartlett; 2007.

Nonprint Materials

R Eyre. Adult complicated urinary tract infections. A Telesymposia series sponsored by Bayer Pharmaceutical for primary care practioners. 2007.

Martin Sanda, MD

Basic Research


Martin Sanda

The principal areas of research in the Sanda laboratory include 1) elucidating mechanisms of T cell tolerance and immune evasion in prostate cancer, and 2) evaluating prostate cancer antigens as targets for immunotherapy and biomarkers for cancer screening and severity assessment. This set of broad research goals provides a unique environment for learning how translational research, utilizing transgenic mice, can concurrently address issues important for developing new therapy while also characterizing fundamental issues of basic tumor immunology. The translational component of this work also focuses on identifying how prostate tumor antigens may be used not only as targets for immunotherapy but also to improve prostate cancer early detection.

Clinical Research

The clinical research focus in the Sanda laboratory concerns prostate cancer clinical outcomes. These studies include the PROST-QA consortium, a national consortium of prostate cancer referral centers (Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Cleveland Clinic, MD Anderson Cancer Center, MGH, UCLA, University of Michigan, and Washington University) wherein combined evaluation of cancer control, satisfaction with care, and quality of life provides comprehensive characterization of prostate cancer care quality. This study, led by Dr. Sanda, has enrolled over 1800 participants, treated by over 40 physicians nationwide, and is the largest ongoing, NCI-funded prospective study of prostate cancer quality of life. Dr. Sanda also participates in Eastern Cooperative Oncology Group (ECOG), where he is the Urology co-Chair of the GU Early Modalities Subcommittee, which develops multi-center Phase II and Phase III protocols for early stage GU cancers.

List of Current Employees

Simo Arredouani, PhD	Instructor in Surgery
Bin Lu, PhD	Postdoctoral Fellow
Amber Solivan, BA, MPH	Clinical Research Coordinator
Donna Cote, RN	Administrative Assistant
Wen Yue, BS, MSci	Research Assistant II
Geraldine Bueti, BA	Research Assistant I
Anu Kaul, BA	Research Assistant I

List of Current Funding

"Harvard/Michigan prostate cancer biomarker clinical center"
National Institutes of Health, **U01 CA011391-01**
Project Period: 2005-2010
Principle Investigator: Martin Sanda, MD

"Survivor HRQOL and spouse satisfaction after prostate cancer therapy"
National Institutes of Health, **R01 CA095662-01**
Project Period: 2002-2007
Principle Investigator: Martin Sanda, MD

"Role of Fas in T cell tolerance in prostate cancer"
UM-BIDMC O'Brien Center for Urology Research
National Institutes of Health, **P50 DK065313-01**
Project Period: 2003-2008
Project Director: Martin Sanda, MD

"SPORE in prostate cancer"
National Institutes of Health, **P50 CA069568-02**
Project Period: 2003-2008
Co-Investigator: Martin Sanda, MD

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Accomplishments and Presentations

In Basic Research, our lab collaborated with Towia Libermann, Glenn Bubley, and Steve Balk from Medicine at BIDMC in using the BIDMC prostatectomy tumor bank to identify prostate cancer antigens not expressed in normal tissue, that may serve as targets for prostate cancer detection and therapy. Dr. Simo Arredouani, a junior faculty member recruited to the Urology research team, is undertaking studies in collaboration with Terry Strom to explore avenues for breaking T cell tolerance to these human prostate cancer TAA's in transgenic mice to develop new strategies of prostate cancer.

In Translational Research, we completed the establishment of a Prostate Reference Set by the NCI-Early Detection Research Network. This resource is a prospectively collected cohort of serum and blood from over 500 prostate cancer patients and non-cancer controls to be stored at NCI-Frederick for general availability to investigators poised to evaluate new prostate biomarkers via a blinded, rigorously defined blood sample set. I was appointed the Group Leader for the GU Collaborative Group of the EDRN, and in this capacity we are spearheading 2 national validation studies of new prostate cancer detection assays. I also was appointed the Director of the Career Development Program of the Dana Farber/Harvard Cancer Center SPORE in Prostate Cancer.

In Clinical Research, we completed accrual and initial analysis of PROST-QA Cosnortium study of patient-reported prostate cancer outcomes and the results were presented at the American Urological Association meeting where the findings were covered by a feature article in USA Today. We have initiated collaborations with the Harvard School of Public Health Physician's Health Study and Health Professional's follow-up Study to evaluates outcomes of patients undergoing deferred management of prostate cancer, and some of this work was recognized by First Place in he Resident Prize Essay competition of the New England Section of the American Urological Association, awarded to Rusty Shappley, MD, PGY-3 in work he conducted in our group. I continue to serve as the Urology co-Chair for the NCI-Radiation Therapy Oncology Group (RTOG) Trial 0232, for a phase III study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for patients with an intermediate risk for prostate cancer that has randomized over 260 patients nationwide, and to lead the GU Early Modalities subgroup of the Eastern Cooperative Oncology Group (ECOG), whrein we are developing several trials for early stage Urological cancers.

The finding from my basic, translational, and clinical research teams were the subject of five presentations at the American Association for Cancer Research and the American Urological Association (AUA) Annual Meeting in April and May, 2007, respectively.

Honors and Awards

I was named to the registry of Best Doctors in Massachusetts, 2007-2008.

Abstracts presented at Local, National, and International meetings

Haram KM, Peltier HJ, Lu B, Libermann TA, ChoyB , Out HH, Latham GJ, Sanda MG. Gene expression profile of Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) reveals murine targets for preclinical development of human prostate cancer therapy. This work was presented at the American Association for Cancer Research Annual Meeting, Apr 14-18, 2007 in Los Angeles, CA.

Report of Teaching

Undergraduate and medical school courses

I participated in the MIT-Harvard Undergraduate HST Program as a Faculty Supervisor. I mentored P Montgomery and Vivian Li, who are going on to graduate school, and Savita Dandapani, PhD and candidate for MD at HMS in May 2008, who applied to match in Radiaiton Oncology this year.

Graduate School and graduate medical courses

I participated in the Urology clerkship at HMS.

CME courses

I was Course Director for "Managing Urological Complications" at the AUA National Meeting. May 2007.

Bibliography (January-December 2007)

Original Articles

Northouse LL, Mood DW, Montie JE, Sandler HM, Forman JD, Hussain M, Pienta KJ, Smith DC, **Sanda MG**, Kershaw T. Living with prostate cancer: patients' and spouses' psychosocial status and quality of life. J Clin Oncol 2007;25(27):4171-7.

Original Articles (in press)

Adey GS, Pedrosa I, Rofsky NM, **Sanda MG**, DeWolf WC. Lower limits of detection using magnetic resonance imaging for solid components in cystic renal neoplasms. Urology 2007; in press.

Dandapani SV, **Sanda MG**. Measuring health-related quality of life consequences from primary treatment for early-stage prostate cancer. Semin Radiat Oncol 2007; in press.

Division of Vascular and Endovascular Surgery

Frank Pomposelli, MD

Chief, Division of Vascular and Endovascular Surgery
Associate Professor of Surgery

Division Members

David Robert Campbell, MB, BCH

Associate Clinical Professor of Surgery

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Elzbieta Kaczmarek, PhD
Elizabeth Maccariello, MD
Jeffrey Siracuse MD
Scott Damrauer, MD
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Marco Scroch, MS
Lynn Choi
Eva Czismadia, MS

Associate Professor of Surgery
Assistant Professor of Surgery
Visiting Research Associate
Research Fellow in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Graduate student from Germany
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Steven Deso, MS
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Instructor in Surgery
Senior Research Fellow
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Research Fellow in Surgery
Harvard Medical School Student
Boston University Medical Student
Boston University Undergraduate Student

Marc Schermerhorn, MD

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Section Chief, Endovascular Surgery

Ami Jhaveri, MD
Kristina Giles, MD

Research Fellow in Surgery
Research Fellow in Surgery

Frank W. LoGerfo, MD
Vascular Surgery Research Laboratory

Christiane Ferran, MD, PhD
Vascular Immunobiology Research Laboratory

Alan Hamdan, MD
Clinical Vascular Surgery Research

Marc Schmerhorn, MD
Vascular Surgery Outcomes Research

VASCULAR SURGERY RESEARCH LABORATORY

BASIC RESEARCH

Frank LoGerfo

The vascular surgery research laboratory has been extensively involved in four main areas of vascular biology research: 1) evaluating mechanisms responsible for prosthetic graft failure, 2) prevention of intimal hyperplasia in vein grafts, 3) defining the role of neuropeptides in diabetic wound healing, and 4) developing novel biomaterial surfaces.

Anastomotic intimal hyperplasia (AIH) is the most common cause of delayed prosthetic arterial graft failure, and delayed failure of vein grafts. As graft healing occurs, genes are either up- or down-regulated as compared to a quiescent arterial wall. We study altered gene expression that results in endothelial cell activation as well as cellular proliferation, migration and extracellular matrix production by smooth muscle cells, leading to AIH. Differential gene expression is assessed using various techniques such as, microarray analysis, qPCR immunohistochemistry, and laser capture microdissection (LCM), a relatively new technology developed by the National Institutes of Health which is available at Beth Israel Deaconess Medical Center. We have now established proficiency with LCM, a tool designed to isolate homogeneous populations of cells for genetic analysis. This technique allows direct microscopic visualization and isolation of selected cell populations from frozen tissue sections and permits selection of cells within a chosen area of tissue. The significance and unique aspect of this work is that our group is the first to identify specific genes that are altered following prosthetic arterial grafting and vein grafting *in vivo* and to examine their role in the cellular environment using various *in vitro* cell culture assays. This information is now being used to identify targets for RNA interference-mediated gene silencing. We have established our ability to silence RNA in cell culture and in the vein graft wall and are working to develop systems for RNA silencing that will be practical for intraoperative use.

For the neuropeptide-diabetic wound healing research, we are currently developing different *in vivo* and *in vitro* models. Both the *in vivo* and *in vitro* projects are conducted in my laboratory by Dr. Leena Pradhan, who is an Instructor in Surgery at Harvard Medical School (HMS). For the *in vivo* project we collaborate with Dr. Aristidis Veves in our Department, who is an Associate Professor of Surgery at HMS in the Division of Podiatry. Peripheral neuropathy and peripheral vascular disease are the major contributors to diabetic foot ulcers and their failure to heal. Therefore, it is important to assess the individual and combined role of neuropathy and vascular disease and their intricate interplay that leads to DFU. To achieve this goal we have successfully developed an *in vivo* diabetic rabbit model of ischemic and neuron-ischemic wound healing. The results of our *in vivo* studies are highly promising implicating a role for neuroinflammation in abnormal diabetic wound healing. Angiogenesis is an important phase of wound healing and dermal microvascular endothelial cells are central to achieving successful closure of the wound. Our *in vitro* studies using dermal vascular endothelial cells are specifically designed to monitor the role of neuropeptides in angiogenesis in a hyperglycemic environment.

For biomaterials research, we have designed and patented several novel biomaterial surfaces. An infection-resistant ionic polyurethane was developed in Phase I and II STTR grants in which quinolone antibiotics were incorporated into the polymer using textile dyeing techniques, with this surface demonstrating antimicrobial activity both *in vitro* and *in vitro*. This biomaterial can be used to comprise a wide range of implantable devices such as catheters, wound dressings and vascular grafts, avenues that

are currently being explored. A similar ionic polyurethane was then employed to seal FDA–approved knitted Dacron vascular grafts using a patented perfusion technology. As part of a Phase II STTR grant, these sealed vascular grafts were evaluated at various acute and chronic time periods using a canine carotid arterial grafting model. A porcine cardiac surgical model to evaluate a novel infection-resistant Dacron prosthetic valve sewing cuff with optimum antimicrobial properties is currently in the development stages in order to complete the objectives of a Phase II SBIR grant. We have also developed *in vitro*, as described in our Phase I STTR proposal, a novel small-diameter nanofibrous polyurethane vascular graft via electrospinning technology. Lastly for metallic implants comprised of titanium such as bone joints and dental posts, we have completed early development of a novel titanium surface with mitogenic properties via covalent linkage of bone morphogenic protein-2 (an osteoblast mitogen). Recently we have developed a surface including activated protein C to prevent thrombosis and to stimulate cellular healing of the Dacron arterial grafts.

VASCULAR IMMUNOBIOLOGY RESEARCH LABORATORY


Christiane Ferran

Most of my time effort, i.e. ninety per cent, is devoted to research. My major research interests are in the field of vascular biology mainly intimal hyperplasia and the micro and macrovascular complications of diabetes, transplantation including xenotransplantation and islet transplantation as well as autoimmune diabetes, acute liver failure and liver regeneration. More specifically, the work in my laboratory is focused on the understanding of the function (s) of the anti-apoptotic genes A20, Bcl-2, Bcl-xL and A1 in different cell types, their relationship to the pathophysiology of diseases and their potential therapeutic use in organ transplantation, diabetes, atherosclerosis, diabetic vasculopathy and liver regeneration. This interest is based on our original finding that these genes, mainly A20 serve a broad cytoprotective function in endothelial cells (EC), islets and hepatocytes and an atheroprotective function in smooth muscle cells (SMC). Expression of A20 in endothelial cells, islets and hepatocytes not only protects the cells from apoptosis by interrupting the activation of the caspase cascade but also exerts a broad anti-inflammatory purpose by blocking activation of the transcription factor NF-κB.

Uniquely, A20 also promotes hepatocyte proliferation hence liver regeneration by down-regulating the cell cycle brake p21waf1. In addition, we have recently demonstrated that A20 also increases the expression of peroxisome proliferator associated receptor α (PPARα), which adds to its anti-inflammatory effect in hepatocytes, and unveil its role in regulating lipid metabolism and cellular energy (**Fig. 1**). These novel findings are strong proof that A20 based therapies may be highly beneficial for patients presenting with severe liver damage but who still have a fraction of viable hepatocytes. Protecting this reduced functional liver mass in the face of ongoing inflammation would meet metabolic demands and allow enough time for regeneration. Expression of A20 is particularly promising for reducing the donor graft size necessary for living donor liver transplantation, allowing the safe use of steatotic organs, and permitting extensive liver resection for the cure of neoplasia.

Expression of A20 in SMC, on the other hand inhibit their proliferation and sensitizes neointimal (i.e. the major component of atherosclerotic lesions), but not medial SMC, to apoptosis through a novel NO dependent mechanism. A20 fulfills most of the criteria required for an ideal atheroprotective therapy that confers an athero-resistant phenotype to both EC and SMC. We propose that A20 based therapies hold strong promise for the prevention and cure of vascular neointimal disease including atherosclerosis, transplant arteriosclerosis, in-stent restenosis and diabetic vasculopathy. This hypothesis is strengthened by our recent demonstration of impaired expression of A20 in failed vein grafts of diabetic patients, which could account for their increased susceptibility to atherosclerosis. Decreased A20 expression in face of HG stems from its post-translational modification by O-glycosylation (a newly recognized, key post-translational modification), which marks it for ubiquitination and degradation by the proteasome. Glucose-mediated degradation of A20 in EC/SMC promotes their acquisition of a pro-atherogenic phenotype, contributing to accelerated atherosclerosis in DM. We have also novel direct in vivo proof of the protective effect of A20 against transplant arteriosclerosis. Expression of A20 in aortic grafts performed in mice with total HLA mismatch prevents transplant arteriosclerosis.

In a similar vein, we have breakthrough evidence that A20 is a negative regulator of angiogenic pathways in EC, both upstream and downstream of Vascular Endothelial Growth Factor (VEGF). Expression of A20

in EC inhibits EC tube formation, *in vitro,* through blockade of PKCβII and ERK1/2 activation while enhancing VEGF mediated AKT phosphorylation. As such, its degradation in the face of high glucose, also contributes, through increased sensitivity to apoptosis and heightened angiogenesis, to diabetic retinopathy. This is the first demonstration that A20 may affect VEGF signaling downstream and upstream of VEGF signaling. Restoring adequate levels of the "atheroprotective" and "anti-angiogenesis" protein A20, in the face of high glucose/hyperglycemia, should protect from the macro and microvascular complications of diabetes.

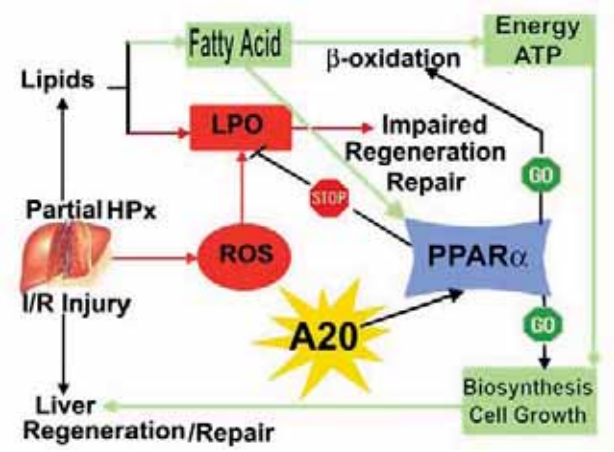


Fig. 1 (left) A20 restores cellular energy in hepatocytes by upregulating PPARα.

Since Dr. Kaczmarek joined our group, an additional line of investigation was initiated in the laboratory, mainly focusing on the induction of A20 and other protective genes such as A1 by extracellular nucleotides. Extracellular nucleotides play a significant biological role in many tissues and cell types, as signaling molecules that regulate cellular function under both normal and pathophysiological conditions. They are released in tissue fluids and plasma in response to different cellular stimuli and as result of tissue damage and cell death. Extracellular nucleotides exert their biological action via specific purinergic P2 receptors that are classified into two main groups: P2X, ligand-gated ion channels and P2Y, G protein-coupled receptors.

Relevant to our line of research, Dr. Kaczmarek has shown that P2 receptor signaling upregulates expression of the two anti-apoptotic "cytoprotective" genes, A20 and A1 in human endothelial cells. In addition, extracellular nucleotides activate endothelial nitric oxide synthase (eNOS), even under high glucose levels. These two observations indicate that P2 receptors may be targets for management of EC dysfunction, and possibly diabetic complications. Treatment with extracellular nucleotides may thus represent an alternative therapeutic avenue to increase expression of A20 that could be much easier to implement than gene therapy.

CLINICAL VASCULAR SURGERY RESEARCH

The clinical research component of the Vascular Division continues to be very vibrant. A major change is the overall increase in the number of cases done by the division and the percentage of cases that are now performed with endovascular techniques. To account for that change we updated our encounter forms to retrieve meaningful data specific to those new techniques. This will allow us to be on the forefront of divisions in regards to understanding our own outcomes as well as being able to publish them and to provide patients as well as insurers with that information. Another significant addition was the hiring of Maya Lele as our Research Coordinator. Jennifer Lambert received her Nurse Practitioner's License and has stayed in the Division, but has stepped down as our Research Coordinator.

Allen Hamdan

VASCULAR SURGERY OUTCOMES RESEARCH

The Division of Vascular Surgery also has an active interest in outcomes research on a national level as well as at the local level here at BIDMC. Our main interest is to compare outcomes after open surgery and endovascular surgery for a variety of vascular diseases. We have access to national data from the Nationwide Inpatient Sample (a 20% sample of all non-federal hospital admissions). This administrative database allows us to evaluate in-hospital outcomes after open vascular surgical or endovascular procedures in large cohorts of patients, representative of the entire nation, as well as allowing estimates of national rates of various vascular interventions (open and endovascular) over time. We also have our own database in the Division with all vascular procedures captured prospectively. This allows detailed evaluation of co-morbidities and various outcomes with physician chart review and angiographic review.

This will allow appropriate risk adjustment for various factors associated with choice of a given treatment strategy. Working with Bruce Landon, MD from the School of Health Policy at HMS we have developed collaboration with the Centers for Medicare and Medicaid Services and have access to data from all Medicare patients. Through this database we have access not only to in-hospital outcomes, but with access to Part B files we can adjust for pre-existing conditions based on diagnoses made prior to the index admission. We also have unique identifiers allowing us to track long term readmission, reintervention, and survival of patients after open or endovascular treatment. Collaboration with James O'Malley from the School of Health Policy at HMS allows us to perform detailed statistical analyses including propensity score matching of patients undergoing open or endovascular surgery.

LIST OF CURRENT EMPLOYEES

Vascular Surgery Research Laboratory

Mauricio A. Contreras, MD	Instructor in Surgery
Leena Pradhan, PhD	Instructor in Surgery
Shen-Qian Wu, MD, PhD	Senior Research Fellow in Surgery
Junaid Malek, MD	Research Fellow in Surgery
Michelle Martin, MD	Research Fellow in Surgery
Nicholas Andersen, BS	Harvard Medical School Student
Steven Deso, MS	Boston University Medical School Student
Monica Jain	Boston University Undergraduate Student

Vascular Immunobiology Research Laboratory

Elzbieta Kaczmarek, PhD	Assistant Professor of Surgery
Elizabeth Maccariello, MD	Visiting Research Associate
Jeffrey Siracuse MD	Research Fellow in Surgery
Scott Damrauer, MD	Research Fellow in Surgery
Cleide Gonçalves Da Silva PhD	Research Fellow in Surgery
Marco Scroch, MS	Graduate student from Germany
Lynn Choi	Medical student, New York University
Eva Czismadia, MS	Senior Research Associate

Clinical Vascular Surgery Research

Maya Lele	Research Coordinator
Diana Igbo	Research Assistant

LIST OF CURRENT FUNDING

"Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery"
NIH/NHLBI, **R0I HL086741-01**
Project period: 2007-2011
PI: Frank W. LoGerfo
Co-Investigator: Christiane Ferran

"Mechanisms of prosthetic arterial graft failure"
NIH/NHLBI, **R01 HL21796-21**
Project period: 2004-2009
PI: Frank W. LoGerfo
Co-Investigator: Christiane Ferran

"Harvard-Longwood research training in vascular surgery"
NIH/NHLBI, **5-T32-HL007734-12**
Project Period: 1997-2009
Director: Frank W. LoGerfo
Co-Director: Christiane Ferran

"William J. von Liebig research and research training in vascular surgery"
William J. von Liebig Foundation
Project Period: 2001-2011

PI: Frank W. LoGerfo

"Impaired wound healing in diabetic foot ulceration"
NIH/NIDDK **1R01DK076937-01**
Project Period: 2007-2011
PI: Aristidis Veves
Co-Investigators: Frank W. LoGerfo and Leena Pradhan

"Role of neuropeptides in wound healing"
JDRF **28-2007-932**
Project Period: 2007-2008
PI: Aristidis Veves
Co-Investigator: Frank W. LoGerfo and Leena Pradhan

"Improved liver function and regeneration with A20"
National Institutes of Health R01 Grant **# DK063275-04**
Project Period: 2003-2008
PI: Christiane Ferran

"Vascular remodeling in transplant arteriosclerosis"
National Institutes of Health Grant **R01 HL080130A1-01**
Project period: 2006-2010
PI: Christiane Ferran

"Protection of endothelial cell dysfunction by P2 receptor signaling"
Juvenile Diabetes Research Foundation JDRF**#5-2007-736**
Project Period: 2007-2008
PI: Elzbieta Kaczmarek
Co-principal Investigator: Christiane Ferran

"STTR Phase I: localized gene delivery from implantable arterial devices"
National Science Foundation **#071141**
Project Period: 2007-2008
Subcontract: Christiane Ferran
PI: Matthew Phaneuf, Biosurfaces Inc.

"Purinergic activation of AMPK as a mechanism of glycemic control"
Juvenile Diabetes Research Foundation Fellowship Grant **#3-2006-617**
Project Period: 2006-2008
Fellow: Cleide Gonçalves Da Silva
Mentors: Christiane Ferran and Elzbieta Kaczmarek

"The therapeutic potential of A20 in diabetic retinopathy"
Juvenile Diabetes Research Foundation grant JDRF**#1-2007-567**
Project Period: 2007-2010
PI: Christiane Ferran

"Harvard Longwood medical area training in transplantation"
National Institutes of Health Grant **T32 AI070085**
Project Period: 2007-2011
Director: John Iacomini
Mentor: Christiane Ferran

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

"Role of talactoferrin in inflammation and wound healing"
NIH/NIAID **1R41AI077224-01**
Project Period: 2009-2010
PI: Aristidis Veves

Co-Investigators: Frank W. LoGerfo and Leena Pradhan

"Topical treatment of diabetic wounds to increase dermal microvascular blood flow"
NIH/NIDDK **1R41DK080555-01**
Project Period: 2009-2010
PI: Aristidis Veves
Co-Investigators: Frank W. LoGerfo and Leena Pradhan

"The protective role of A20 in diabetic vasculopathy".
Juvenile Diabetes Research Foundation
Project Period: 2008-2011
PI: Christiane Ferran

"Purinergic signaling and angiogenic responses in diabetes"
National Institutes of Health Grant **RO1 DK077017-01**
Project Period: 2008-2013
PI: Elzbieta Kaczmarek
Co-Principal Investigator: Christiane Ferran

"Improved liver function and regeneration with A20"
National Institutes of Health Grant **R01063275-06**
Project Period: 2008-2012
PI: Christiane Ferran
Competitive Renewal of an already funded R01: Received a score of 144 Pending council meeting

P2 receptor signaling protects endothelium from hyperglycemic damage"
American Diabetes Association
Project Period: 2007-2010
PI: Elzbieta Kaczmarek
Collaborator: Christiane Ferran

DIVISIONAL ACCOMPLISHMENTS IN THE PAST YEAR

Research Accomplishments

VASCULAR BIOLOGY RESEARCH LABORATORY

1. Mechanisms of Bypass Graft Failure

   Intimal hyperplasia (IH) is the pathologic process of vessel wall thickening and lumen narrowing that occurs in blood vessels in response to injury. This process remains the most common cause of delayed bypass graft failure, a consequence of focal gene expression. As graft healing occurs, genes are either up or down-regulated compared to a quiescent arterial or venous wall. Our hypothesis is that altered gene expression results in cellular proliferation, migration, and extracellular matrix production by smooth muscle cells leading to IH.

   Our continued investigation is to assess gene expression at different time points (24 hours to 60 days) after surgical implantation of either ePTFE prosthetic grafts or reversed cephalic vein grafts in a canine vascular bypass model.

   To date, we have completed all surgical implantations and have collected specimens for all time intervals (n=3 per time interval). Once specimens are harvested, frozen sections of either normal common carotid artery as compared to the distal anastomosis in the case of prosthetic grafts or unaltered cephalic vein as compared to the mid-portion of the vein graft are generated for laser capture microdissection (LCM). In the case of prosthetic grafts, smooth muscle cells from the graft neointima and control arterial wall are dissected out using LCM. In the case of vein grafts, endothelial cells as well as smooth muscle cells are harvested from the graft neointima and control vein wall. RNA was extracted and amplified for Affymetrix microarray analysis. Gene fold-change expression was validated using Q-RT-PCR and immunohistochemistry.

   At present we are evaluating our prosthetic graft microarray results with the assistance of our BIDMC

core facility Director, Dr. Towia A. Libermann and Biostatistician Manoj Bhasin. Microarray results are performed using the Affymetrix Canine 2.0 Chip. Analysis of these results is performed using MAS5 software. A listing of genes that are greater than 2-fold over- or under-expressed is being generated for each different time period under study (1, 7, 14, 30, and 60 days).

For the vein graft, significant work has been performed in perfecting the techniques used to isolate and harvest endothelial cells. Currently, we employ a rapid immunohistochemical stain designed to visually identify endothelial cell proteins. Q-RT-PCR of CD31 expression can be used to validate the purity and homogeneity of captured endothelial samples. We are in the process of harvesting these distinct cell populations. Once performed, RNA can be extracted and amplified from each cell population. Affymetrix gene chip microarray will be run for each sample followed by validation of gene expression using Q-RT-PCR and immunohistochemistry.

We believe identifying alterations in gene expression, their time courses, cellular localization (immunohistochemistry) and computational analysis will provide a valuable guide to a comprehensive understanding of IH.

2. Prevention of Intimal Hyperplasia in Vein Grafts
Intimal hyperplasia in arterialized vein bypass grafts is a significant cause of vein graft stenosis and delayed graft failure. Injury at the time of implantation or as a consequence of transplantation into the high pressure arterial system may contribute to these delayed events. Alterations in gene expression accompany implantation and arterialization injury. These alterations lead to intimal hyperplasia, including transformation of endothelial cells to an inflammatory state and initiating migration and transformation of smooth muscle cells from the contractile to secretory states thus creating the lesion of intimal hyperplasia. It is our hypothesis that silencing of genes upregulated by injury to the vein wall will diminish intimal hyperplasia. Furthermore, gene silencing can be accomplished within the constraints of operating room conditions. We have demonstrated the ability to identify candidate genes associated with intimal hyperplasia and our ability to knockdown gene expression with siRNA. Using LCM we have separated genetic events in the endothelium from those in smooth muscle. Currently we are applying these technologies to (1) systematically identify silencing targets, (2) to silence target genes in vitro, (3) to silence target genes under surgical conditions, (4) to demonstrate inhibition of intimal hyperplasia in vein grafts in vivo. We are performing studies in both human tissue and canine models as well as in vitro using human smooth muscle cells and human coronary artery endothelial cells. In 2006, the work of Dr. Thomas Monahan characterized the contributions of two novel target genes identified by our lab, Cadherin 11 (CDH11) and the myristoylated alanine-rich C kinase substrate (MARCKS), to the pathologic in vitro phenotypes associated with intimal hyperplasia and identified both as promising targets for therapeutic gene silencing in vein grafts. The first manuscript describing the ability of CDH11 inhibition to reduce pathologic smooth muscle cell phenotypes in vitro was published in The Journal of Vascular Surgery in 2007. The work of Nicholas Andersen focused on translating siRNA technology for use in vascular surgical procedures, including the validation of siRNA technology in vascular cells cultured in vitro to the rapid transfection of human vein segments under operating room conditions. Promising results were obtained on both fronts and a manuscript summarizing our experience with siRNA transfection in human vascular cells in vitro was published in the Journal of the American College of Surgeons. In 2007, Junaid Malek made significant progress towards the goal of using laser capture microdissection to separately characterize gene alterations associated with intimal hyperplasia in the endothelial and smooth muscle layers of implanted vein grafts. This work was presented at multiple meetings and should be published shortly. A second BIDMC general surgery resident, Michelle Martin, also joined our laboratory this past year and will be working to develop new in vivo models to test the ability of MARCKS siRNA to reduce intimal hyperplasia formation in animals.

3. A Nanofiber Biocomposite Small Diameter Graft
The specific aim of this study, is to assess blood permeation, graft patency and healing of our novel nanofibrous biocomposite vascular graft (ESDC-rHir-VEGF) using a canine arterial grafting model. ESDC-rHir-VEGF (n = 9) grafts have been synthesized to date using electro spinning methodology as described in the Experimental Designs and Methods Section of the Phase II proposal. During this time period, several parameters such as varying electro spinning time to alter graft wall thickness, crimp versus straight construct, unstretched versus various percentages of stretch, incorporation of rHir/VEGF into the nanofibrous construct, and the effects of graft sterilization via ethylene oxide on biologic activity were examined.

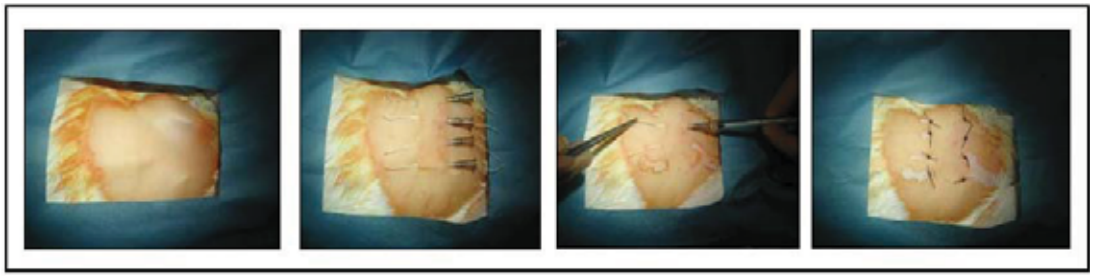
In an effort to establish a better compliance match at the graft/artery anastomosis, electro spinning time was decreased to 30 minutes, in order to determine if wall thickness could be decreased while preserving tensile strength (only grafts electro spun for 20 minutes demonstrated any strength loss as compared to the standard electro spinning time of 40 minutes).

4. Incorporation of rHir/VEGF into the Nanofibrous Construct
In order to provide a slow, sustained localized release of rHir and VEGF, we investigated incorporation of the biologically active agents directly into the nanofibers of the graft wall. The advantages are that no binding agent such as collagen would be required. Both rHir and VEGF were directly dissolved in the polymer solution. The synthesis process remained unchanged.

5. Effects of Ethylene Oxide Sterilization on Biologic Activity
Biologic activity pre-and post-sterilization and graft strength were evaluated. ESDC-rHir-VEGF grafts were synthesized and cut in half. One set was sent for ethylene oxide sterilization (54°C, 10 lbs pressure, cycle time = 2.2 hours) and the other was left unchanged. rHir release and activity was determined as well as tensile strength of the materials pre/post-sterilization. rHir was released over a 6 day wash period, with thrombin inhibition properties of the wash solution unchanged. Tensile strength was also not adversely affected upon sterilization.

Implantation of ESDC-rHir-VEGF and Conventional Dacron (Control) Grafts: After evaluation of the various parameters, nanofibrous grafts with the optimized properties were implanted. We have successfully completed surgical implantations at 7, 14 and 30 days (n =3/time interval), with just one last time interval remaining at 60 days. All Nanofiber Hir-VEGF prosthetic grafts have been patent, as well as the standard Dacron (control) grafts, however, thrombus deposition on the luminal surface and healing characteristics are different between the two. Grafts explanted at these various times (7,14 and 30 days), were placed in 10% buffered formalin. After tissue fixation, specimens were dehydrated through graded alcohols and xylene. The distal anastomosis of each graft was then embedded in paraffin and later sectioned (3µm thickness). Slides were stained with hematoxylin and eosin.

The 4 Figures, below (1X and 10X), show a cross-section of an ESDC-rHir VEGF graft at 14 days. There is no thrombus deposition; there is a strong cellular infiltration through out the wall of the nanofiber prosthetic graft, supported by a rich network of capillaries. On the luminal surface of the graft there is a cellular lining resembling endothelial cells, CD 31 immunostaining will be performed to confirm cell type. This healing pattern looks very different from that found in other prosthetic grafts. We are now evaluating the mid-portion of these grafts to determine if the healing pattern and cell types are different.



Development of a nanofibrous bioactive small-diameter vascular graft would have a significant impact on small vessel repair and replacement. These grafts could be utilized in peripheral bypass (specifically below-knee) as well as for coronary artery bypass, in which there are over 500,000 bypass grafts implanted annually in the United States. Thus, the potential annual market value for an "off-the-shelf" synthetic small-diameter arterial bypass graft could exceed $1.5 billion. Additionally, this type of nanofibrous structure could play a significant role in creating other novel implantable biocompatible devices. Surfaces on these implants could be designed to create a material to which selected biologically-active proteins could be immobilized in order to localize the beneficial effects directly at the material surface.

6. Development of Infection-Resistant Suture Materials

Infection remains as one of the major complications associated with utilizing biomaterials. Surgical site infections account for approximately 14-16% of the 2.4-million nosocomial infections in the United States, with these infections resulting in increased patient morbidity and mortality. The inherent bulk properties of various biomaterials, including those that comprise sutures, provide a milieu for initial bacterial adhesion with subsequent biofilm production and growth. Once the pathogen(s) adheres to the biomaterial surface, treatment with antimicrobial agents is ineffective due to limited penetration of the agent through the bacterial biofilm. Thus, development of a novel infection-resistant suture would provide a localized bactericidal environment. In Phase I, Ciprofloxacin (Cipro), Linezolid and Doxycycline were successfully incorporated into nylon, silk and polyester (Dacron) suture materials using textile-dyeing techniques, resulting in infection-resistant suture materials with optimum antimicrobial properties while maintaining the physical properties of the materials.

The goal of this Phase II is to evaluate these novel infection-resistant sutures in vivo using a wound infection model. Our hypothesis is that antibiotic-dyed sutures will release antibiotic in a slow, sustained fashion over a period of time as demonstrated in our Phase I in vitro studies, preventing bacterial infection at the suture surface as well as in the surrounding tissue. Current non-degradable suture materials do not possess these characteristics.

Infection-resistance of the novel sutures characterized will be evaluated using a rabbit wound (sub-cutaneous) infection model. This model is based on a suture animal model recently described by others and permits direct comparison of infection-resistance between control and test suture materials, eliminating potential intra-species variability.

The animals are anesthetized, placed prone and their backs shaved and scrubbed. A 20g catheter is inserted (two on each side of the spine in a random fashion, under the skin caudally, remaining as superficial as possible. The catheter insertion will proceed in the cranial direction for a distance of approximately 5cm before exiting the skin. The catheter needle is then removed and an antibiotic-dyed 2-0 suture is passed into the catheter until it protrudes from the tip. A sterile syringe containing 0.5ml of *S. aureus* (1 X 107 cfu) is connected to the hub and infused until fluid begins to exit at the opposite end. The catheter is pulled back slightly and sealed with Dermabond® skin adhesive. The remainder of the syringe content is infused and the catheter removed. Suture is cut flush and sealed with the skin adhesive. The same procedure is performed on the opposite side of the spine with the untreated suture (control). Skin silk sutures are placed as a reference to where subcutaneous suture implants were done. Time periods of 7 and 14 days (n = 4 animals/time period/suture treatment) will be evaluated in order to examine infection-resistance as well as healing of the suture materials.

Preliminary histology results at 7 days show that the Cipro-tretaed sutures (Nylon &Plain-PET sutures) have an effective antibacterial activity when compared to the untreated sutures. Our studies are on going and we plan to continue with our 7 and 14 day subcutaneous suture implants.

7. Development of a Biologically-Active Prosthetic Grafts

Surface thrombosis and lack of cell ingrowth lead to prosthetic vascular graft implantation failure. Biological modification of existing materials remains one of the most promising approaches to overcome the problems. Activated protein C (APC) is a potent anticoagulant and the ligand for endothelial cell protein C receptor (EPCR), which is primarily expressed on endothelial cells and on some hematopoietic stem cells. This project sets out to test the feasibility of immobilizing APC to Dacron and to evaluate the biocompatibility of APC bond Dacron. When modified with the crosslinker sulfo-SMCC, APC covalently bound to Dacron and this APC bounded Dacron underwent multi-step modification. Surface bound APC has promising physical and functional stability as tested using a static system and a simulated arterial flow system. The APC bonded Dacron surface demonstrated good anti-coagulant activity as indicated by chromogenic assay and clotting assay. Our preliminary studies also indicated that binding of APC significantly increases human coronary artery endothelial cell viability and proliferation when these cells are seeded on Dacron surface. The above study has been presented at the Annual Meeting of the Society for Biomaterial. We have submitted a STTR grant application to the NIH for the fiscal year of 2007. A patent based on the above study is pending.

8. Role of Neuropeptides in Diabetic Foot Ulcerations

Abnormal wound healing is a major complication of both type I and type II diabetes and is the most

frequent cause of non-traumatic lower limb amputation. Wound healing requires the orchestrated integration of complex biological and molecular events. Inflammation, proliferation and migration of cells followed by angiogenesis and re-epithelization are essential phases of wound healing. Recently, dysregulation of neuropeptides, such as Substance P (SP) and Neuropeptide Y (NPY), secreted from peripheral nerves have been implicated in abnormal wound healing. The link between wound healing and the nervous system is clinically apparent as peripheral neuropathy is reported in 30-50% of diabetic patients and is the most common and sensitive predictor of foot ulceration. Furthermore, molecular studies have shown SP and NPY levels are reduced in diabetic patients. Receptors for SP are found on relevant wound healing cells including monocytes, mast cells, endothelial cells (ECs) and keratinocytes. SP is known to evoke an acute inflammatory response, consistent with the inflammatory phase of wound healing. It also has a proliferative effect on ECs, an important step in angiogenesis. Thus, SP affects numerous phases of wound healing and any dysfunction in the production, release or signaling of SP could impair wound healing. NPY has a similar proliferative effect on ECs, and NPY receptor null mice demonstrate impaired wound healing. Although SP and NPY production and metabolism appear to play a role in diabetic wound healing, the exact molecular and cellular mechanisms underlying these complex interactions remain elusive. Our hypothesis is that inadequate levels of neuropeptides such as SP and NPY and/or dysregulation in their signaling pathways lead to abnormal wound healing in diabetes.

In vivo model: Both peripheral vascular disease and peripheral neuropathy are major contributors to diabetic foot ulcers hence we have developed 3 different models that will mimic these 2 processes and thus will help understand the complex pathology underlying non-healing ulcers in diabetic patients. The surgeries for the 3 different models are performed in one of the ears of the rabbits whereas the other ear serves as a sham control. Following surgery, skin punch biopsy wounds are made in the rabbit ears and wound healing is monitored. At the end of the study period of 10 days post-surgery, molecular analysis is performed on the wounds.

The 3 different rabbit models of diabetic wound healing:
A. Ischemic Model: Central and the Rostral arteries in the ear are ligated
B. Denervation Model: The Central and the Rostral nerves are severed
C. Neuroischemic Model: The central and rostral arteries are ligated and the central and rostral nerves are severed.

All the surgeries in the ischemic and neuroischemic wound healing model have been completed. Our findings suggest that compared to control rabbits, diabetic rabbits have a chronic baseline increase in inflammatory cytokines, IL-6 and IL-8 and a decrease in neuropeptides SP and NPY. In the control rabbits sham ears heal faster than ischemic ears. Compared to sham ears, ischemic wounds heal significantly slowly in both diabetic and control rabbits. Sham wounds heal significantly slower in diabetic rabbits compared to controls. Upon injury, compared to control rabbits, diabetic rabbits fail to achieve an acute inflammatory response that probably hinders wound healing in both ischemic and sham ears.

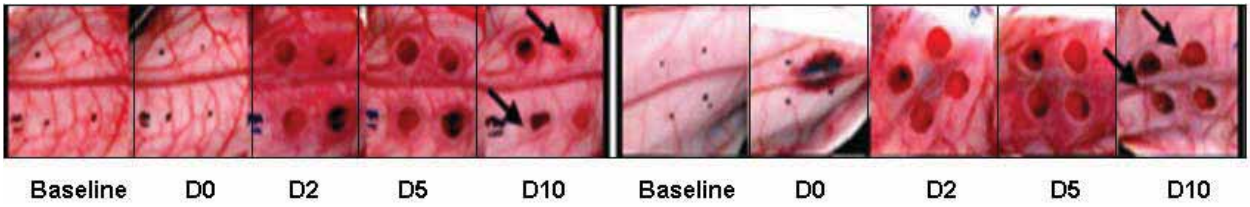
This work will be presented at the Wound Healing Society Meeting at San Diego, California and at American Diabetes Association 68th Scientific sessions in San Francisco, California in 2008.

In vitro model: Since angiogenesis is an important phase of wound healing, and diabetes is known to impair angiogenesis, the goal of the *in vitro* studies is to investigate the effects of hyperglycemia on endothelial cells.

The *in vitro* studies are conducted in Human Dermal Microvascular Endothelial Cells (DMVECs). DMVECs were treated with different concentration of glucose in the absence or presence of SP, NPY and inflammatory cytokines IL-6 and IL-8. Our data so far suggest that high glucose blunts DMVEC proliferation and angiogenic tube formation where as co-exposure to neuropeptides and inflammatory cytokines ameliorates the inhibitory effects of high glucose. Current studies are being performed using siRNA to further delineate the signaling pathways in the neuropeptide-cytokine axis.

Based on these above results, 2 STTR grants were submitted and are under review at the NIH.

Control



VASCULAR IMMUNOBIOLOGY RESEARCH LABORATORY

The past year, we have mainly extended our program to studying the impact of A20 upon diabetic vasculopathy and diabetic retinopathy. Our preliminary results resulted in the discovery that diabetes mellitus impairs the expression of atheroprotective genes such as A20. A20 is blunted in diabetic patients due to metabolic disturbances aggravated by genetically determined factors specific to patients with type I DM. This work has set the basis for a follow-up grant (we had received a novel 3 years funding from the Juvenile Diabetes Research Foundation grant aimed at evaluating the role of A20 upon diabetic retinopathy. The work on the role of A20 in the development of DV was also the subject of a proposal to the JDRF following an invitation from this agency after the approval of a letter of intent.
We have also been successful in expanding our work demonstrating the beneficial effect of A20 expression in medial smooth muscle in preventing intimal hyperplasia to studying its impact on already established disease. Our data demonstrate that expression of A20 in neointimal smooth muscle cells induces the regression of established lesions via its unique capacity to sensitize neointimal SMC to apoptosis via a NO dependent mechanism. These provocative and exciting results have been finalized in a manuscript now under revision for publication to FASEB journal. This work was the subject of a proposal to the NIH LRP that was successfully awarded to Virendra Patel last year. In addition, it has served as a basis to 2 grant proposals. Both were successful in securing funding. The first grant received funding from the Roche Organ Transplant Research Foundation for one year. The second grant received funding as an RO1 from the National Institutes of Health. This later work has also been submitted in a proposal to the NIH loan repayment program (LRP) that was successfully awarded to Mark Fisher.

We have expanded our research interest in collaboration with Dr. Elzbieta Kaczmarek who joined our laboratory in July of this year. Dr. Kaczmarek, an expert in P2 receptor signaling has recently demonstrated that P2 receptor signaling upregulate expression of A20 and A1 in human endothelial cells (EC). In addition, extracellular nucleotides activate endothelial nitric oxide synthase (eNOS), even under high glucose levels. These two observations indicate that P2 receptors may be targets for management of EC dysfunction, and possibly diabetic complications. The molecular mechanisms of these purinergic regulations of A20 expression and eNOS activity are under investigation. Two grants to the ADA and the NIH based on this work were submitted and results are pending.

We have also expanded our work on the effect of A20 upon liver regeneration and demonstrated that this gene has the unique capacity to promote liver regeneration via decreasing the expression of the cell cycle brake p21waf1. This data has been published in Hepatology. New stimulating data generated, implicating an effect of A20 on the Cyclin Dependent Kinase p21waf1 and PPARα, were solid leads that constituted the basis for the competitive renewal of this grant that is pending review.

CLINICAL VASCULAR SURGERY RESEARCH

1. Inflammatory marker trial: This is a prospective trial looking at about 300 patients in concert with the Brigham and Women's Hospital under the direction of Dr. Mike Conte. Patients are prospectively followed who undergo vein bypass grafts. A number of inflammatory markers including C-reactive protein are evaluated pre and post-operative to see if there is any impact on progression of vascular disease. C reactive protein elevation has already been shown to be related to increased perioperative events (presented at the Society of Vascular Surgery national meeting), and has been published in the Journal of Vascular Surgery. We continue to actively enroll patients.
2. CREST Trial: Dr. Schermerhorn is now the site PI for this trial. It is a randomized trial looking at carotid stent vs. carotid endarterectomy. All of the surgeons are eligible to perform carotid endarterectomy in the trial. Dr. Schermerhorn is eligible to perform endarterectomy as well as carotid stenting. He is one of the few surgeons in the country who has this dual nomination. We are actively enrolling patients in this very important trial.

3. EMPiRe: This is a registry evaluating a novel embolic protection device to allow safer use of carotid stents. It involves creating flow reversal in the carotid artery during treatment which makes it essentially impossible to embolize during the procedure. Dr Schermerhorn is the site PI and the BIDMC is one of the few centers that will have access to this potentially revolutionary device.
4. Insulin Drip Trial: This trial is an institutional randomized study spearheaded by the department of Anesthesia in collaboration with ours. Patients undergoing major vascular procedures are assigned to standard insulin therapy or more extensive insulin drip therapy. This has been shown to prevent perioperative complications after cardiac surgery. We already have seen a trend toward improvement in myocardial ischemia in the extensive insulin drip group
5. Zilver PTX trial: This trial will compare outcomes of drug eluting stents versus angioplasty in the superficial femoral artery (SFA). Restenosis is common after angioplasty of the SFA. This trial will examine the potential benefit of a drug eluting stent in terms of restenosis after SFA interventions.
6. Durability Trial: This trial will compare routine stenting of the SFA with a nitinol stent versus selective angioplasty with selective stenting. This new stent is available in long lengths and has potentially lower fracture rates than prior devices which may enhance freedom from restenosis in the SFA.
7. Sonoma Registry: This carotid stent registry will evaluate the function of the Filterwire and the Nex stent for treatment of carotid stenosis in patients at high risk for endarterectomy.
8. Choice Registry: This carotid stent registry will evaluate the function of two carotid stent / embolic protection filters for patients with carotid stenosis at high risk for endarterectomy.
9. Sapphire Worldwide: This carotid stent registry will evaluate the Angioguard filter and the Precise stent for carotid stenting in patients at high risk for endarterectomy.
10. TAG 05-02: This post market registry will evaluate long term outcomes after thoracic stent graft treatment of descending thoracic aortic aneurysms.
11. AAA 03-02 This investigational device used to treat abdominal aortic aneurysms with large proximal necks will be evaluated to compare short and long term outcomes with historical control data with open surgical repair.

VASCULAR SURGERY OUTCOMES RESEARCH

Currently, there are two Harvard-Longwood Research in Vascular Surgery (T-32) fellows working on Outcomes Research; Ami Jhaveri MD and Kristina Giles, MD.

With access to the Medicare database, we have analyzed outcomes after Open and Endovascular repair of Abdominal Aortic Aneurysms in the Medicare population. Our work has confirmed the perioperative benefit seen in recent randomized trials and demonstrated that these results nay be generalized to the entire Medicare population. Additionally, we are the first to demonstrate that laparotomy related problems such as bowel obstruction or abdominal wall hernia require frequent intervention after open surgery, matching the need for aneurysm related reintervention after endovascular repair. This is to be published in the Jan 31, 2008 New England Journal of Medicine and was presented at the 2007 annual meeting of the New England Society for Vascular Surgery. We will also be analyzing predictors of perioperative and late moratlity after open and endovascular aneurysm repair, morbidity and mortality associated with reinterventions after aneurysm repair, volume outcome relationships over time as endovascular repair is dispersed across the country, and aneurysm related mortality after introduction of endovascular repair – all using the Medicare database.

Using the Nationwide Inpatient Sample (NIS), a 20% sample of all non-federal hospital admissions, we are evaluating the overall aneurysm related mortality (elective repair, plus rupture repair, plus rupture death without repair) over time and have noted a decrease in overall aneurysm related mortality after introduction of endovasulcar repair with fewer ruptures and more elective repairs. Kristina Giles has submitted an abstract to the annual meeting of the Society for Vascular Surgery (SVS) and will submit a manuscript to the Journal of Vascular Surgery (JVS). Kristina has also used the NIS database to demonstrate a lower operative mortality with endovascular repair of ruptured aortic aneurysms compared to open repair. She has also demonstrated a volume-outcome effect in that higher volume hospitals have lower mortality with ruptured AAA repair. This too was submitted to the SVS annual meeting and will be

submitted to JVS. Ami Jhaveri has used the NIS database to compare in-hospital mortality and amputation rates after lower extremity bypass or angioplasty stratified by indication for intervention (claudication, rest pain, ulcer, or gangrene). She has also identified trends of increasing utilization of angioplasty compared to bypass over time. This was also submitted to the SVS and will be submitted to JVS. We have analyzed the national outcomes with open repair of descending thoracic aortic aneurysms in the era prior to endovascular stentgrafting to serve as a benchmark comparison for future reports with stentgrafting. I will present this data at the annual meeting of the Society for Clinical Vascular Surgery and submit a manuscript to JVS.

We are continuing to update our own database of all vascular procedures with detailed prospective data collection of all common procedures. We have analyzed our own outcomes at BIDMC reporting the largest US series of infrapopliteal angioplasty for critical limb ischemia presented by Seth Blattman at the New England Society for Vascular Surgery (NESVS) and submitted by Kristina Giles for publication in JVS. Hector Simosa has presented our data with the largest series worldwide of lower extremity vein graft angioplasty, presented at NESVS and submitted to JVS. I have submitted a manuscript detailing our series of aortic arch debranching and stentgrafting procedures for publication in the JVS.

We participate in the Society of Vascular Surgery's national registry of carotid stenting and endarterectomy. I am co-authoring a submission by the SVS outcomes committee demonstrating outcomes after carotid stenting and endarterectomy using the SVS registry, submitted for presentation at the SVS meeting with a manuscript for JVS.

Invited Presentations (Local, National and International)

Christiane Ferran
"Sweet A20 and the vascular complications of diabetes." Annual Retreat of the Center of Vascular Biology. Beth Israel Deaconess Medical Center. Boston, MA; February 2007.

"A20: the thrive to maintain and restore homeostasis." Pulmonary Grand rounds: Beth Israel Deaconess Medical Center, Harvard Medical School. Boston, MA; April 2007.

"Vascular disease and the failure of homeostatic responses." Clowes Visiting Professor: Beth Israel Deaconess Medical Center, Harvard Medical School. Boston, MA; November 2007.

"Vascular homeostasis: a casualty of unfettered inflammation." Trans-Institute Angiogenesis Research Program (TARP) annual workshop of the National Cancer Institute and National Heart Lung Blood Institute: Inflammation and the Perivascular environment. Bethesda, MD; November 2007

Mark Fisher
Fisher MD, Wada H, Patel VI, Scali ST, Shrikhande GV, Da Silva C, Ramsey, H, Daniel S, Aird W, Ferran C. "Neointimal hyperplasia: role of A20 in homing of EC and SMC progenitors." Resident's competition: Surgical Grand Rounds. Beth Israel Deaconess Medical Center. Boston, MA; June, 2007.

Ami Jhaveri
"Staged total aortic reconstruction using a combination of open and endovascular repair." 34th Annual Meeting of the New England Society for Vascular Surgery. Ledyard, CT; October 5-7, 2007.

Frank W. LoGerfo
"Vein bypass grafts to the dorsalis pedis artery: vascular surgery in the endovascular era." Northwestern University. Evanstown, IL; Dec 13, 2007.

Junaid Malek
Malek J, Andersen N, Martin M, Gasperan S, Monahan TS, Contreras M, LoGerfo FW. "Selective isolation of vein graft endothelium and neointima by laser capture microdissection for temporal gene expression analysis." 3rd Annual Academic Surgical Congress. Huntington Beach, CA; February 12-15, 2007.

Malek J, Monahan T, Andersen N, Wu S, Contreras M, LoGerfo FW. "Temporal gene expression of prosthetic graft neointima isolated by laser capture microdissection." 8th Annual Conference of Arteriosclerosis, Thrombosis, and Vascular Biology. Chicago, IL; April 19-21, 2007.

Malek J, Monahan T, Andersen N, Wu S, Contreras M, LoGerfo FW. "Selective isolation of anastomotic intimal hyperplasia for microarray analysis using laser capture microdissection." 34th Annual Meeting of the New England Society for Vascular Surgery. Ledyard, CT; October 5-7, 2007.

Leena Pradhan

Pradhan L, Cai X, Andersen N, Jain M, Malek J, Contreras M, Veves A, LoGerfo FW. "A new rabbit model of diabetic ischemic wound healing using hyperspectral imaging and molecular analysis." 2nd Annual Academic Surgical Congress. Phoenix, AR; February 6-9, 2007.

Pradhan L, Jain M, Andersen N, Cai X, Ferran C, LoGerfo FW. "In vitro analysis of angiogenesis in diabetic wound healing: the role of cytokines and neuropeptides." 2nd Annual Academic Surgical Congress. Phoenix, AR; February 6-9, 2007.

Pradhan L, Cai X, Andersen N, Jain M, Malek J, Contreras M, Veves A, LoGerfo FW. "Role of neuroinflammatory markers in ischemic diabetic wound healing." 17th Annual Wound Healing Society Meeting and Exhibition. Tampa Convention Center. Tampa, Florida; April 28 - May 1, 2007.

Pradhan L, Cai X, Andersen N, Malek J, Contreras M, Veves A, LoGerfo FW. "Role of neuroinflammatory markers in diabetic wound healing." American Diabetes Association's 67th Scientific Sessions. Chicago, IL; June 22-26, 2007.

Marc Schmerhorn

"Selecting patients for carotid stenting." Updates and Advances in Vascular and Endovascular Surgery. Boston, MA; May 10, 2007.

"Carotid stenting, understanding when to stop and when not to start." The Society for Vascular Surgery annual meeting: postgraduate course. Baltimore, MD; June 6, 2007.

"Bypass is still preferred for TASC C and D disease of the SFA – Con." The Society for Vascular Surgery annual meeting. Baltimore, MD; June 9, 2007.

"Management of endoleaks." Annual Meeting of the New England Society for Vascular Surgery. Foxwoods, CT; October 5, 2007.

Schermerhorn ML, O'Malley J, Jhaveri A, Cotteril P, Pomposelli F, Landon B. "Endovascular vs open repair of abdominal aortic aneurysms in the medicare population." 34th Annual Meeting of the New England Society for Vascular Surgery. Ledyard, CT; October 5-7, 2007.

Patent Disclosures

- Application of Antibiotics to Polyurethane Biomaterials Using Textile Dyeing Technology (09/834,978).
- Development of a Dacron Vascular Graft with an Ionic Polyurethane Sealant with Protein Binding Capabilities (60/186,154).
- Method for Making Infection-Resistant Fabricated Textile Articles for Biomedical Applications (09,876,604).
- Methods for Making Infection-Resistant Fabricated Textile Articles and Devices Suitable for Non-Implantable Biomedical, Environmental, Safety and Other Protective Applications (Full Patent Submitted).
- Bioactive Surface for Titanium Implants (Full Patent Submitted).
- Development of a Bifunctionalized Dacron Surface (Full Patent Submitted).
- Monahan TS, Andersen ND, and LoGerfo FW. Methods of inhibiting vascular smooth muscle cell migration and proliferation. Utility patent filed U.S. Patent Office February 9, 2006. Docket Number 1440.2045-002.
- Ferran, C, inventor; No assignee. Use of Pro-apoptotic factors in treatment of atherosclerosis. US serial no 09/765,519. 2001, January 19.
- Christiane Ferran co-inventor: Measurement of protective genes in allograft rejection, Patent

number: US 6,900,015 B2. Date of patent: May 31, 2005.

Individual Accomplishments

Nicholas Andersen, BS (Harvard Medical Student IV)

- 2007 National Student Research Forum, Biochemistry/Molecular Biology Award

Christiane Ferran

- Reviewer for the XXII International Congress of the Transplantation Society 2008. Sydney, Australia.
- Reviewer for the NIH Study Section Tolerance, Transplantation and Tumor Immunology (TTT) (May 31-June 1, 2007)
- Reviewer for the American Transplant Congress 2008 Toronto.
- Reviewer for the Wiener Wissenschafts Forshtungs und Technologiefonds, Vienna Austria.
- Member of the Scientific Advisory Committee for the Roche Organ Transplant Research Foundation (ROTRF).
- Reviewer for Several peer review highly ranked journals including: Blood, Journal of Clinical Investigation, Circulation, Atherosclerosis Thrombosis and Vascular Biology, Transplantation, American Journal of Transplantation, American Journal of Kidney Diseases, Nephrology Dialysis and Transplantation, Kidney International, Oncogene, American J. of Rheumatology, Diabetes.

Ami Jhaveri

- "Perioperative and 3-year outcomes of endovascular and open AAA repair in the US medicare population." New England Surgical Society. 3rd place in the Clinical Sciences division, 34th Annual Meeting of the New England Society for Vascular Surgery. Ledyard, CT; October 5-7, 2007.

Marc Schermerhorn

- VESAP Question writer for preparatory review for vascular surgery qualifiying board examination 2007.

REPORT OF TEACHING

Undergraduate and Medical School Courses

Frank LoGerfo

1. Program Director, William J. von Liebig Research Training in Vascular Surgery

The William von Liebig Training Fellowship in Vascular Surgery is held for 10-12 weeks during the summer months. Students receive research training in molecular and cell biology, biomechanics, coagulation and thrombosis and angiogenesis, with a focus on clinically relevant problems such as atherogenesis, intimal hyperplasia, prosthetic/host interactions and thrombosis. Trainees pursue a program of intense research activity. Students carry out their research projects under the guidance of a faculty advisor, selected from renowned vascular researchers based at Harvard Medical School hospitals (Beth Israel Deaconess Medical Center and Brigham and Women's Hospital).
For summer of 2007, six students were enrolled in the program.

Mentor	**Student**
Frank W. LoGerfo, MD	Steven Deso Boston University School of Medicine Project: Neuropeptides and Inflammatory Cytokines in an In-Vivo Model of Diabetic Wound Healing
	Samuel Gasperan 3rd Medical Faculty Charles University Prague Project: Temporal Gene Expression of Prosthetic Graft Neointima

Christiane Ferran, MD, PhD	Karam Moon Case Western Reserve University Project: The Anti-Inflammatory Role of A20 in Neointimal Hyperplasia
Bruce Furie, MD	Prathima Nandivada Stony Brook University School of Medicine Project: Endothelial Cell Activation: Imaging Calcium Mobilization *in vitro* and *in vivo*
Richard N. Mitchell, MD, PhD	Danielle Bergsrud University of Florida Project: Cell Patterning and Migration: an in vitro Model of Smooth Muscle Cell Chemotaxis in Graft Arterial Disease
Michael S. Conte, MD	Timothy Love University of Miami School of Medicine Project: Inflammation and Vein Graft Disease: *in vivo* Correlation and *in vitro* Modulation of Oxide Production

2. Nicholas Andersen, fourth year medical student from Harvard Medical School and graduate of our 2004 William J. von Liebig Summer Research Fellowship is currently working part time in the laboratory on prevention of intimal hyperplasia in vein grafts.
3. Steven Deso, from Boston University School of Medicine and graduate of our 2007 William J. von Liebig Summer Research Fellowship, is currently working part time in the laboratory under the guidance of Leena Pradhan to study the role of neuropeptides and inflammatory cytokines in diabetic wound healing using i*n vivo* models.
4. Monica Jain, an undergraduate student at Boston University also works part time in the laboratory under the guidance of Leena Pradhan to study the role of neuropeptides and inflammatory cytokines in diabetic wound healing using i*n vitro* models.
5. Course Director: HMS SU526M.128: This is a Vascular Surgery elective for HMS and other 4th year medical students. 3 students this year for 4 weeks each were enrolled in this course.
6. Tutorial for HMS 3 students during their surgical clerkship; I worked with 4 students 1 hour per week.
7. I continued as Director, Harvard-Longwood Research Training Program in Vascular Surgery (T32).

This NIH-funded T32 training program is designed to provide two years of intense basic research training in vascular surgery for academic clinicians. The training program addresses the absence of adequate research training for vascular surgeons as it applies to specific areas of clinical disease. This program is in its fourteenth year. Trainees pursue a program of research activity supplemented with course work in research design, ethics, statistics and evaluation of published research in the areas of molecular and cell biology, biomechanics, coagulation and thrombosis and angiogenesis. Clinically relevant problems such as atherogenesis, intimal hyperplasia, prosthetic/host interactions and thrombosis will be the main focus of these research projects. Trainees carry out their research projects under the guidance of a faculty advisor selected from 20 renowned vascular researchers based at four Harvard Medical School hospitals (Beth Israel Deaconess Medical Center, Brigham and Women's, Children's Hospital (Boston) and Joslin Diabetes Institute) and the Massachusetts Institute of Technology. Upon completion of the program, trainees are capable of independent research and possess the scientific and research background needed to obtain peer-reviewed grants. Selection of trainees is based on candidate's demonstrated ability and career choice of academic practice. Applicants are resident physicians who have completed either 2/3 years of clinical post-doctoral experience (surgical residency) or 5 years of clinical training (i.e. are board eligible). Only those applicants with career goals in academic surgery, with a keen interest in basic research in vascular surgery are compatible. Trainees in the program are not involved in any clinical activities unless research related.

Trainees

Second Year (recruited July 2006)

Junaid Malek, MD	Beth Israel Deaconess Medical Center
Patrick O'Neal, MD	Beth Israel Deaconess Medical Center
Andrew Hoel, MD	Brigham and Women's Hospital
Ami Jhaveri, MD	

First Year (recruited July 2007)

Scott Damrauer, MD	Massachusetts General Hospital
Kristina Giles, MD	Beth Israel Deaconess Medical Center
Eric Griffiths, MD	University of Texas Southwestern, Dallas, TX
Michelle Martin, MD	Beth Israel Deaconess Medical Center
Jeffrey Siracuse, MD	Beth Israel Deaconess Medical Center

In my laboratory, Junaid Malek, MD assessed the contribution of gene expression of specific cell populations (namely vascular smooth muscle cells and endothelial cells) to the phenotypic transformation of endothelial and vascular smooth muscle cells and ultimately to the pathologic process of intimal hyperplasia and Michelle Martin, MD studied process that regulate intimal hyperplasia (IH) in vein and prosthetic bypass grafts. Shen-Qian Wu, MD also worked on development of biologically active surfaces.

Christiane Ferran

I had 2 undergraduate students, 1 medical student and 1 Master's student as well as the William J. Von Liebig summer fellow. All benefited from bench top teaching as well as didactic teaching sessions.

A) Marco Scroch: Masters student from Bonn, Germany
B) Lynn Choi : Scholar of the 2006 William J. Von Liebig Fellowship for Vascular Biology, Medical student at New York University, NY (11 weeks summer training). Recipient of the Howard Hughes fellowship award for medical students.
C) Karam Moon: Medical student, recipient of the 2008 William J. Von Liebig Fellowship.
D) Rakesh Patel, BS, Boston Univeristy.
E) Roy Arjoon, BS, Boston University.

I also had weekly teaching sessions for the 2 surgical residents, 1 PhD, 1 Master of Science and one visiting MD that are working in the laboratory. In addition to informal bench based teaching.

- Elizabeth Macariello, MD. Visiting Scholar, BIDMC.
- Jeffrey Siracuse, MD. Surgical Resident, BIDMC.
- Scott Damrauer, MD, Surgical Resident, Massachusetts General Hospital
- Cleide Gonçalves Da Silva, Ph.D., Research fellow, BIDMC
- Marco Scroch, MS, Research Associate.

Allen Hamdan
Frank Pomposelli
Marc Schermerhorn
We taught fellows and surgical residents how to do clinical research, present at meetings, and write abstracts and papers. This year we worked with Dr. Simosa, who presented work concerning vein graft angioplasty at the New England Society for Vascular Surgery annual meeting. The work was finished, manuscript prepared, and was recently accepted for publication in the Journal of Vascular Surgery. We also mentored Dr. Jeff Kalish.

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Monahan TS, Andersen ND, Panossian H, Kalish JA, Daniel S, Shrikhande GV, **Ferran C, Logerfo FW**. A novel function for cadherin 11/osteoblast-cadherin in vascular smooth muscle cells: modulation of cell migration and proliferation. J Vasc Surg 2007; 45(3):581-9.

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