



January–December 2011



# From the Chairman

This issue of our Annual Research Report celebrates the tradition of clinical innovation carried on by the Department of Surgery at Beth Israel Deaconess Medical Center since its inception with the Harvard Fifth Surgical Service more than 150 years ago.

Opportunities for innovation lie at the interfaces of disciplines — where individuals with diverse viewpoints communicate, examine problems through prisms that reflect very different perspectives, and share distinct ideas from highly disparate fields. This is what germinates new solutions to what were previously perceived as intractable clinical problems.

The broad scope of the clinical and fundamental investigations summarized in this report highlight the qualities that are at the core of our department — our desire to nurture intellectual diversity, embrace individual freedom, encourage flexibility, and promote spontaneity and originality.

We foster and celebrate these qualities because imaginative and inventive surgeons and investigators, students, residents, and fellows who are given the opportunity to work in diverse collaborations and teams have always been central to the creation of new pathways leading to therapeutic breakthroughs. It is the inspiration and ingenuity of our academic community that contribute to the arena of ideas, which has always distinguished surgery at Beth Israel Deaconess Medical Center and Harvard medicine.

This report is but a snapshot of the environment and activities within our department and its highly interdisciplinary collaborations in the medical, biological, chemical, mathematical, computational, and engineering sciences. As the pace of these scientific and technological advances accelerates, we have many meaningful opportunities to advance the care of our patients in every clinical discipline of surgery.

As you will read in this report, our department has a robust research enterprise with nearly \$20 million dollars in funding and 40 NIH grants, as well as some 400 publications generated by our faculty and students. The impressive work within our department continues to attract the brightest young women and men, who perform cutting-edge science that crosses boundaries.

The individuals whose research is highlighted in this report represent the very best of our department and the medical center. One and all, they are dedicated to fulfilling our mission — of serving our communities, improving health through innovation and discovery, and preparing future leaders in American surgery.

*“We need to cut passages between shafts we have already dug instead of merely digging the same old shafts deeper and deeper.”*

*Stringfellow Barr (1897–1982), author and educator*



**Elliot L. Chaikof, MD, PhD**

Johnson and Johnson  
Professor of Surgery  
Chairman,  
Department of Surgery  
Surgeon-in-Chief



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## Overview of Surgical Research–2011

### Introduction

In addition to delivering outstanding patient care, research (basic, clinical, and translational) constitutes one of the cornerstones and missions of the Department of Surgery. Research programs in Surgery at Beth Israel Deaconess Medical Center (BIDMC) include Cancer Biology, Inflammation, Development, Vascular Biology, Cardiothoracic research, Transplantation-Immunology, Obesity-Nutrition-Metabolism, Wound Healing, Epithelial and Endothelial Biology, Bioengineering, and Clinical Outcomes.

The Office for Surgical Research provides an administrative infrastructure to facilitate research in the Department of Surgery. Surgical Research is headed by Per-Olof Hasselgren, MD, PhD, who is Vice Chairman for Research in Surgery at Beth Israel Deaconess Medical Center (BIDMC) and the George H.A. Clowes Jr. Professor of Surgery at Harvard Medical School. Susan J. Hagen, PhD, who is Associate Vice-Chair for Research in Surgery and Associate Professor of Surgery at Harvard Medical School, assists with the management of Surgical Research. Surgical Research activities are supported by an administrative pool, with Rachel St. Fort as the former Administrative Supervisor and Molly Jay as the Administrative Assistant.

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 (collaborative or T32 grant applications) and interaction with the BIDMC Office of Sponsored Programs; 2) Management of research space, including laboratory and office space. 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 research seminars and other departmental research functions; 4) Tracking academic benchmarks in the Department of Surgery (grant submissions, grant funding, publications, etc.) and preparing the 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 assistance with 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 with the Department of Surgery Appointment, Reappointment, and Promotion Committee); and 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.

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### Research Faculty

All divisions in Surgery have at least one active research program. Overall in 2011, research in the Department was conducted by 204 individuals, including: 44 faculty, 59 postdoctoral research fellows, 27 research assistants, 14 surgical residents, two nurse educators/practitioners, and many undergraduate, graduate, or medical students. Numerous research coordinators, administrative assistants, and administrative coordinators provide important administrative support for research efforts in the department.

## Overview of Surgical Research

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 2011, many of the Research Faculty in Surgery were invited speakers around the world. Faculty members spoke in interesting locations that varied from Norway (Junger), Cape Town, South Africa (Callery), Tokyo (Hagen) and Nagoya Japan, (Hasselgren) Egypt (Jones), Hawaii (Tseng), Switzerland (Koulmanda), London (Otterbein), Qatar (Arredouani), and Chile (Sanda).

Surgery investigators also received prestigious awards in 2011 including the Egil Amundson Medal (Junger), the Kenneth W. Warren Lectureship Award (Blackburn), the AHPBA Travel Grant Award (Kent), Young Investigator Awards from the American Transplant Congress and International Society for Applied Cardiovascular Biology (Peterson), the University of Rochester School of Medicine Alumni Service Award (LoGerfo), and the Eleanor and Miles Shore Scholars in Medicine Award from HMS (Poylin).

Research faculty in the Department of Surgery also participated in 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, Undergraduate 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.

Research Funding

All research, both basic and clinical, in the Department of Surgery is supported by external funding and more than two-thirds of this funding is in the form of NIH grants. In 2011, Surgery held: 41 NIH investigator-initiated grants (R01, R21, U01, R41, and RC1); one T32 training grant; numerous non-federal and industry-partnered grants; one Department of Defense grant, and one F32 training grant, for a total of 18.9 million dollars in total awarded grant funding (Figure 1). It should be noted that in 2011, Surgery funding levels continued to be robust, exceeding 2006-2008 levels despite considerable budget restraints imposed on the NIH (Figure 1). This level of continued funding is due to the persistence and acclaim of our research programs. The level of funding is also remarkable considering that a number of faculty members who contribute substantial grant funds to the research effort are also clinically and administratively very active.

The current distribution of external funding among the different divisions in the Department of Surgery is illustrated in Figure 2. The Transplantation Surgery and Vascular/Endovascular Surgery divisions have the largest external funds, constituting more than 50% of the total departmental funding.

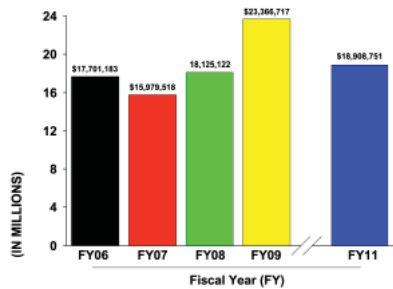


Figure 1: Total (direct and indirect, federal and non-federal) awarded funds during the 5-year period 2006-2011\*.

\* No data was collected in 2010.

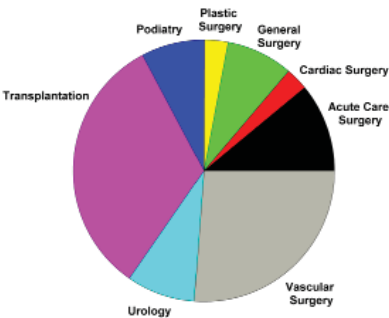


Figure 2

### T32 Training Grants

In 2011, the Department of Surgery continued its longstanding NIH training grant in Vascular Surgery research (PI, Frank LoGerfo, MD). Investigators in Surgery also actively participated in a GI Surgery Research Training Grant, which is a joint training grant among the three Harvard Medical School teaching hospitals, led by Richard Hodin, MD, (PI), at Massachusetts General Hospital, with Per-Olof Hasselgren, MD, PhD, serving as a member of the executive committee. An additional NIH training grant for transplant immunology research is based at Brigham and Women's Hospital and is led by John Iacomini, PhD.

## Surgical Residents and Research

### Residents Scholarship Program

A Clinical Scholarship Program, directed by Jim Rodrigue, PhD, Marc Schermerhorn, MD, and Scott Johnson, MD, was launched in 2011 that paired all nine first-year categorical General Surgery residents with a faculty research mentor. Mentors guide the residents throughout the year as they acquire the requisite skills to develop and implement a clinical research project. Residents were given one month of protected time, in the Spring/Summer of 2012, to complete their clinical research project.

The objectives of the Clinical Scholarship Program are to provide residents with a robust foundation for scholarship early in their training, increase their academic productivity, and enhance their opportunities to compete for outstanding fellowships and extramural research funding. Providing this experience early in the training program will facilitate residents' interest in scholarship, research, and an academic career.

The curriculum includes participating in monthly Surgical Outcomes Club meetings; completing assigned readings; and attending presentations on five core research competencies, including clinical study design, biostatistics, communicating about research, ethics and regulatory issues, and grant writing.

Residents are expected to prepare, submit, and present their research at the annual Harvard Medical School Department of Surgery Research Day, as well as submit abstracts for presentations at conferences and manuscripts for publication in peer-reviewed scientific journals.

### Residents Research Rotation

Over the past few years, approximately 10 residents per year elected to spend time in a basic or clinical research laboratory as part of their surgical training. In 2011, however, 14 residents elected to do research (*Figure 3*). Most of the residents performed research in a basic science laboratory doing bench research. The present policy is to have residents dedicate time to research between their third and fourth clinical years.

The majority of residents perform research in laboratories within the Department of Surgery, but some residents spend time in other departments at Beth Israel Deaconess Medical Center or in laboratories off-site in Boston (for example, MIT, Massachusetts General Hospital, and Boston Children's Hospital) or other institutions, including research laboratories abroad.

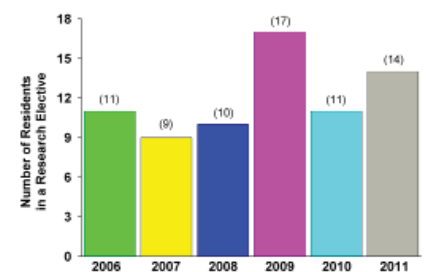


Figure 3



Figure 4

An important aspect of a Residents' research training is obtaining funding. The process that has been adopted in the department in past 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. It is only rarely that the resident has to rely on departmental financial support for the time in the laboratory. To assist residents in obtaining funding, the Office for Surgical Research has made available a 63-page booklet entitled “Funding Sources for Surgical Residents” (*Figure 4*), which describes various funding sources, deadlines, financial support available, and application forms. This booklet is updated annually. It is also available electronically at: [www.bidmc.org/~media/Files/CentersandDepartments/Surgery/Residents%20Funding%20Sources\\_2009.ashx](http://www.bidmc.org/~media/Files/CentersandDepartments/Surgery/Residents%20Funding%20Sources_2009.ashx)

### Research Abstract Competition

The annual Research Abstract Competition was held again in 2011 to coincide with the George H. A. Clowes Visiting Professor event in the Department of Surgery. The abstract competition was open to all research trainees in the Department of Surgery, including postdoctoral research fellows (includes residents on a research rotation), and graduate and undergraduate students working in research labs in the department. The winners of this competition in the basic science and clinical research categories received a cash prize.

The abstracts submitted in 2011 were truly outstanding, with eight clinical and 33 basic science abstracts submitted for the competition. Peer-review grading by members of the surgical faculty identified seven basic science and four clinical abstracts as semi-finalists for the competition, which were presented to a judging panel that included the Clowes Visiting Professor, Jeffrey B. Matthews, MD. The semi-finalists in 2011 were:

#### Basic Science

**Ana Tellechea, PharmD** “Impaired MasT-cell Function Affects Wound Healing in Diabetes”

Mentor: Aris Veves, MD, DSC

**Ji Hye Seo, PhD** “N-methyl-D-aspartate (NMDA) Channels Regulate Apoptosis in *Helicobacter pylori* Infection by Ammonia-induced Calcium Permeation Mechanisms”

Mentor: Susan Hagen, PhD

**Harwig Moll, PhD** “A20 Inhibits Interferon- $\gamma$  Signaling in Human Smooth Muscle Cells to Contain Pathological Vascular Remodeling of Transplant Arteriosclerosis”

Mentor: Christiane Ferran, MD, PhD

**Antonio Lassaletta, MD** “Rapamycin is not Cardioprotective in Acute Ischemia-reperfusion Injury in Swine”

Mentor: Frank Sellke, MD

**Marco Hefti, MD** “Disordered ATP Signaling Leads to Dysregulated Breast Cancer Cell Motility”

Mentor: Wolfgang Junger, PhD

**Akihiro Masuzawa, MD** “Autogeneic Mitochondrial Transplantation for Myocardial Protection in the Ischemic in situ Blood Perfused Heart”

Mentors: James McCully, PhD, and Sidney Levitsky, MD

**Julianty Angsana, BS** “Expression of Syndecan-1 Enhances Macrophage Motility”

Mentor: Elliot Chaikof, MD, PhD

### Clinical Research

**Rodney Bensley, MD** “Ultrasound-guided Percutaneous EVAR Success is Predicted by Vessel Diameter”

Mentor: Marc Schermerhorn, MD

**Martin Dib, MD** “Is Viable Tumor after Radiofrequency Ablation a Predictor of Post-Transplant Recurrence After Liver Transplantation for Hepatocellular Carcinoma?”

Mentors: Douglas Hanto, MD, PhD, and Michael Curry, MD

**Denis Gilmore, MD** “Real-Time Image Guided Lymphatic Mapping and Nodal Targeting in Lung Cancer”

Mentor: Yolanda Colson, MD, PhD

**Francesco Tecilazich, MD** “Muscle Energy Reserves Changes During Exercise”

Mentor: Aris Veves, MD, DSC

This year’s first place prize in the basic science category was awarded to Harwig Moll, PhD, and in the clinical research category was awarded to Denis Gilmore, MD.

## Surgery Seminars

### Surgical Horizons

In the fall of 2011, Surgical Research began a new seminar program in the Department of Surgery entitled “Surgical Horizons.” The objective of the Surgical Horizon’s Seminar Program is to invite young emerging leaders, as well as senior leaders, from both surgical and non-surgical disciplines—including those who work in the engineering, physical, and social sciences—whose endeavors promise to dramatically alter the landscape of care for the surgical patient.

The Surgical Horizons program includes a lecture from the invited speaker and a dinner in honor of the speaker attended by a small group of invited faculty and residents. Additional meetings with surgical faculty and residents also occur. The faculty hosts and speakers for 2011 are listed below:

September 12, 2011

**John V. Frangioni, MD, PhD**

Professor of Medicine, HMS; Co-Director,  
Center for Molecular Imaging, BIDMC

**Alex Vahrmeijer, MD, PhD**

Attending, Surgical Oncology; Leiden  
University Medical Center, The Netherlands

“Image-Guided Surgery  
Using Invisible Near-  
Infrared Light: The Dutch-  
American Experience”

Faculty Host: Mark Callery, MD

October 17, 2011

**Hasan B. Alam, MD**

Professor of Surgery, HMS; Program Director,  
Acute Care Surgery/SCC Fellowship program, MGH

“Novel Resuscitation  
Strategies”

Faculty Hosts: Carl Hauser, MD, and Wolfgang Junger, PhD

November 14, 2011

**Yolonda L. Colson, MD, PhD**

Associate Professor of Surgery, HMS;  
Director, Women’s Lung Surgery  
Program, BWH

“We Deliver! Polymers  
and Particles Improving  
Surgical Oncology”

Faculty Host: Sidhu Gangadharan, MD

December 12, 2011

**Carl J. Hauser, MD**

Lecturer on Surgery, HMS

“Danger’ Molecules as  
Inflammatory Agonists  
and Biomarkers in Sepsis  
and SIRS”

### Seminars in Clinical Investigation

In the spring of 2011, Surgical Research organized a number of luncheon seminars for clinical research staff. Below is a list of the speakers and topics:

April 25, 2011

**Babu Krishnamurthy, MD, PhD**

Assistant Professor of Neurology, HMS;  
Director, Human Subjects Protein Office,  
BIDMC

“Seven Secrets of the  
Prepared Investigator”

May 23, 2011

**Jorge Arroyo, MD**

Associate Professor of Ophthalmology, HMS;  
Director, Retina Service, Longwood Medical,  
Eye Center, Division of Ophthalmology, BIDMC

“Qualifications Necessary  
for Clinical Staff to  
Effectively Manage  
Current Projects in the  
Retina Service”

**Alyssa K. Gateman, MPH, CCRP**

East Coast Representative,  
Society of Clinical Research Associates;  
Deputy Director, Quality Assurance Office  
for Clinical Trials, DFCI

“An Overview of the  
Society of Clinical  
Research Associates  
(SoCRA)”

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### Annual Research Reports

The Office for Surgical Research continues to highlight progress in research by producing the Annual Research Report for the Department of Surgery. The last report was published in 2009 and highlights the program of our research faculty in Surgery.



The Annual Research Report for 2009 (*Figure 5*), can be found at:

<http://www.bidmc.org/Research/Departments/Surgery/~media/Files/Research/Annual%20Reports/2009%20DeptOfSurgeryAnnualResearchReport.ashx>

### Affinity Research Collaboratives (ARC)

In 2011, the Department of Surgery, in collaboration with BIDMC Research and Academic Affairs, launched a new grant program to promote interdisciplinary bench-to-bedside research in the Department of Surgery that investigates innovative solutions to unmet clinical needs. This program was developed by Christiane Ferran, MD, PhD, with assistance from Surgical Research.

Eleven projects across multiple disciplines were submitted for competitive review. The projects lead investigator had to be a full-time member of the Department of Surgery, and the project had to involve four to five investigators across disciplines. Successful applicants were awarded funds to nucleate the group in year one; to support seminars, group meetings, etc. Competitive renewal of the project will result in substantial grant funds that can be used to prepare preliminary data for grant applications.

The successful ARC projects are listed below:

Per-Olof Hasselgren, MD, PhD: “Transcription Factors, Nuclear Co-factors, and Muscle Wasting”

Carl J. Hauser, MD: “Activation of Innate Immunity by Surgery and Injury”

Samuel J. Lin, MD: “The Use of Functional Electrochemical Stimulation in Nerve Paralysis Rehabilitation”

Frank LoGerfo, MD/Aris Veves, MD, DSc: “Neuropeptides in Wound Healing, Health, and Disease”

### Appointments, Reappointments, and Promotion Committee

Surgical Research is involved in the Appointments, Reappointments, and Promotion Committee formed in 2003 to assist the chairman. The purpose of this committee is to review the credentials of faculty members who are being considered for reappointment or promotion at Harvard Medical School (HMS). In addition, the credentials of new faculty being recruited are reviewed by the committee before the individual is proposed for appointment at HMS. The Committee is chaired by Per-Olof Hasselgren, PhD, and presently consists of eight members of the surgical faculty at the professor or associate professor level. The committee meets monthly.

### Research Facilities and Spaces

In 2011, research in the Department of Surgery occupied approximately 27,979 square feet of 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 also has research space in several different locations. These spaces include (in square feet): 8,053 in CLS (Center for Life Sciences), 13,152



*Figure 5*

in Dana/Research West, 488 in Slosberg-Landy, 2,638 in Research North, and 1,069 in Stoneman. Clinical research space (in square feet) includes: 452 in Palmer, 1,501 in Feldberg, and 626 in the Lowry, Deaconess, and Shapiro buildings. The overall dollar density in 2011 for research space in the Department of Surgery was approximately \$200/sq foot.

### Tracking Academic Performance

In addition to a strong performance in obtaining external research grant funding (see Figure 1), publications are an additional benchmark of the academic performance in surgery. There were 121 published original articles and 53 in press articles in 2011, many of which were in high impact journals such as *PNAS*, *Nature*, *Plos1*, journals in *Immunology*, *Gastroenterology*, *JAMA*, *Biochemical Journal*, etc. There were 31 review articles contributed in 2011 and a number of case reports, commentaries, and educational materials. Of particular note in 2011 were two in press books edited by Daniel Jones, MD, and colleagues; “Pocket Surgery: The Beth Israel Deaconess Medical Center Handbook of Surgery,” with contributions from Drs. Hasselgren, Lee, Nagle, Poylin, and Slavin, and Fischer’s “Handbook of Surgery” with contributions from Drs. Evanson, Hamdan, Hasselgren, Jones, Lee, Lin, Sanda, and Wagner. Below is the integrated bibliography for 2011; faculty in Surgery at BIDMC are highlighted in **bold**.

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**Wegiel B**, Gallo D, **Otterbein LE**. Carbon monoxide accelerates vessel healing through enhanced reendothelialization acting through eNOS and P-selectin pathways. American Transplant Society Annual Congress, 2011, April 30-May 4th, Philadelphia (poster) and European Vascular Biology Congress, Krakow, Poland, September 21-24th 2011 (oral presentation)

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Yoshida S, Bensley RP, **Hamdan AD**, Pomposelli FB, **Wyers MC**, **Chaikof EL**, **Schermerhorn ML**. Increased risk of adverse events in physiologically high-risk patients undergoing carotid artery stenting. Poster presentation at the 2011 annual meeting of the SCVS, March 16-19, 2011, Orlando, Florida.

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Yoshida S, Nabzdyk CS, Glaser JD, Bensley RP, **Hamdan AD**, Pomposelli FB, **Wyers MC**, **Chaikof EL**, **Schermerhorn ML**. Patients considered “High Risk” for carotid endarterectomy are at increased risk of adverse events following carotid artery stenting. Oral Presentation at the 2011 annual meeting of the NESVS, September 2011, Providence, Rhode Island

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## Division of Acute Care Surgery Members

Michael J. Cahalane, MD, AGAF	Acting Chief, Division of Acute Care Surgery; Associate Professor of Surgery, Harvard Medical School
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Alok Gupta, MD	Instructor in Surgery
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Carl J. Hauser, MD	Lecturer on Surgery
Kiyoshi Itagaki, PhD	Instructor in Surgery and Laboratory Manager
Cong Zhao, PhD	Research Fellow in Surgery

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Wolfgang G. Junger, PhD	Professor of Surgery
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Marco Hefti, MD	Surgical Resident
Yasutaka Kurishita	Visiting PhD student
Carola Ledderose, PhD	Postdoctoral Fellow
Linglin Li, MD	Laboratory Manager

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Stephen R. Odom, MD	Instructor in Surgery
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Teresa Sanchez, PhD	Assistant Professor of Surgery
Guoqi Zhang, MD, PhD	Research Associate
Li Yang, MD, PhD	Postdoctoral Fellow
Gab Seok Kim, PhD	Postdoctoral Fellow

## Division of Acute Care Surgery



## Research Focus

Our laboratory has continued to study the regulation of innate immunity in trauma with an important emphasis on translational biology.

In a landmark article published in *Nature* in March 2010, we established that molecular patterns from mitochondria act as DAMPs (damage-associated molecular patterns, a.k.a. ‘alarmins’) when they are released from injured cells. DAMPs found so far include mitochondrial DNA and formylated peptides that activate immunity through formyl peptide receptors (FPR1, FPRL-1 and FPRL-2) as well as Toll-like receptors. These insights have opened an entire new field of translational investigation into disease processes where cell damage and death predispose to inflammation. Mt-DAMPs cause PMN and endothelial cell (EC) activation in vitro and induce lung injury in vivo. PMN and EC conversion to their inflammatory phenotypes is a critical event predisposing to organ failure. We have a longstanding interest in the events leading to PMN activation, especially the role of  $\text{Ca}^{2+}$  influx. We have now established novel systems that can evaluate PMN-EC interactions in vitro using “real-time” permeability changes. So we now routinely perform ex vivo experiments that evaluate the interactions between PMN and EC, the two major cell types involved in acute inflammatory lung injury. Using these systems, we have now investigated the mechanisms by which bacterial DNA and mt-DAMPs activate PMN-EC adherence and activation programs. We are also studying the endosomal Toll receptors by which mitochondrial DNA is sensed. These new findings will lead to a better understanding of the pathways by which tissue injury leads to inflammation and organ failure in a wide variety of illnesses.



**Carl J. Hauser, MD**

Lecturer on Surgery

Lab Group

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Cong Zhao, PhD

## Research Support

“Mitochondrial DAMPS and inflammation after injury”

National Institutes of Health, 5R01GM089711

Project Period: 09/07/2010–07/31/2014

PI: Carl J. Hauser, MD

## Bibliography (January-December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Dutton RP, Parr M, Tortella BJ, Champion HR, Bernard GR, Boffard K, Bouillon B, Croce MA, Dimsits J, Holcomb JB, Leppaniemi A, Vincent JL, **Hauser CJ**; CONTROL Study Group. Recombinant activated factor VII safety in trauma patients: results from the CONTROL trial. *J Trauma* 2011;71(1):12-9.

Holcomb JB, Weiskopf R, Champion H, Gould SA, Sauer RM, Brasel K, Bochicchio G, Bulger E, Cotton BA, Davis D, Dutton R, **Hauser CJ**, Hess JR, Hides GA, Knudson P, MacKenzie E, McGinnis RL, Michalek J, Moore FA, Omert L, Pollock BH, Tortella B, Sugarman J, Schreiber MA, Wade CE. Challenges to effective research in acute trauma resuscitation: consent and endpoints. *Shock* 2011;35(2):107-13.

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**Carl J. Hauser, MD**

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Commentary

Vincent JL, Dutton R, Parr M, Hauser C. Massive bleeding in polytrauma: how can we make progress? Crit Care 2011;15(5):196.



## Research Focus

We are studying the inflammatory response to trauma. In trauma patients, excessive activation of immune cells can cause severe secondary organ damage and post-traumatic complications that are a leading cause of death among patients who survive their initial traumatic injuries. Our goal is to define the molecular and cellular mechanisms involved in this inflammatory process and to develop new therapeutic strategies that improve clinical outcomes after trauma. There are several ongoing projects focusing on these goals. In one project, we study the feasibility of modulating neutrophil responses with pharmacological agents that influence ATP signaling. This concept is based on our intriguing finding that ATP release and autocrine feed forward signaling through purinergic receptors is a critical early event in immune cell activation. We found that purinergic signaling is an indispensable requirement for the activation of neutrophils and other immune cell types including T-cells. Another project focuses on ATP that is released from damaged tissues and by bacteria and how these often large amounts of ATP influence the innate purinergic signaling mechanisms of neutrophils and other immune cell types. In a third project, we investigate how purinergic signaling is linked to the much better known and well-characterized calcium signaling in immune cells. In this project, we have been focusing on the development of new methods to record ATP signaling in real time.

We have several ongoing clinical projects to study the role of ATP release and purinergic signaling in patients. Ongoing collaborations with former laboratory members in Japan (Drs. Sumi and Inoue) focus on the questions how injury severity and mode of injury influence the levels of ATP and its degradation products in plasma. We also study how injury influences the expression of the many purinergic receptors that allow immune cells to respond to extracellular ATP and its products. Finally, we are investigating how hypertonic resuscitation fluids, which we found to induce the release of ATP, affect inflammation, immune cell function, and clinical outcome in trauma patients. The latter study is a large scale clinical trial that involved 11 Level-1 Trauma Centers in Canada and the United States of America.

## Research Support

“Hypertonic saline and neutrophil function”  
National Institutes of Health, R01 GM060475-06  
04/01/2006-06/30/2012  
PI: Wolfgang G. Junger, PhD

“Hypertonic saline resuscitation, gamma-delta T-cell function, and post-traumatic organ failure”  
Department of Defense, W81XWH-05-1-0488  
09/15/2005-09/14/2011  
PI: Wolfgang G. Junger, PhD

“Hypertonic modulation of inflammation”  
National Institutes of Health, R01 GM076101-01  
06/11/2007-06/10/2012  
Subcontract PI: Wolfgang G. Junger, PhD

“Purinergic receptors in inflammation”  
National Institutes of Health, R01 AI080582  
06/15/2009-05/31/2013  
PI: Wolfgang Junger, PhD



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Carola Ledderose, PhD  
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Yasutaka Kurishita

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“Autocrine control of neutrophil chemotaxis”  
National Institutes of Health, R01 AI072287  
05/15/2009-04/30/2012  
PI: Wolfgang Junger, PhD

**Applications Submitted and Pending Review/Funding**

“Visualization of ATP release”  
National Institutes of Health, R01  
PI: Wolfgang G. Junger, PhD

“Purinergic signaling and multi-organ failure”  
DOD  
PI: Wolfgang G. Junger, PhD

“Improved hypertonic resuscitation fluid”  
National Institutes of Health, R01  
PI: Wolfgang G. Junger, PhD

“Inflammation in trauma, shock, and sepsis”  
National Institutes of Health, T32  
PI: Wolfgang G. Junger, PhD

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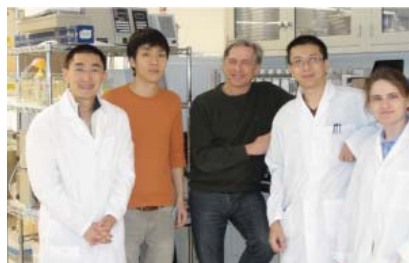
**Accomplishments in the Past Year**

**Research Progress**

Yu Chen, MD, and Yi Bao found that pannexin-1, a gap junction molecule that causes ATP release, elicits local excitation of neutrophils at the leading edge as well as global inhibition at the receding edge through P2Y2 and A2a receptors, respectively. The finding that these two G protein coupled receptors are activated by ATP define for the first time the molecular identities of a long hypothesized but elusive local excitation/global inhibition mechanism that is required for chemotaxis of mammalian cells. Masayuki Sato, PhD, and Yi Bao, in collaboration with the group of Itaru Hamachi, PhD, from Kyoto University have developed fluorescence methods to visualize ATP release using live cell imaging. Monali Bhate has successfully defended her PhD thesis on the role of purinergic signaling in gamma-delta T-cells. Linglin Li, PhD, has been able to measure the concentrations of ATP, ADP, AMP, and adenosine in blood samples using an improved high performance liquid chromatography (HPLC) method. Using this method, he and Dr. Sumi, who is now an Associate Professor at Juntendo University, were able to establish that trauma patients with sepsis have a pronounced increase in plasma ATP levels and that these levels correlate with injury severity and inflammatory markers.

**Individual Accomplishments**

- Reviewer, scientific journals (e.g., Science, Nature, Nature Biotechnology, Shock, J. Immunol., J. Surg. Res., J. Leukocyte Biol., Am. J. Physiol., FASEB J., Cytokine, etc)
- Reviewer, Wellcome Trust Grant, DoD US ARMY grant submissions, ARRA grant submissions, NIH-ZRG1-BST, NIH-CSR-RC1 study sections, NIH P50 grant applications, Swiss National Science Foundation.
- Honors, Egil Amundson Medal, Institute for Surgical Research, Oslo University, Norway



*Junger Lab (from left): Dr. Li, Mr. Kurishita, Drs. Junger and Bao, and Ms. Wehils (PhD student in 2011)*

### Invited Presentations

“Purinergic Signaling and Inflammation.” Oslo University, Plenary Lecture, Egil Amundson Lecture. Oslo, Norway.

“Purinergic Signaling and Inflammation.” Brigham and Women’s Hospital, Transplant Institute seminar. Boston, MA .

“ATP and Immune Cell Signaling.” Beth Israel Deaconess Medical Center, Transplant Center seminar. Boston, MA.

## Teaching, Training, and Education

### Undergraduate Courses

Project Success, research apprenticeship program for underprivileged high school and college students, Harvard Medical School, Boston

### Graduate School and Graduate Medical Courses

Faculty advisor to visiting PhD students. Students taught:

- Monali Bhate
- Anna Weihs

### Other Teaching Contributions

Mentoring junior faculty and residents:

- Ionita Ghiran, MD, BIDMC (successfully received R01 grant)
- Yu Chen, MD, BIDMC (obtained position in industry)
- Marco Heft, MD, BIDMC (submitted multiple fellowship and grant applications)

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Inoue Y, Tanaka H, Sumi Y, Woehrle T, Chen Y, Hirsh MI, **Junger WG**. A3 adenosine receptor inhibition improves the efficacy of hypertonic saline resuscitation. *Shock* 2011;35(2):178-83.

Itagaki K, Adibnia Y, Sun S, Zhao C, Sursal T, Chen Y, **Junger W**, Hauser CJ. Bacterial DNA induces pulmonary damage via TLR-9 through cross-talk with neutrophils. *Shock* 2011;36(6):548-52.

Bulger EM, Tower CM, Warner KJ, Garland T, Cuschieri J, Rizoli S, Rhind S, **Junger WG**. Increased neutrophil adenosine a3 receptor expression is associated with hemorrhagic shock and injury severity in trauma patients. *Shock* 2011;36(5):435-9.

**Wolfgang Junger, PhD**

**Wolfgang Junger, PhD**

**Other Peer-Reviewed Publications**

Reviews

**Junger WG.** Immune cell regulation by autocrine purinergic signalling. Nat Rev Immunol 2011;11(3):201-12.

## Research Focus

My laboratory investigates the signaling pathways that regulate the responses of the vascular endothelium to injury. Endothelial cells are constantly adapting to changes within the extracellular environment and responding in ways that are usually beneficial but at times, could be deleterious to the organism. Dysregulation of these tightly regulated physiological events results in endothelial dysfunction, which plays a critical role in the pathophysiology of atherosclerosis, sepsis, ischemic stroke, diabetic vasculopathy, and pathological angiogenesis, among others. More specifically, we are focused on the signaling pathways activated by sphingosine-1-phosphate (S1P) and the role of S1P in the regulation of endothelial responses to injury. S1P, a bioactive sphingolipid present at high levels in plasma and lymph, regulates multiple cellular responses by activating the endothelial differentiation gene family of G protein-coupled receptors (EDG-1-5, renamed S1P1-5R).

To better understand the role of S1P in the regulation of endothelial cell function, we have established several *in vitro* and *in vivo* systems. Using pharmacological modulators of S1P receptors and genetic models, we have shown that S1P is a critical modulator of endothelial cell migration and endothelial barrier function *in vitro*, as well as angiogenesis, vascular permeability, and vascular inflammation *in vivo*.

Interestingly, we found that vascular responses to S1P depend on the balance of expression of two of its receptors, S1P1R and S1P2R. Indeed, while activation of S1P1R inhibits vascular permeability and inflammation, activation of S1P2R promotes vascular permeability and endothelial inflammation (*Figure 1*). In addition, our studies have revealed the molecular mechanisms underlying the antagonistic effects of S1P1R and S1P2R in the regulation of endothelial responses. While S1P1R activates phosphatidylinositol-3-kinase (PI3K), S1P2R counteracts the actions of S1P1R by activating the phosphatase PTEN, which antagonizes the actions of PI3K. In agreement with this model, we found that PTEN activity was required to inhibit endothelial cell migration and induction of endothelial permeability by S1P2R.

Our findings emphasize the importance of understanding how S1P signaling is regulated in the endothelium. Since S1P receptors can be pharmacologically targeted by specific agonists and antagonists, understanding how S1P signaling is regulated both in health and disease will be critical in the design of new therapies to treat disorders of vascular permeability, inflammation, and vascular growth. We are presently using molecular and cell biology approaches in combination with animal models in order to further elucidate the signaling pathways activated by S1P receptors in several pathophysiological conditions, such as sepsis and stroke. Our ultimate goal is to develop new therapeutic and diagnostic approaches for vascular disease.

## Translational Research

In collaboration with Jonathan Edlow, MD, Nate Shapiro, MD (Emergency Medicine Department, BIDMC), and Magdy Selim, MD, PhD, (Neurology Department, BIDMC) we are currently conducting a clinical study to investigate the role of S1P and the endothelium in stroke. We are currently analyzing plasma S1P levels and the levels of other endothelial markers from stroke patients to test if they can be used as biomarkers to predict stroke outcomes.

In addition, in collaboration with Scott Rodig, MD, and Michael Kluk, MD, PhD, (Department of Pathology, Brigham and Women's Hospital), we are investigating the role of S1P signaling in lymphoma progression and spreading.



**Teresa Sanchez, PhD**

Assistant Professor of Surgery

### Lab Group

Guoqi Zhang, MD, PhD

Li Yang, MD, PhD

Gab Seok Kim, PhD

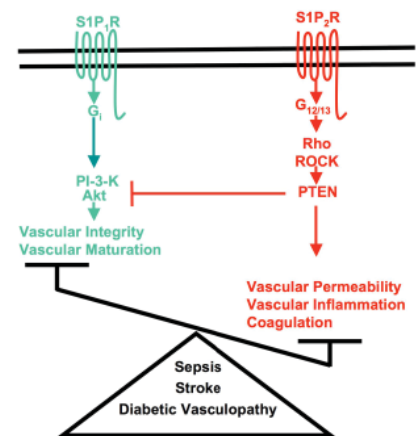


Figure 1

Teresa Sanchez, PhD

## Research Support

“Sphingolipid signaling in endothelial responses to injury”

National Institutes of Health, NHLBI 1R01HL094465

Project Period: 8/1/09-7/31/14

PI: Teresa Sanchez, PhD

### Applications Submitted and Pending Review/Funding

“Targeting sphingosine-1-phosphate receptors as vasoprotective therapy for stroke”

American Heart Association, Grant-in-Aid

Project Period: 7/1/12-6/30/15

PI: Teresa Sanchez, PhD

“Assessment of timing for intra-arterial administration of stem cells following stroke”

National Institutes of Health, R03

7/1/12-6/30/14

PI: Ajith Thomas, MD

Collaborator: Teresa Sanchez, PhD

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## Accomplishments in the Past Year

### Research Progress

In the past year, we made significant progress with the sepsis project in the lab. Sepsis is another example of dysregulation of endothelial responses to injury. During sepsis, the endothelium becomes hyperactivated and exhibits increased permeability and activation of inflammatory and coagulation pathways, which results in edema, endothelial dysfunction and organ failure. Using a mouse model of endotoxemia to induce systemic inflammation, we found that pharmacological inhibition or genetic deletion of S1P2R signaling results in less morbidity and less vascular permeability and inflammation in several organs, including kidney, liver and lung. In addition, our in vitro studies showed the critical role of S1P2R in the pro-coagulant and pro-adhesion phenotype of the endothelium during inflammation. This manuscript is currently under review in *Blood*.

In addition, we established the Middle Cerebral Artery Occlusion (MCAO) mouse model of stroke. In this model, transient cerebral ischemia is induced by inserting a 6-0 nylon monofilament into the internal carotid artery to block the middle cerebral artery. Then, reperfusion is established by removing the filament. Blood flow in the territory of the middle cerebral artery is monitored during the entire procedure by Laser Doppler. Using this model, we found that S1P2R plays a critical role in the regulation of brain edema and hemorrhagic transformation, two serious complications of current stroke reperfusion therapies. We are currently studying the mechanisms involved and the contribution of each cell lineage to the phenotype observed.

Finally, in collaboration with Drs. Scott Rodig and Michael Kluk (Department of Pathology, Brigham and Women's Hospital) we obtained interesting data on the role of S1P in classical Hodgkin lymphoma. Using molecular and cell biology approaches, we found that S1P potently induces motility of the classical Hodgkin lymphoma cell lines KMH2 and SupHD1 through S1P1R. Interestingly, pretreatment with the FDA-approved S1P1R functional antagonist, Fingolimod, reduced S1P-induced migration. In addition, assessment



of primary tumor samples from patients with Classical Hodgkin lymphoma revealed a subset of cases with very strong, membranous expression of S1P1R in Hodgkin-Reed Sternberg cells. Our data indicate that S1P1R is an attractive pharmacologic target in cases of Classical Hodgkin Lymphoma which exhibit elevated S1P1R expression. This work was selected for a Platform presentation at the United States and Canadian Academy of Pathology annual meeting (March 2011).

### Administrative Accomplishments

- Continued as a member of the committee in charge of organizing the Center for Vascular Biology Research Annual Summer Retreat, which was held in North Falmouth, MA on June 15–16, 2011.
- Continued to be part of the Seminar Committee in the Center for Vascular Biology Research. This committee is in charge of organizing all the seminars series that take place in the center: Translational Seminar Series, Visiting Professor Series, Research Seminar Series, and Journal and Data Club.

### Individual Accomplishments

- Peer reviewer (ad-hoc) for Cancer Immunology Immunotherapy and the Journal of Thrombosis and Haemostasis.
- Session Chair, Abstract Reviewer, and Poster Grader in the Center for Vascular Biology Research Annual Summer Retreat in North Falmouth, MA.

### Invited Presentations

- “The unique properties of the brain vasculature” Beth Israel Deaconess Medical Center, Center for Vascular Biology Research Translational Seminar Series. Boston, MA. March 22, 2011.
- “Induction of Vascular Inflammation by Sphingosine-1-Phosphate Receptor-2.” Beth Israel Deaconess Medical Center, Center for Vascular Biology Research Annual Summer Retreat. North Falmouth, MA. June 15, 2011.

## Teaching, Training and Education

### Other Teaching Contributions

This year, I continued to be the coordinator and instructor of the Center for Vascular Biology Research (CVBR) Journal Club and Data Club. The CVBR Journal Club and Data Club consists of presentations by students, Postdoctoral and research fellows in the center. The Data club gives our students and fellows the opportunity to present and discuss their latest research findings, receive feedback from faculty members, and enhance their presentation skills. In the Journal Club, students and fellows present a recent high impact article in Vascular Biology and related disciplines. The objectives of the Data and Journal Club are to promote interactions and collaborations among our junior scientists, as well as encourage critical thinking in a relaxed and friendly atmosphere. After every seminar, I meet with the presenter to give them feedback on a range of topics including, interpretation of their data, presentation content and style and future directions. In addition, I discuss the strengths of their presentation as well as the areas for improvement. The Data and

**Teresa Sanchez, PhD**

Journal Club takes place every Friday from noon–1:00pm. We have around 45 speakers per academic year.

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### **Bibliography (January – December 2011)**

#### **Peer-Reviewed Publications in Print or Other Media**

##### **Research Investigations (Submitted or in Press)**

Zhang G, Ryan KP, Yang L, Lu S, Aird WC, Shapiro N, Yano K, **Sanchez T**. Critical role of sphingosine-1-phosphate receptor 2 (S1PR2) in acute vascular inflammation. *Blood* 2011; in press.

#### **Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Kluk MJ, Ryan KP, Kutok JL, Rodig SJ\*, **Sanchez T\***. Role of sphingosine-1-phosphate receptor-1 (S1PR1) in classical Hodgkin lymphoma (cHL). Platform presentation at the United States and Canadian Academy of Pathology Annual Meeting, San Antonio, TX; 2011. \*Equal contribution

Zhang G, Ryan KP, Liu S, Yano K, **Sanchez T**. Blockade of S1PR2 signaling protects from sepsis morbidity. Presented as a poster at the Center for Vascular Biology Research Annual Summer Retreat. North Falmouth, MA; 2011.

## Division of Cardiac Surgery Members

Kamal R. Khabbaz, MD	Chief, Division of Cardiac Surgery; Associate Professor of Surgery,
Elizabeth Kirwan, RN Mary Trovato, RN	Clinical Research Nurse Clinical Research Administrator
Robert C. Hagberg, MD	Assistant Professor of Surgery
Sidney Levitsky, MD	Cheever Professor of Surgery
David C. Liu, MD	Instructor in Surgery
James D. McCully, PhD	Associate Professor of Surgery, Levitsky/McCully Lab Group
Kendra Black, MA Akihiro Masuzawa, MD	Research Assistant in Surgery Research Fellow in Surgery
Venkatachalam Sentilnathan, MD	Instructor in Surgery

## Division of Cardiac Surgery



## Research Focus

The focus of our research is to do translational studies in an area of high relevance for our cardiac surgery population. To this end, there are several funded and non-funded trials underway along with many collaborative efforts.

Several of our projects are in collaboration with the Cardiothoracic Research Group in our Division (see the report by Drs. McCully and Levitsky). With them, we are examining the role of collagen type XI on aortic aneurysm formation. Collagen type XI alpha-1 (Col11a1) is thought to play an important role in collagen synthesis and fibrillogenesis and is known to occur in vascular tissues including the aorta. Preliminary evaluation of genomic DNA from patients with abdominal aortic aneurysms showed mutations in exon 6A of Col11a1. The purpose this study is to determine changes in Col11a1 DNA, mRNA, and protein, which may be the key element for the aneurysm formation. We collaborate with the same group to examine the role of autogeneic mitochondrial transplantation for myocardial protection in the ischemic in situ blood perfused heart, which is a trial that aims to evaluate the efficacy of autogeneic mitochondria from skeletal muscle that are transplanted into the blood perfused ischemic heart.

Several collaborative clinical research projects have been developed between the Division of Cardiac Surgery and other groups within HMS and BIDMC. The most notable is with the Division of Cardiology at BIDMC as part of a national multicenter trial to investigate newer percutaneous aortic valve replacement options. The U.S. CoreValve® Pivotal Clinical Trial uses the Medtronic CoreValve® System, which is a minimally invasive, non-surgical treatment option for patients requiring aortic valve replacement who are considered at extreme or high risk for conventional surgical aortic valve replacement. CoreValve® is delivered via transcatheter aortic valve implantation (TAVI) rather than open-heart surgery. The CoreValve® system received CE Mark in March 2007 and has been implanted in more than 12,000 patients worldwide in 42 countries outside the United States.

Another major focus on the clinical investigational front has been in collaboration with the Cardiac Anesthesia group in understanding mitral valve geometry and three dimensional changes utilizing various repair techniques and different annuloplasty rings. Our collaboration with investigators at the University of Pennsylvania resulted in a multicenter NIH grant to look at echocardiography's predictive value after mitral valve repair. The goal of this project is to investigate changes in mitral leaflet geometry, which can be assessed by intraoperative three-dimensional transesophageal echocardiography. Recurrent ischemic mitral regurgitation and ischemic mitral regurgitation is a significant problem after myocardial infarction and the incidence is likely to increase with the aging population.

We are also continuing our collaboration with the Vascular Surgery Division to further our research on aortic aneurysms and aortic dissections. This has been an on-going collaboration and together we have initiated studies involving complicated Type B aortic dissections (TAG 08-01), descending thoracic aortic aneurysms (TAG 05-02), and endovascular treatment of blunt thoracic aortic injuries (RESCUE).



**Kamal R. Khabbaz, MD**

Associate Professor of Surgery  
Chief, Division of Cardiac Surgery

Research Staff  
Mary Trovato, RN  
Elizabeth Kirwan, RN



**Robert C. Hagberg, MD**

Assistant Professor of Surgery



**David Liu, MD**

Instructor in Surgery

**Kamal R. Khabbaz, MD**

**Robert C. Hagberg, MD**

**David Liu, MD**

Below outlines all of our current research projects and collaborators:

- **Jeff Popma, MD (Cardiology)**  
Medtronic CoreValve® U.S. Pivotal Trial for extreme risk patients, Echocardiography to predict recurrent ischemic mitral regurgitation after surgical mitral valve repair, and Clinical Trial of the On-X® Valve using low dose anticoagulation.
- **Sidney Levitsky, MD (Surgery)**  
The role of collagen type XI- $\alpha$ 1 on aortic aneurysm formation
- **Jim McCully PhD (Surgery)**  
Autogenic mitochondria protection in heart ischemia
- **Lynn Uhl, MD (Blood Bank)**  
RED CELL Storage Duration Study (RECESS)
- **Samir Parikh, MD (Nephrology)**  
Renal biomarkers in cardiac surgery patients
- **Elena Aikawa, MD**  
Cardiac valve pathobiology in disease and substitution
- **Murray Mittleman, MD (Cardiology)**  
Atrial fibrillation, epigenetics, and ambient exposures
- **Marc Schermerhorn, MD (Vascular Surgery)**  
Evaluation of the GORE Conformable TAG® Thoracic Endoprosthesis for Treatment of Acute Complicated Type B Aortic Dissection (TAG 08-01); A Clinical Evaluation of the GORE TAG Endoprosthesis in the Primary Treatment of Descending Thoracic Aortic Aneurysms (TAG 05-02 Study); Evaluation of the Clinical Performance of the Valiant Thoracic Stent Graft with the Captivia Delivery System for the Endovascular treatment of Blunt Thoracic Aortic Injuries (RESCUE US Clinical Trial); Retrospective Review of Medical Records in Patients with Type A Aortic Dissections; Clinical, Clopidogrel Usage in Coronary Artery Bypass Patients and its Effects on Peri-operative Bleeding; Comparison of postoperative transthoracic and intraoperative transesophageal echocardiographic assessment of patients following mitral valve repair
- **Bala Subramanian, MD (Anesthesia)**  
Dynamic biomarkers of intraoperative instability

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## Research Support

“Autogenic mitochondria: surgical cardioprotection”

NIH R01 HL103642

07/1/2010-06/30/2014

PI: James McCully, PhD

Collaborator: Sidney Levitsky, MD

Collaborator: Kamal Khabbaz, MD

“Echocardiography to predict recurrent ischemic mitral regurgitation after surgical mitral valve repair”

NIH R01HL103723

06/06/2011-05/13/2015

PI: Robert C. Gorman, MD (University of Pennsylvania)

BIDMC site PI: Kamal Khabbaz, MD



“Transfusion medicine/hemostasis clinical trials network”

NIH, 5U01 HL072291-07

2/12/10-8/12/2012

PI: Ellis J. Neufeld, MD (Children’s Hospital Boston)

BIDMC project: “Red cell storage duration study (RECESS)”

PI: Lynn Uhl, MD (Blood Bank) and Kamal Khabbaz, MD

“Medtronic CoreValve® U.S. pivotal trial (extreme risk patients)”

Medtronic

1/1/2011-12/1/2017

PI: Jeffrey Popma, MD

Collaborator: Kamal Khabbaz, MD

“Clinical trial of the On-X® valve using low dose anticoagulation”

On-X Life Technologies Inc.

6/1/2006-6/1/2018

PI: Robert Hagberg, MD

“Evaluation of the GORE conformable TAG® thoracic endoprosthesis for treatment of acute complicated type B aortic dissection (TAG 08-01)”

W.L. Gore & Associates

9/1/2009-12/1/2013

PI: Marc Schermerhorn, MD

Collaborator: Kamal Khabbaz, MD

“Evaluation of the clinical performance of the valiant thoracic stent graft with the Captivia Delivery System for the endovascular treatment of blunt thoracic aortic injuries (RESCUE US clinical trial)”

Medtronic Vascular

2/1/2010-12/1/2015

PI: Marc Schermerhorn, MD

Collaborator: Kamal Khabbaz, MD

#### Applications Submitted and Pending Review/Funding

“Evaluation of XIENCE PRIME™ Everolimus Eluting Stent System (EECSS) or XIENCE V®EECSS versus coronary artery bypass surgery for effectiveness of left main revascularization”

Pending IRB approval

PI: Donald Cutlip, MD

“The use of ACT plus device with and without Heparinase to quantify serum heparin concentrations and the impact of recombinant antithrombin III on ACT in cardiac surgical patients”

Pending IRB approval

PI: Adam Lerner, MD

“Evaluation of impact of renal transplant on outcomes in cardiac surgery”

Pending IRB approval

PI: John Mitchell, MD

Kamal R. Khabbaz, MD

Robert C. Hagberg, MD

David Liu, MD

Kamal R. Khabbaz, MD

Robert C. Hagberg, MD

David Liu, MD

## Accomplishments in the Past Year

### Research Progress

The cardiology collaborative Medtronic CoreValve® U.S. Pivotal Clinical Trial has been a major research focus for the Division. Prospective subjects are evaluated weekly and inquiries into the trial have been on a rise. Our echocardiography to predict recurrent ischemic mitral regurgitation after surgical mitral valve repair study, funded by a NIH grant and in collaboration with the University of Pennsylvania, is underway and we are actively screening for subjects. The on-going clinical trial of the On-X® Valve using low dose anticoagulation is approaching final enrollment. With the high-risk AVR group closed to enrollment already, we hope to have promising preliminary data posted soon.

### Administrative Accomplishments

Kamal Khabbaz, MD

- Division Chief for Cardiac Surgery and Program Director, Thoracic Surgery Training Program

#### *Major Committee Assignments*

- Cardiac Surgery Quality Initiative Committee
- Surgical Care Committee
- Inpatient MD/Nurse Manager Partners Committee
- Cardiovascular Institute Supply Steering Committee
- Cardiovascular Institute Inpatient Operations Committee
- Department of Surgery Quality Assessment Committee
- Department of Surgery Surgical Care Committee
- Cardiovascular Institute Executive Committee
- Massachusetts PCI Data Registry Publications Committee

Robert Hagberg, MD

- Director, Graduate Medical Education, Section of Cardiac Surgery

David Liu, MD

- Committee for Simulation Based Learning and the Surgical Event Committee

### Individual Accomplishments

Kamal Khabbaz, MD

- Editorial Board Member
- *Journal of Cardiothoracic and Vascular Anesthesia*, Ad Hoc Reviewer

- *Annals of Thoracic Surgery, Chest, Circulation, Journal of Cardiothoracic Surgery, Journal of Thoracic and Cardiovascular Surgery, New England Journal of Medicine*

#### Honors and Awards

For the American Association for Thoracic Surgery Leadership Academy, I was asked to peer review selection of promising young chiefs.

Robert Hagberg, MD

- Ad Hoc Reviewer for the *Journal of Thoracic & Cardiovascular Surgery and Circulation*

David Liu, MD

- Cardiac Surgery Mission, Arequipa, Peru. September 2011.

#### Invited Presentations

Kamal Khabbaz, MD

“Mitral Valve Geometry: Pringle or Lay?” Twenty-First Century Cardiothoracic Surgical Society Meeting. Rio Grande, PR. February 2011.

“Update on Mitral Valve Surgery.” Beth Israel Deaconess Medical Center, Department of Anesthesia, Grand Rounds. Boston, MA. February 2011.

“Cardiac Surgery at Beth Israel Deaconess Medical Center in 2011.” Beth Israel Deaconess Medical Center, Department of Anesthesia, Grand Rounds. Boston, MA. November 2011.

## Teaching, Training, and Education

#### Graduate Medical Courses

Harvard Medical School-Thoracic and Cardiovascular Surgery  
Course SU526M.12 (4th year medical students)

Harvard Medical School-Core Clerkship in Surgery  
Course SU600M.5 (3rd and 4th year medical students)

#### CME Courses

Perioperative and Critical Care Echocardiography and Echo Boards Review Course.  
Boston, MA. (Serve as faculty lecturer and panelist for annual course)

## Bibliography (January – December 2011)

#### Peer-Reviewed Publications in Print or Other Media

##### Research Investigations

Eisenberg RL, Khabbaz KR. Are chest radiographs routinely indicated after chest tube removal following cardiac surgery? *AJR Am J Roentgenol*

Kamal R. Khabbaz, MD

Robert C. Hagberg, MD

David Liu, MD

**Kamal R. Khabbaz, MD**

**Robert C. Hagberg, MD**

**David Liu, MD**

2011;197(1):122-4.

Ejaz A, LoGerfo FW, **Khabbaz K**, Pradhan L. Expression of neuropeptide Y, substance P, and their receptors in the right atrium of diabetic patients. Clin Transl Sci. 2011;4(5):346-50.

Feng J, Liu Y, Chu LM, Clements RT, **Khabbaz KR**, Robich MP, Bianchi C, Sellke FW. Thromboxane-induced contractile response of human coronary arterioles is diminished after cardioplegic arrest. Ann Thorac Surg 2011;92(3):829-36.

Feng J, Liu Y, **Khabbaz KR**, **Hagberg R**, Robich MP, Clements RT, Bianchi C, Selke FW. Decreased contractile response to endothelin-1 of peripheral microvasculature from diabetic patients. Surgery 2011;149(2):247-52.

Feng J, Liu Y, Singh AK, Dobrilovic N, Feng WC, Chu LM, Robich MP, **Khabbaz KR**, Sellke FW. Impaired contractile response of human peripheral arterioles to thromboxane A-2 after cardiopulmonary bypass. Surgery 2011;150(2):263-71.

Matyal R, Mahmood F, Robich M, Glazer H, **Khabbaz K**, Hess P, Bianchi C, Hagberg R, Hu SX, Sellke FW. Chronic type II diabetes mellitus leads to changes in neuropeptide Y receptor expression and distribution in human myocardial tissue. Eur J Pharmacol 2011;665(1-3):19-28.

Matyal R, Warraich HJ, Karthik S, Panzica P, Shahul S, **Khabbaz KR**, Mahmood F. Anterior myocardial infarction with dynamic left ventricular outflow tract obstruction. Ann Thoracic Surg 2011;91(3):e39-40.

Matyal R, Warraich HJ, Panzica P, **Khabbaz KR**, Mahmood F. Echo rounds: bifid atrial septal aneurysm: visualization with three-dimensional transesophageal echocardiography. Anesth Analg 2011;112(6):1300-2.

Stamou SC, Kouchoukos NT, **Hagberg RC**, **Khabbaz KR**, Robicsek F, Nussbaum M, Lobdell KW. Does the technique of distal anastomosis influence clinical outcomes in acute type A aortic dissection? Interact Cardiovasc Thorac Surg 2011;12(3):404-8.

Warraich H, Matyal R, Shahul S, Mitchell J, Panzica P, **Khabbaz K**, Mahmood F. Giant saphenous vein graft pseudoaneurysm causing tricuspid valve stenosis. J Card Surg 2011;26(2):177-80.

Research Investigations (Submitted or in Press)

Mahmood F, Warraich HJ, Gorman JH III, Gorman RC, Chen T-H, Panzica P, Maslow A, **Khabbaz KR**. Changes in mitral annular geometry after aortic valve replacement-A three dimensional transesophageal echocardiographic study. J Heart Valve Dis 2011, in press.

Robich M, **Hagberg R**, Schermerhorn M, Pomposelli F, Nilson M, Gendron M, Sellke FW, Rodriguez R. Hypothermia severely effects performance of nitinol based endografts in vitro. Ann Thoracic Surg 2011; in press.

Warraich HJ, Matyal R, Shahul S, Sentilnathan V, Mahmood F. Anomalous right coronary artery arising from the pulmonary artery: visualization using 64-slice coronary computer assisted tomography angiogram and transesophageal echocardiography. Ann Thoracic Surg 2011; in press.

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media (Submitted or in Press)**

Reviews, Chapters, Monographs, or Editorials (Submitted or in Press)

**Liu D, Khabbaz K, Fann J.** The use of simulation in cardiac surgery training. In: Tsudo S, Scott D, Jones DB, editors. Textbook of simulation: skills and team training. Cine-Med 2011, in press.

**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Burke D, Litmanovich D, Bankier, **Hagberg R**, Ridge C, Raptopoulos, Popma J. Multimodality aortic annulus size measurement for novel technique of transcatheter aortic valve implantation- initial single – center experience. Presented at the North American Society of Cardiovascular Imaging Conference 39th annual meeting, Baltimore, MD (September 24-27, 2011).

Feng, J, Liu YH, Singh AK, Dobrilovic N, Feng WC, Chu LM, Robich MP, **Khabbaz KR**, Selke FW. Impaired contractile response of human peripheral arterioles to thromboxane A-2 after cardiopulmonary bypass. 6th Annual Academic Surgical Congress. Huntington Beach, February 1-3 2011.

Shaw J, Hong S, **Hagberg RC**, Knowles B, Manning W, Peters D. Patients with histologically abnormal left atrial myocardium demonstrate greater left atrial late gadolinium enhancement. Presented at the 19th annual meeting and Exhibition of the International Society of Magnetic Resonance in Medicine; 2011 May7-13, Montreal, QC

Subramaniam B, Lerner AB, **Khabbaz KR**, Hess PE, Talmor D. Preoperative HbA1C influences glycemic variability and postoperative outcomes in patients undergoing cardiac surgery. Presented at the American Society of Anesthesiologists Annual Meeting, Chicago, IL, 2011.

**Kamal R. Khabbaz, MD**

**Robert C. Hagberg, MD**

**David Liu, MD**





## Research Focus

The primary focus of the 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 in the mature and aged male and female with particular emphasis on the development of novel and specific cardioprotective protocols. Our studies 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 male and female cardiac surgical patient.

Our current research is focused on the following studies:

### Integrated Transcriptomic/Proteomic Analysis of Cardioprotection

Large scale database studies have demonstrated that aged women undergoing coronary artery bypass grafting (CABG) have a significantly higher operative mortality (4.5%) compared with that of men (2.6%;  $P < 0.0001$ ) and have a significant increase in the incidence of perioperative myocardial infarction as compared to men (4.5% vs. 3.1%;  $p < 0.05$ ).

In the analysis of co-morbidities and anatomy relating to early mortality, it was noted that preoperative risk factors are more prevalent among women than men. These factors include age above 70, angina class 3 or 4, urgent operation, preoperative intraaortic balloon pump usage, congestive heart failure, previous percutaneous transluminal coronary angioplasty, diabetes, hypertension, peripheral vascular disease and smaller coronary artery size, and smaller mean body surface area as compared to men. After adjusting for all co-morbidities including body surface area, female gender is an independent predictor of increased mortality following coronary artery bypass surgery, with a risk adjusted operative mortality of 3.81% for women as compared to 2.43% for men.

The present paradigm to alleviate surgically induced ischemia/reperfusion injury requires the use of cardioplegia, however, in recent studies we have shown that the cardioprotection afforded by cardioplegia is significantly decreased and left ventricular end diastolic pressure (LVEDP) and infarct size are significantly increased in the aged female as compared to the aged male heart. Recently we have shown that the cardioprotection afforded by cardioplegia is modulated by RNA and protein synthesis and that the inhibition of these mechanisms significantly decreases cardioprotection.

While the mechanisms for reduced cardioprotection in the aged female remain to be fully elucidated, previous studies have shown that RNA transcription and translation are significantly decreased in the aged heart and that mRNA levels in the aged female are significantly decreased as compared to males under normal and pathological conditions.

Our data led us to hypothesize that the mechanisms modulating cardioprotection afforded by cardioplegia involves RNA and protein synthesis in the aged female and that these mechanisms directly contribute to increased morbidity and mortality in the aged female. To test this hypothesis we designed a series of studies to demonstrate that the cardioprotection afforded by cardioplegia is modulated by RNA and protein synthesis in the aged female.



**James D. McCully, PhD**

Associate Professor of Surgery

#### Lab Members

Akihiro Masuzawa, MD

Kendra M. Black, MS



**Sidney Levitsky, MD**

Cheever Professor of Surgery

James D. McCully, PhD

Sidney Levitsky, MD

For this study, we constructed rabbit heart cDNA libraries and isolated and 5' sequenced 8647 rabbit heart cDNAs and have identified and stored .3000 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 relative abundance levels of the multiple transcriptomic /proteomic products associated with global ischemia and with the cardioprotection afforded by cardioplegia.

Our published results (Physiol Genomics. 2009, 38:125-137; *Figure 1*) demonstrate that that cardioplegia partially ameliorates the effects of global ischemia and that cardioprotection is modulated by RNA and protein dependent mechanisms. Transcriptomic and proteomic enrichment analysis indicated that global ischemia down-regulates genes/proteins associated with the mitochondrion function and energy production and cofactor catabolism, generation of precursor metabolites of energy. In contrast, cardioplegia significantly increases differentially expressed genes/proteins associated with the mitochondrion and mitochondrial function and significantly up-regulates the biological processes of muscle contraction, involuntary muscle contraction, carboxylic acid and fatty acid catabolic processes, fatty acid beta-oxidation and fatty acid metabolic processes.

These preliminary studies provide the basis for the integration of the genomics and proteomics data to enhance biochemical understanding in terms of signaling pathways, biological processes, and compartmentalization and allow for the development of protocols leading to enhanced cardioprotection in the aged female through directed modulation of cardioprotection.

The laboratory focus in this area is to:

- Identify co-regulated RNA transcripts and functionally related gene groups and protein biomarkers to allow for enhanced cardioprotection in the aged female.
- Develop methodologies allowing for the beneficial therapeutic modulation of molecular biomarkers to enhance cardioprotection and ameliorate cardiac morbidity and mortality following cardiac surgery in the aged female.

### Autogeneic Mitochondrial Transplantation for Surgical Cardioprotection

Cell-based therapies for myocardial repair or regeneration have shown great potential; however, debate as to the efficacy of specific cell populations, the logistics of cell harvesting and expansion, the mechanisms of cell-based myocardial repair or regeneration remain to be elucidated. Most importantly difficulties over cell isolation, immune tolerance, cellular engraftment and integration remain. Therefore strategies to augment cell delivery, cell function/survival are crucial in permitting successful myocardial repair/regeneration through cellular therapy.

Recently, we demonstrated (*Figure 2*) that autogeneic mitochondria isolated from the patient's own body, from remote skeletal tissue unaffected by ischemia, and then directly injected into the ischemic zone of the myocardium during early reperfusion, significantly decreases myonecrosis (necrosis and apoptosis) and significantly enhances post-ischemic functional recovery. Our studies also demonstrated that transplanted mitochondria are viable, respiration competent, maintain membrane potential, are present in the myocardium for at least 21 days after injection and are distributed from the epi- to the sub-endocardium at significant distance from the site of injection.

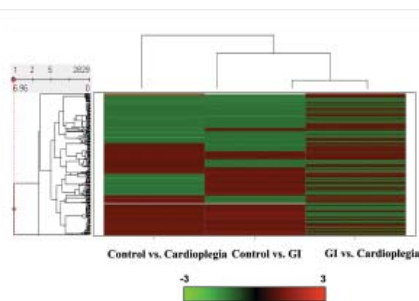


Figure 1

James D. McCully, PhD

Sidney Levitsky, MD

The isolation and preparation of autogeneic mitochondria from remote skeletal muscle is rapid and can be performed in less than 90 minutes—a time frame reasonable within the clinical interventions of both coronary artery bypass grafting (CABG) and percutaneous coronary intervention for coronary revascularization for ST segment elevation myocardial infarction (PCI-STEMI). Autogeneic mitochondrial transplantation provides immunological advantages for practical application without the use of anti-rejection drug therapy. The transplantation of autogenic mitochondria could be used either as an exclusive intervention to ameliorate myonecrosis and enhance myocardial function or could be used as a primary intervention prior to subsequent auto-, allo- or xeno-geneic cellular regenerative interventions.

The laboratory focus in this area is to:

- Demonstrate that autogeneic mitochondrial transplantation enhances myocardial protection in the blood perfused CABG and PCI-STEMI in situ heart model.
- Optimize mitochondrial storage time in syringe, storage temperature, needle bore size, rate of ejection, mitochondrial sub fraction, the concentration of mitochondria injected, the injection route/delivery technique, the number of injection sites and the location of injection sites for use in CABG and PCI-STEMI to enhance the amelioration of myonecrosis and enhance functional recovery.
- Identify specific mechanism(s) through which autogenic mitochondrial transplantation significantly enhances post-ischemic functional recovery and significantly decreases myonecrosis using biochemical /immunohistochemical, NMR and integrated transcriptomic and proteomic analysis.

### The Role of Collagen Type XI Alpha-1 on Aortic Aneurysm Formation

The laboratory is also involved in the analysis of the role of collagen type XI alpha-1 in human aortic aneurysm formation.

The major disease processes affecting the aorta are aortic aneurysms and dissections and these diseases represent a leading cause of morbidity and mortality worldwide, especially in ages above 65. Aortic aneurysms tend to expand asymptotically until a catastrophic event occurs such as aortic rupture or dissection.

The most common location for aneurysms is the infrarenal abdominal aorta, followed by the ascending thoracic aorta (*Figure 3*). The formation of thoracic aortic aneurysms (TAAs) and abdominal aortic aneurysms (AAAs) is a complex and chronic process that results from the interaction of genetic and environmental factors. The average age of patients with AAAs is 75 years and the affected men to women ratio as high as 6:1. In contrast, the average age of patients with TAA is 65 years, and men are at a slightly increased risk compared to women (1.7:1).

Despite the high incidence of AAAs and TAAs in the general population and the catastrophic consequences of rupture, relatively little is understood with respect to aortic aneurysm pathology and pathogenesis. Therefore, the elucidation of the molecular mechanism leading to aneurysm formation will provide valuable information and will help to develop accurate diagnostic tests in order to detect the disease in its early stages.

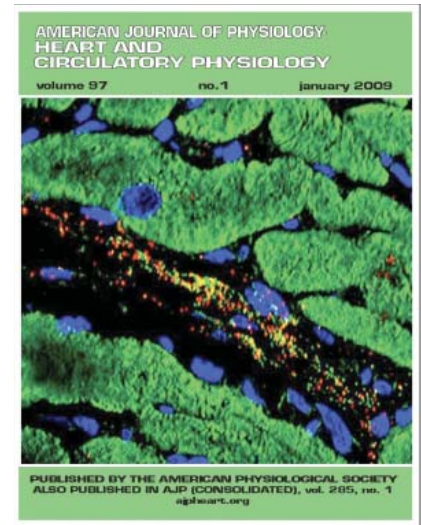


Figure 2

**James D. McCully, PhD**

**Sidney Levitsky, MD**

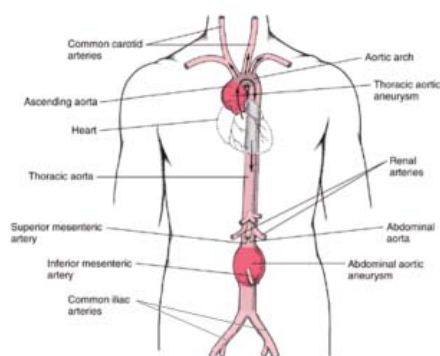


Figure 3

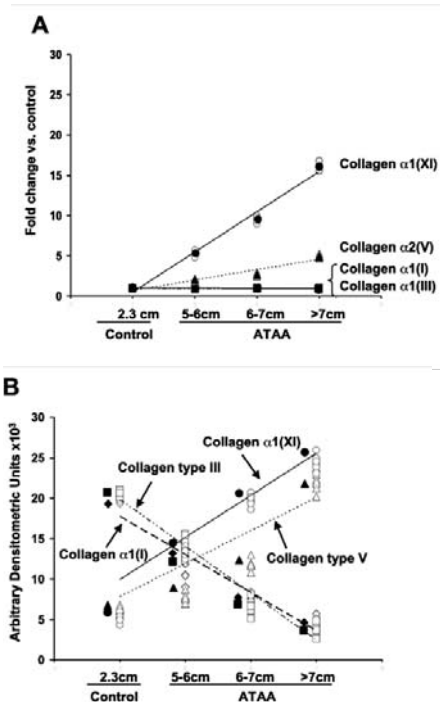


Figure 4

Recently (Ann Thorac Surg 2009; 88:506-513) we showed that ATAAs have greater disorganization of extracellular matrix constituents as compared to control and that ATAAs have an increase in collagen  $\alpha 1(XI)$  within regions of cystic medial degenerative lesions (Figure 4). We also showed, using real-time quantitative RT-PCR, that in ATAA tissue samples collagens type V and  $\alpha 1(XI)$  are significantly and linearly increased as compared to control ( $P < 0.001$ ). Western blot analysis also showed that collagens  $\alpha 1(XI)$  and V were significantly increased and were linearly correlated with the size of the aneurysm ( $P < 0.001$  for both). These results demonstrated that increased collagen  $\alpha 1(XI)$  and collagen V mRNA and protein levels are linearly correlated with the size of the aneurysm and provide a potential mechanism for the generation and progression of aneurysmal enlargement.

The laboratory focus in this area is to:

- Demonstrate the clinical and diagnostic utility of collagens  $\alpha 1(XI)$  and V alterations in the detection and analysis of ATAAs in humans

## Research Support

“Autogenic mitochondria: surgical cardioprotection”

NIH R01 HL103642

07/1/2010-06/30/2014

PI: James McCully, PhD

Collaborator: Sidney Levitsky, MD

## Accomplishments in the Past Year

### Research Progress

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

### Invited Presentations

“Protecting the heart: biomarker identification to organelle transplantation”  
Louisiana University School of Health Sciences, Department of Physiology

“The mitochondria in cardioprotection”  
University of Central Florida, Burnett School of Biomedical Sciences

“Surgical protection of the myocardium”  
Tufts Medical School, Molecular Medicine Series

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

Research Investigations (Submitted or in Press)

Black KM, Barnett RJ, Bhasin MK, Daly C, Dillon ST, Libermann TA, Levitsky S, McCully JD. Microarray and proteomic analysis of cardioprotection in the mature and aged male and female. Physiol Genomics 2011; in press.



**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

## Reviews, Chapters, Monographs, and Editorials

Levitsky S, McCully JD. Myocardial protection, chapter 66. In: Sellke FW, Swanson S, del Nido P, editors. Sabiston & Spencer surgery of the chest, 8th edition. Philadelphia, PA: 2011, p. 977-8.

McCully JD, Levitsky S. Intraoperative protection of the myocardium: effects of age and gender. In: Podesser BK, Chambers DJ, editors. New solutions for the heart—an update in advanced perioperative protection. New York, NY: Springer-Verlag/Wien; 2011. p. 73-92.

**Clinical Guidelines and Reports**

Sade RM; American Association for Thoracic Surgery Ethics Committee—Drs Robert M. Sade, Charleston, SC (Chair); Cary W. Akins, Boston, Mass; Thomas A. D’Amico, Durham, NC; James W. Jones, Houston, Tex; Martin McKneally, Toronto, Ontario, Canada; Keith Naunheim, St. Louis, Mo; and Andrew S. Wechsler, Philadelphia, Pa; and The Society of Thoracic Surgeons Standards and Ethics Committee—Drs Robert M. Sade, Charleston, SC (Chair); Charles R. Bridges, Philadelphia, Pa; David N. Campbell, Aurora, Colo; Kathleen N. Fenton, Memphis, Tenn; Mark K. Ferguson, Chicago, Ill; Steven W. Guyton, Seattle, Wash; John W. Hammon, Jr, Winston-Salem, NC; Leslie J. Kohman, Syracuse, NY; Jeffrey B. Kramer, Kansas City, Kan; **Sidney Levitsky**, Boston, Mass; Gordon F. Murray, Southport, NC; Mark B. Orringer, Ann Arbor, Mich; Ross M. Ungerleider, Portland, Ore; and Richard I. Whyte, Stanford, Calif. Standards for relations of cardiothoracic surgical organizations with industry. Ann Thorac Surg 2011; 92:3-8.

**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Black KM, Barnett R, Ablasser K, Bhasin MK, Daly C, Dillon SJ, Libermann TA, Masuzawa A, **Levitsky S, McCully JD**. Microarray and proteomic analysis of cardioprotection in the mature and aged male and female: role of the mitochondrion and differential mitochondrial pathways. The American Heart Association Scientific Sessions, November 13-15, 2011, Orlando, FL.

Masuzawa A, Black KM, Cowan DB, Ericsson M, **Levitsky S, McCully JD**. Autogeneic mitochondrial transplantation for myocardial protection in the ischemic in situ blood perfused heart. The Society of Thoracic Surgery 48th Annual Meeting, 2011.

**Technological and Other Scientific Innovations**

Deposit of non-redundant rabbit heart cDNA microarray data.  
NCBI Gene Expression Omnibus (GEO) for Mature and Aged Male and Female Heart:  
GSE30261  
GSM749632 - GSM749652  
<http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE30261>

Deposit of non-redundant rabbit heart cDNA microarray data.  
NCBI Gene Expression Omnibus (GEO) for Neonatal Right Heart and Neonatal Left Heart Hypertrophy:  
GSE30194  
GSM747418 - GSM747423  
<http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE30194>

**James D. McCully, PhD****Sidney Levitsky, MD**



## Division of Colon and Rectal Surgery Members

Deborah A. Nagle, MD

Samantha Koehler, BA  
Kristin Marcet  
Joseph Marinelli

Chief, Division of Colon and Rectal  
Surgery; Assistant Professor of Surgery  
Research Assistant  
Research Student  
Administrative Associate

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Kristin Messer, RN

Clinical Nurse

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Vitaliy Y. Poylin, MD

Instructor in Surgery

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Jeanne Quinn, NP

Nurse Practitioner

## Division of Colon and Rectal Surgery





## Research Focus

The Division of Colon and Rectal Surgery is a relatively new division in the Department of Surgery and is actively growing division members and research directions. Our primary focus is outcomes-oriented clinical research. We are collaborating in translational basic science research to understand the contribution of neuropeptides to the physiologic process of inflammatory bowel disease.

### Basic Research

Investigation into the role of neuropeptides in the pathophysiology of inflammatory bowel disease (IBD) is the initial translational science project of the division. Vitaliy Poylin, MD, was awarded the Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine for 2011-2012 to support this investigation. The Fellowship program was established to help junior faculty, women and men, at the point in their careers when they must teach, do research, compete for grants, publish, or practice (if a clinical faculty member) at the same time they may be assuming increased family or other responsibilities.

Neuropeptides have been studied extensively in the setting of inflammation in vascular disease. There has been some animal investigation in IBD, but few human studies. This effort to characterize the impact of neuropeptide changes in human IBD is one of the first investigations of this subject. We anticipate analyzing multiple control and affected specimens using an adapted assay for neuropeptide activity. We hope that this initial effort will promote further investigations that lead to an understanding of the mechanisms underlying IBD.

### Clinical Research

Our division comprises a cross-section of providers from nurses to nurse practitioners to physicians. Our clinical research focus is currently two-fold: minimally invasive surgery and optimizing clinical outcomes for colon and rectal surgery patients. In minimally invasive colon and rectal surgery, we are leaders in single incision laparoscopic colectomy, robotic colon and rectal surgery and minimally invasive transanal surgery. We have developed and matured a prospective database of colon resection patients at Beth Israel Deaconess Medical Center and this evolving structure supports our investigations. We have multiple open IRB investigations that involve surgical residents, nurses, nurse practitioners and physicians. We developed and refined a fast-track management program for colectomy patients that is the springboard for our investigations into quality and safety. We continue to initiate projects that meld the possibility of best patient care practices with optimal outcomes and educational experiences.

## Research Support

“A multicenter, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of intravenous (iv) ulimorelin administered post-operatively to accelerate recovery of gastrointestinal (gi) motility in subjects who have undergone partial bowel resection”

Tranzyme  
2011-2012

PI: Deborah Nagle, MD



**Deborah A. Nagle, MD**

Chief, Division of Colon and Rectal Surgery

Assistant Professor of Surgery



**Vitaliy Y. Poylin, MD**

Instructor in Surgery



**Jeanne Quinn, NP**



**Kristin Messer, RN**

**Deborah A. Nagle, MD**

**Vitaliy Y. Poylin, MD**

**Jeanne Quinn, NP**

**Kristin Messer, RN**

“Single incision laparoscopic colectomy”

2008-present

PI: Deborah Nagle, MD

Co-Investigators: Vitaliy Poylin, MD; Steven C. Tizio, MD

“Indications for surgical resection for small rectal carcinoid tumors”

2011-present

PI: Deborah Nagle, MD

Co-Investigators: Vitaliy Poylin, MD; Thomas Curran, MD

“Predictors of pathologic complete response to the neoadjuvant treatment for rectal cancer”

2011- present

PI: Michael Goldstein, MD

Co-investigators: Deborah Nagle, MD; Jeremy Warner, MD; Rebecca Miksad, MD

“Role of neuropeptides in inflammatory bowel disease and post operative ileus”

Eleanor and Miles Shore Fellowship, Harvard Medical School

08/2011-present

PI: Vitaliy Poylin, MD

Co-Investigators: Leena Pradhan, PhD; Frank Logerfo, MD; Deborah Nagle, MD

“Outcomes following open or minimally invasive colectomy with rapid recovery pathway”

07/2010- present

PI: Vitaliy Poylin, MD

Co-Investigators: Deborah Nagle, MD

“Effect of oral gabapentin on post operative pain after hemorrhoid surgery”

10/2011-9/2012

PI: Vitaliy Poylin, MD

Co-Investigators: Deborah Nagle, MD; Jeanne Quinn, NP; Kristin Messer, RN

#### **Applications Submitted and Pending Review/Funding**

“Role of neuropeptides in inflammatory bowel disease and post operative ileus”

Career Development Award

American Society of Colon and Rectal Surgeons

PI: Vitaliy Poylin, MD

“Anal fissures prospective database”

2012-

PI: Deborah Nagle, MD

Co-Investigators: Vitaliy Poylin; Kristin Messer, RN

“Pancreatic and colorectal surgery in the elderly: correlation between postoperative delirium and dementia”

PI: Vitaliy Poylin, MD

Co-Investigators: Tara Sotsky Kent, MD; Eliza Lee, MD

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### **Accomplishments in the Past Year**

#### **Individual Accomplishments**

Deborah Nagle, MD

- Served as Vice-Chair, Program Committee, American College of Surgeons

- Member of Public Relations Committee, American Society of Colon & Rectal Surgeons
- Member of Membership Committee, Society for Surgery of the Alimentary Tract
- Member of Robotics Committee, Beth Israel Deaconess Medical Center
- Member of Surgical Care Infection Prevention Committee, Beth Israel Deaconess Medical Center
- Course Director for Reduced Port Laparoscopic Surgery, American College of Surgeons Clinical Congress
- Served as Ad-Hoc reviewer for: *New England Journal of Medicine*, *Diseases of Colon & Rectum*, *Inflammatory Bowel Diseases*, *Journal of the American College of Surgeons*, *Journal of Gastrointestinal Surgery*, *Annals of Surgery*

Vitaliy Poylin, MD

- Awarded Eleanor and Miles Shore Scholars in Medicine Fellowship
- Served as Member of the Utilization Review Committee, Beth Israel Deaconess Medical Center
- Served as Member of the New Technologies Committee, American Society of Colon and Rectal Surgeons
- Served as Ad-Hoc Reviewer for *Gastroenterology Research and Practice*
- Served as Ad-Hoc Reviewer for *Disease of Colon and Rectum*

#### Invited Presentations

Deborah Nagle, MD

- “Neoadjuvant treatment of rectal cancer.” Cleveland Clinic Florida Colorectal Symposium. Fort Lauderdale, FL. February 2011.
- “Avoiding complications in laparoscopic surgery.” Cleveland Clinic Florida Colorectal Symposium. Fort Lauderdale, FL. February 2011.
- “Avoiding complications in laparoscopic surgery.” Tufts Medical Center, Grand Rounds. Boston, MA. June 2011.
- “Single incision colectomy.” American College of Surgeons Clinical Congress. San Francisco, CA. October 2011.
- “Avoiding complications in laparoscopic surgery.” Lawrence General Hospital, Grand Rounds. Lawrence, MA. November 2011.
- “Anorectal disease.” Mount Auburn Hospital, OB/gyn Grand Rounds. Cambridge, MA. November 2011.

Vitaly Poylin, MD

- “Diverticulitis: new approach to the old disease.” Lawrence General Hospital. Lawrence, MA. January 2011.

**Deborah A. Nagle, MD**

**Vitaliy Y. Poylin, MD**

**Jeanne Quinn, NP**

**Kristin Messer, RN**

**Deborah A. Nagle, MD**

**Vitaliy Y. Poylin, MD**

**Jeanne Quinn, NP**

**Kristin Messer, RN**

“Colorectal cancer screening.” Health Care Community Outreach. January 2011.

“Diverticulitis: new approach to the old disease.” St Luke’s Hospital. February 2011.

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## Teaching, Training, and Education

### Graduate School and Graduate Medical Courses

Deborah Nagle, MD

07/2011            Boston Update in Inflammatory Bowel Disease  
Beth Israel Deaconess Medical Center

Vitaliy Poylin, MD

10/2011            Controversies in GI Motility and Functional GI Disease:  
A Team Based Approach  
Harvard Medical School

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## Bibliography (January – December 2011)

### Peer Reviewed Publications in Print or Other Media

#### Research Investigations

Adair J, Gromski MA, **Nagle D**. Single-incision laparoscopic sigmoidectomy and rectopexy case series. Am J Surg 2011;202(2):243-5.

**Poylin V**, Serrot FJ, Madoff RD, Ikumuddin S, Mellgren A, Lowry AC, Melton GB. Obesity and bariatric surgery: a systematic review of associations with defecatory dysfunction. Colorectal Dis 2011;13(6):e92-103.

#### Research Investigations (Submitted or in Press)

Champagne BJ, Papaconstantinou HT, Parmar SS, **Nagle D**, Young-Fadok TM, Lee EC, Delaney CP. Single-incision versus standard multiport laparoscopic colectomy: a multicenter, case-controlled comparison. Ann Surg 2011; in press.

### Non-Peer Reviewed Publications in Print or Other Media

#### Reviews, Chapters, Monographs, and Editorials

Do NL, **Nagle D**, **Poylin VY**. Radiation proctitis: current strategies in management. Gastroenterol Res Pract 2011;2011:917941.

#### Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Nandivada P, **Poylin V**, **Nagle D**. Advances in the surgical management of inflammatory bowel disease. Curr Opin Gastroenterol 2011; in press.

#### Books, Monographs, and Text Books

**Poylin V**, **Nagle D**. Familial colorectal cancer type X. In: Ellis CN, editor. Inherited cancer syndromes, 2nd edition. Springer, New York, NY: 2011. p.127-34.

## Books, Monographs, and Text Books (Submitted or in Press)

Poylin V, Nagle D. Anorectal disorders. In: Goldfarb M, Gromski M, Hurst JM, Jones DB, editors. Pocket surgery: the Beth Israel Deaconess Medical Center handbook of surgery, 1st edition. Philadelphia: Lippincott, William & Wilkins: 2011; in press.

Tomassi M, Parry L, Nagle D. Colon disorders. In: Goldfarb M, Gromski M, Hurst JM, Jones DB, editors. Pocket surgery: the Beth Israel Deaconess Medical Center handbook of surgery, 1st edition. Philadelphia: Lippincott, William & Wilkins: 2011; in press.

**Abstracts Presented at Local, National, and International Meetings**

Gilmore D, Curran T, Nagle D, Poylin V. Early week surgery decreases hospital stay. Paper Session, American College of Surgeons. May 2011.

**Deborah A. Nagle, MD****Vitaliy Y. Poylin, MD****Jeanne Quinn, NP****Kristin Messer, RN**





## Division of General Surgery Members

**Mark P. Callery, MD, FACS**

Ammara Abbasi, MD  
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Brian Kalish  
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Satish Nadig, MD  
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Surgical Resident, Stanford  
HMS IV  
HMS IV  
Surgical Resident  
Surgical Resident  
Surgical Fellow  
Surgical Resident,  
Washington University  
Surgical Resident  
Clinical Research Fellow

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Anne McNamara, RN

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Clinical Research Nurse

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**Rosemary Duda, MD**

**Associate Professor of Surgery**

**Dana K. Fugelso, MD**

**Assistant Clinical Professor of Surgery**

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Andrea Calhoun, BS  
Molly Jay, BA  
Lena Liu, BS  
JiHye Seo, PhD  
Rachel St. Fort, BS  
Suzanne White, BS  
Yi Zheng, PhD

**Associate Professor of Surgery;  
Associate Vice-Chair for Research;  
Director, Microscopy and Histology  
Core Facilities**  
Confocal Core Supervisor  
Electron Microscopy Specialist  
Administrative Assistant  
Research Histotech  
Research Fellow in Surgery  
Administrative Supervisor  
Research Histotech Supervisor  
Confocal Specialist

## Division of General Surgery

**Per-Olof Hasselgren, MD, PhD**

Nima Alamdari, PhD  
Zaira Aversa, MD  
Estibaliz Castillero, PhD  
Aniket Gurav  
Sally Gwin

**George H.A. Clowes Professor of Surgery; Director of Endocrine Surgery; Vice-Chairman for Research**  
Instructor in Surgery; Lab Director  
Research Fellow  
Research Fellow  
Research Assistant  
Administrative Coordinator

**Mary Jane Houlihan, MD**

**Assistant Professor of Surgery**

**Daniel B. Jones, MD**

Maritza Avendano  
Linda Trainor, RN

Collaborators

Robert Andrews, MS  
Ben Schneider, MD  
Christina C. Wee, MD, MPH  
George Blackburn, MD, PhD  
Caroline Cao, PhD  
Ram Chuttani, MD  
Jonathan Critchlow, MD  
Suvranu De, Sc.D.

Stephanie Jones, MD  
Steven Loring, MD, PhD  
Steven D. Schwaitzberg, MD

Grace Zhou, PhD

MIS Fellows (BIDMC)

Abe Frech, MD  
Arpan Goel, MD  
Raul Gupta, MD  
Yusef Kudsi, MD

Simulation and Skills Center  
David Fobert

Mike McBride, RN  
Darren Tavernelli, RN

**Professor of Surgery; Director, Center for Minimally Invasive Surgery; Vice-Chair, Office of Technology & Simulation**  
Administrator  
Nurse Educator

Surgery, Section of MIS, BIDMC  
Surgery, Section of MIS, BIDMC  
Medicine, BIDMC  
Surgery, Section of Nutrition, BIDMC  
Tufts, Human Performance  
Medicine, BIDMC  
Surgery, Section of MIS, BIDMC  
Mechanical, Aerospace and Nuclear Engineering, Rensselaer Polytechnic Institute  
Anesthesiology, BIDMC  
Anesthesiology, BIDMC  
Surgery, Section of MIS, BIDMC (Cambridge Health Alliance)  
Tufts, Human Performance

Surgery, MIS Clinical Fellow  
Surgery, MIS Clinical Fellow  
Surgery, MIS Clinical Fellow  
Surgery, MIS Clinical Fellow

Simulation and Skills Center  
Coordinator  
SASC Staff  
SASC Staff

**Tara Kent, MD**

**Instructor in Surgery**

**Peter M. Mowschenson, MD**

**Assistant Clinical Professor of Surgery**

**Benjamin E. Schneider, MD**

**Instructor in Surgery**

Ranjna Sharma, MD	Instructor in Surgery
Nicholas E. Tawa, MD, PhD	Assistant Professor of Surgery
Michael D. Wertheimer, MD	Associate Professor of Surgery
Jin-Rong Zhou, PhD	Assistant Professor of Surgery
Hamid Abdolmaleky, MD	Research Fellow
Mohamad-Reza Eskandari, MD	Research Fellow
Yi Gong, PhD	Research Fellow



## Research Focus

The Section of Surgical Nutrition focuses on a wide range of scientific endeavors in both clinical research, led by George L. Blackburn, MD, PhD, and collaborators in the Center for the Study of Nutrition Medicine (CSNM), and basic bench research led by Jin-Rong Zhou, PhD, and collaborators in the Nutrition Metabolism laboratory (NML).

In the CSNM, active research projects include surgical metabolism and the study of protein sparing therapy in the prevention of starvation in patients with sepsis and trauma, prevalence of protein-calorie malnutrition in the hospitalized patient, the human metabolic response to ketosis without calorie restriction which lead me to my current focus on healthy living and the prevention and treatment of overweight and obesity and their related comorbidities. It includes the role of fatty acids and proteins on energy biochemistry, the nutrient effects of bioactive components on cellular and molecular function, and the metabolic correlates of weight loss following surgical treatment of obesity. Multidisciplinary collaborations and the dissemination of best practices in both surgical and nonsurgical interventions for the treatment of obesity and obesity-related diseases are ongoing priorities, as are several novel collaborations that bring together neurocognitive science and the science of exercise and eating behavior. The collaborators who participate in our scientific endeavors are as follows:

Daniel B. Jones, MD, MS, Surgery, Section of MIS, BIDMC  
Ben Schneider, MD, Surgery, Section of MIS, BIDMC  
Christina C. Wee, MD, MPH Medicine, BIDMC  
Christos Mantzoros MD Medicine, BIDMC  
Alvaro Pascual-Leone MD, PhD Neurology, BIDMC  
Miguel Alonso-Alonso MD, MSc Neurology, BIDMC  
Edward Horton, MD, Medicine, Joslin Diabetes Center  
David Nathan, MD, Massachusetts General Hospital

The focus of basic research in the NML is the study of the role that diet and nutrition may play in the prevention and treatment of certain types of cancer such as breast, prostate, pancreatic and bladder cancers, and to investigate the mechanisms of action of active dietary and nutritional components. Research strategies include application of an integrated research system to evaluate the efficacies of dietary/nutritional regimens, to elucidate underlying cellular, molecular and epigenetic mechanisms of actions, to identify novel anti-cancer components, and to define risk factors of cancer development and progression for designing effective nutritional regimens for cancer prevention.

Specific projects in each group are outlined below.

### Center for the Study of Nutrition Medicine

We're studying the neurocognitive correlates of diet and physical activity patterns in lean and obese subjects with the Berenson-Allen Center for Noninvasive Brain Stimulation. The work is progressing. This is leading-edge research—the first to demonstrate a link between variations in healthy eating, brain structure, and cognitive processes. Our findings suggest the need for novel and specific neurocognitive resources to translate nutrition advice into healthy dietary behaviors at the individual level.

To enhance the safety of weight loss surgery, we've developed and studied an achievable and effective progressive resistance training (PRT) exercise protocol for severely obese patients. A research symposium at Experimental



**George L. Blackburn, MD, PhD**

S. Daniel Abraham Associate  
Professor in Nutrition Medicine

Director, Center for the Study of  
Nutrition Medicine

Group Members, Center for the  
Study of Nutrition Medicine (CSNM)  
Barbara Ainsley, D.T.R.  
Hans Fisher, PhD  
Greta Magerowski  
Anne McNamara, RN



**Jin-Rong Zhou, PhD**

Associate Professor of Surgery

Lab Members, Nutrition Metabolism  
Laboratory (NML)  
Hamid Abdolmaleky, MD  
Mohamad-Reza Eskandari, MD  
Yi Gong, PhD

**George L. Blackburn, MD, PhD**

**Jin-Rong Zhou, PhD**

Biology 2010 (“The Science of Exercise for Obesity”) featured this unique application of exercise medicine. Novel studies in this area will target the relations between exercise-induced changes in brain structure, neurochemistry, and executive function; alterations that might affect dietary impulse control.

We have further collaborations with the Berenson-Allen Center for Noninvasive Brain Stimulation in the area of enhancement of the brain circuit of inhibitory control in obese patients undergoing laparoscopic adjusted gastric banding and brain fNIRS-based methodology for the assessment of inhibitory control over food in obesity.

### **Nutrition Metabolism Laboratory**

One important research contribution from the NML is the establishment and application of clinically relevant animal models of cancer progression and metastasis for nutritional intervention research. The models include orthotopic tumor animal models of prostate, breast, pancreatic and bladder cancers; an orthotopic prostate tumor model of androgen ablation-induced progression of androgen independency; an orthotopic breast tumor animal model of insufficient estrogen-induced tamoxifen-insensitive breast cancer; and genetically modified animal models of prostate, breast, and pancreatic cancers. These animal models provide important in vivo systems to evaluate the efficacy of dietary active components in the prevention and treatment of cancer and to elucidate the mechanisms of action.

By using these clinically relevant animal models, we continue to identify effective dietary/nutritional regimens for cancer prevention. We are the first group to demonstrate the synergistic combination effect between soybean and tea active components on preventing breast and prostate cancers. We are also among the first few research groups to propose metabolic syndrome as a potential etiological risk factor for the development and progression of several types of cancer, and in particular, maternal metabolic disorder status as a risk factor for cancer in offspring. We are actively conducting the related research. We are applying cell function-guided extraction, fractionation and purification strategies to identify active components from Chinese herbal medicines for the prevention and therapy of cancer. In addition, we are investigating the roles that nutritional components may play in targeting cancer stem cells. Our research findings can be directly translated into future clinical investigations. Identified novel etiological risk factors may provide potential novel targets for cancer chemoprevention and therapy.

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### **Research Support**

“Look AHEAD action for health in diabetes”

NIH/NIDDK, U01 DK057154

09/30/1999-09/30/2013

PI: David Nathan, MD

Subcontract PI: George L. Blackburn, MD, PhD

“Boston Nutrition Obesity Research Center (BNORC) – administrative core”

NIH/NIDDK, 2 P30DK46200

4/01/08-03/31/13

PI: Susan Fried, PhD

Associate Director: George L. Blackburn, MD, PhD

**George L. Blackburn, MD, PhD**

**Jin-Rong Zhou, PhD**

“Understanding how patients value bariatric surgery”

NIH/NIDDK, R01 DK073302-01A1

7/1/2007-6/30/2012

PI: Christina Wee, MD

Co-Investigator: George L. Blackburn, MD, PhD

“Lifestyle intervention study in adjuvant treatment of early breast cancer (LISA)”

Novartis Pharmaceuticals, DFCI Protocol 08-053

07/16/08-2014

Site PI: George Blackburn, MD, PhD

“Tanshinones as effective therapeutic agents for prostate cancer progression - Idea Award”

Department of Defense, PC073988

06/01/2008-05/31/2011

PI: Jin-Rong Zhou, PhD

“Tanshinones for prevention of bladder cancer progression”

NCI/NIH, 1R03 CA159348

07/01/2011-06/30/2013

PI: Jin-Rong Zhou, PhD

“Targeting prostate cancer stem cells to delay prostate cancer progression”

NCI/NIH, 1R21 CA153355-01A1

07/01/2011-06/30/2013

PI: Jin-Rong Zhou, PhD

“Effects of AglyMax on the prevention and treatment of obesity and prostate cancer”

Nichimo Co., Japan, Industry grant

03/01/2001-02/28/2012

PI: Jin-Rong Zhou, PhD

#### **Applications Submitted and Pending Review/Funding**

“Targeting Bmi-1 in prostate cancer stem cells by tanshinone I for the therapy of androgen-ablation-resistant prostate cancer”

Harvard Stem Cell Institute Seed Grant

PI: Jin-Rong Zhou, PhD

“Tanshinone I as a novel therapeutic agent against prostate cancer progression”

Creativity Award, Prostate Cancer Foundation

PI: Jin-Rong Zhou, PhD

“Targeting epigenetic regulation of HAP1 for breast cancer chemoprevention”

NCI/NIH, RO1 CA157544

PI: Jin-Rong Zhou, PhD



George L. Blackburn, MD, PhD

Jin-Rong Zhou, PhD



*BIDMC/Joslin Look AHEAD Team*

## Accomplishments in the Past Year

### Research Progress

Center for the Study of Nutrition Medicine

#### LookAHEAD

The Look AHEAD study has proceeded very smoothly. Intervention and assessment activities have been conducted according to the protocol and manual of operations. Specific accomplishments during this year include the following:

##### *Weight Loss Intervention*

Weight loss for participants assigned to the Lifestyle Intervention of the trial has been excellent. On average participants lost 8.6% at year 1; 4.7% at year four; and 4.5% at year seven. The intervention has been effective in all age, gender, and race/ethnicity groups. Across all clinics, 68% of participants had a >5% weight loss at year one and 47% had a > 5% weight loss at year seven. Fitness increased by 13.5% at year one and 2.4% at year four, relative to baseline. All centers have maintained the regular contact schedule with Lifestyle participants and conducted study wide campaigns.

##### *Diabetes Support and Education (DSE)*

The classes for DSE participants are considered optional and are used primarily for retention purposes. In year one, four classes were offered, with 1 class on diabetes required. In subsequent years, three optional classes were provided. Attendance averaged 2.9 classes per participant in year one, and 1.6, 1.4, and 1.2 classes in years two–four respectively. During months 49–60, attendance averaged .50 sessions per year; during months 61–72, it has averaged .41 sessions per year; during months 73–84 it has averaged .36 sessions per year.

##### *Participant Retention*

The primary outcome measures in Look AHEAD, related to CVD mortality and morbidity, are collected by phone interview at six-month intervals and as part of the annual clinic visit. Outcomes interviews (with deaths excluded) were completed by 94.6% of participants at 84 months. Although participants sometimes miss one of these contacts, they are often willing to complete the subsequent contact. Currently 5.1% of the total sample is considered “inactive” because they have missed their two most recent outcomes assessments (excluding those who are deceased). If the participants who did not transfer from the UCLA site are omitted from these calculations, only 4.2% of the remaining cohort is inactive.

##### *Outcome Visits*

The study has completed the majority of the year eight visits on our participants. Several new measures have been added to the eight-year visits (with an ARRA funding supplement). These include self-report measures of falls and physical activity.

*Safety/Adjudication*

The Safety Committee has continued to review all serious adverse events. The Adjudication Committee has increased its membership since the number of study outcomes has accelerated.

*Publications and Presentations*

To date, there have been 80 peer-reviewed presentations and 56 peer-reviewed manuscripts. Six other manuscripts are currently under review. The year four data have been published in *Archives of Internal Medicine* and several other year four papers are currently under review. The June 2011 meeting of the American Diabetes Association will include a full symposium devoted to presenting four year results from the Look AHEAD trial.

*Data Safety and Monitoring Board (DSMB) Review*

The DSMB met in May 2010 and reviewed all aspects of the study. The DSMB was impressed with the study progress to date and had no concerns. The subsequent meeting of the DSMB was cancelled due to issues related to conflict-of-interest for DSMB members. NIH is currently working to reconstitute the DSMB membership.

*ARRA Supplement*

The ARRA supplements ended in September of 2011 and the goals of the supplement were successfully accomplished. The year eight exam was expanded to include a questionnaire on falls and vitamin supplements and the questionnaire on physical activity. In addition, the ARRA supplements allowed sites to provide home visits as needed to collect outcomes data on this aging cohort, and to continue to offer intensive lifestyle programs.

To accomplish the aims of the ARRA Supplement, the Joslin Diabetes Center and Beth Israel Deaconess Medical Center increased the hours of the research assistant on the study to allow additional time to assist with collection of data. In addition, the effort of a lifestyle interventionist was increased to permit further efforts to maintain the outstanding weight losses seen to date in Look AHEAD.

*Planning for the Future*

Look AHEAD continues to devote significant time and effort to delivering the ongoing intervention and conducting assessments of all participants. In addition, the Look AHEAD study group has developed a genetics working group to consider future funding in this area. A grant application has been submitted to extend our genetic analyses and participants are currently being consented for a future GWAS study. The steering committee has also begun to actively plan for the close-out of the trial. A time-line of key activities has been developed and each committee is considering how best to complete assessment and intervention activities and to communicate the results to the participants and the scientific community. The study group is considering future grant applications that would allow for further follow-up of this well characterized cohort and/or provide novel approaches to long-term weight loss interventions.

George L. Blackburn, MD, PhD

Jin-Rong Zhou, PhD

George L. Blackburn, MD, PhD

Jin-Rong Zhou, PhD

The Joslin Diabetes Center/Beth Israel Deaconess Medical Center site: The study has continued to proceed very smoothly at The Joslin Diabetes Center/Beth Israel Deaconess Medical Center site. Our average weight loss for participants in the lifestyle arm is 8.3% at 1 year and 7.9% at 2 year, 6.4% at year 6 and 4.6% at year 8. We have been able to retain most participants in the trial and completed the outcomes assessment on 83% at year 7. Members of our group are participating in writing groups for manuscripts related to 4 year results.

#### **Boston Nutrition Obesity Research Center (BNORC) – Administrative Core**

The Boston Nutrition Obesity Research Center (BNORC), administratively based at Boston Medical Center (BMC), provides resources and support for studies in the area of nutrition and obesity. Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), the Center was established to explore the natural history of obesity, to investigate energy metabolism in health and disease, and to educate and train new investigators in these areas. Progress in the last year is as follows:

#### **Understanding How Patients Value Bariatric Surgery**

Christina Wee, MD, (PI) and the team studied over 650 patients seeking WLS and examined their expectations, motivations, and the lengths they are willing to undertake to undergo these procedures. We also explored the factors associated with unrealistic weight loss expectations and patients' willingness.

#### **Lifestyle Intervention Study in Adjuvant Treatment of Early Breast Cancer (LISA)**

The goal of this project is to determine if a telephone and mail-based individualized lifestyle intervention program focusing on weight management can improve outcomes in postmenopausal women with early stage breast cancer.

The LISA study has enrolled 313 patients overall. The patient count at BIDMC is currently 24. The funding for this study has been reduced and this study is closed for enrollment. All cancer clinical trials were suspended and audited by an independent auditor. We fulfilled all of the auditors' requirements and the suspension was lifted.

#### **Neurocognitive Correlates of Binge Eating Disorder**

This study, led by Miguel Alonso-Alonso, MD, sought to explore the neurocognitive correlates of binge eating disorder using brain stimulation to modulate activity in areas linked to inhibitory control. This study was a double-blinded placebo-controlled pilot study where a total of 16 subjects were randomized to receive ten days of 20 Hz repetitive transcranial magnetic stimulation (rTMS) over the right dorsolateral prefrontal cortex (DLPFC), left DLPFC, or sham stimulation. Participants were assessed using a combination of clinical (binge diaries, questionnaires on eating behavior, mood and obsessions), and experimental (a multi-choice buffet meal test, computer-based tasks and neuroimaging) measures.

### Effects of BMI on Transcranial Direct Current Stimulation (tDCS)

Currently, researchers do not design tDCS studies to account for BMI differences between subjects. However, the amount of cranial fat varies with BMI. tDCS is gaining popularity as a research tool for neuromodulation and understanding how the effects of tDCS differ due to subject variability is of critical importance to ensure consistent results as more studies are conducted in diverse subject pools.

Miguel Alonso-Alonso, MD, and team partnered with Dr. Marom Bikson at the neural engineering laboratory at the City College of New York to determine if BMI would affect the current distribution when tDCS using models of brains from subjects with varying BMIs. As of December 2011, the team had developed a repository of 5 MRIs to develop models from and was in the process of building the 3D models.

### Neuroband

This project will involve testing the effectiveness of tDCS in modulating activity in patients undergoing gastric banding to replicate the brain changes seen in patients who underwent roux-en-Y gastric bypass and attempt to improve the overall weight loss of these patients.

A brain fNIRS-based methodology for the assessment of inhibitory control over food in obesity The aim of the group under the leadership of Alonso-Alonso is to develop a novel methodology for its objective assessment via brain changes using functional near-infrared spectroscopy (fNIRS). Compared to other available techniques (i.e., fMRI), fNIRS is faster and more affordable, convenient, and comfortable for subjects, and thus, easier to incorporate into routine clinical practice.

### Neurocognitive Evaluation of a Dietary Intervention with Different Carbohydrate Sources (Fructose, Glucose, High Fructose Corn Syrup and Sucrose)

This is an ancillary study proposal related to the parent project being conducted at another facility. It is entitled: “A Comparison of the Metabolic Effects of Fructose, Glucose, High Fructose Corn Syrup and Sucrose at Normal Population Consumed Levels on Liver and Muscle Fatty Infiltration, Insulin Resistance, Glucose, Insulin, Leptin, Ghrelin, Postprandial Triglycerides, LDL Particle Size, Uric Acid and Appetite in Adults Aged 20-60 Years Old.”

### Testing Causality in the Association Between Exercise and Neurocognitive Gains: A Translational Research Study

We propose to conduct a multidisciplinary research study to investigate whether or not the grey matter volume changes that are observed after increased, intensive exercise are directly responsible for enhanced cognitive function. This investigation addresses a fundamental question that is of high relevance in the field, due to the vast range of implications for athletic training, cognitive development, neurological disorders, age-related cognitive decline, and obesity. To accomplish this, we will use transcranial magnetic stimulation (TMS) to disrupt brain activity during cognitive performance, both before and after an exercise intervention, and assess whether exercise can lead to increase resistance to disruption by TMS.

**George L. Blackburn, MD, PhD**

**Jin-Rong Zhou, PhD**

George L. Blackburn, MD, PhD

Jin-Rong Zhou, PhD

## The Relationship of Medications that Cause Hypoglycemia and Glucose Control to Weight Loss in Year-One of the Look AHEAD Study

We hypothesize that the use of insulin and sulfonylurea drugs and the degree of diabetic control associated with their use will be inversely proportional to weight gain and will give both greater hypoglycemia and weight gain than other diabetic drugs being tracked in the Look AHEAD database during the first year of the trial in the intensive lifestyle intervention.

## Nutrition Metabolism Laboratory

### Tanshinones as Effective Therapeutic Agents for Prostate Cancer Progression

The goals of this study were to define the therapeutic efficacy of tanshinone I (T1) and tanshinone IIA (T2A), alone and in combinations on prostate cancer progression in clinically relevant animal models of prostate tumor progression, and to identify the cellular and molecular biomarkers associated with therapeutic activities of T1 and T2A to gain insights into possible mechanisms of action. In 2011, we conducted the LNCaP tumor animal study to determine the effects of T1 and T2A, alone and in combinations on the growth of androgen-sensitive prostate tumors. Since cryptotanshinone (CT) is another major tanshinone in Danshen, we also evaluated its effect on the growth inhibition of LNCaP tumors so that the anti-LNCaP activities of all three major tanshinones could be compared simultaneously. In brief, male SCID mice were fed the AIN-93M diet for one week of adaptation before being inoculated orthotopically with  $2 \times 10^6$  of LNCaP cells. Mice were randomly assigned into one of the following experimental groups ( $n=12$ /group) and treated with the assigned experimental treatments: (1) Control (100 l corn oil as vehicle), (2)-(3) T1 in corn oil at 100mg/kg BW and 200 mg/kg BW by gavage daily, (4)-(5) T2A in corn oil at 100mg/kg BW and 200 mg/kg BW by gavage daily, (6)-(7) CT in corn oil at 100mg/kg BW and 200 mg/kg BW by gavage daily, (8)-(9) T1/T2A combinations at 100/100 and 200/200 mg/kg BW. Food intake and body weight were measured weekly. At the end of the experiments (12 weeks after cell inoculation), the mice were sacrificed; primary tumors were excised and weighed. A tumor slice from each primary tumor tissue was carefully dissected and fixed in 10% buffer-neutralized formalin, paraffin-embedded, and sectioned at 4 m thickness for immunohistochemistry. An aliquot of each tumor sample was used to extract total RNA for real-time PCR. The results are shown as follows. We found that:

- Both T1 and CT showed dose-dependent effects on inhibiting the growth of LNCaP tumors, but to our surprise, T2A did not show significant effect.
- Interestingly, CT also showed significant activity. Our in vitro studies showed CT had the least potent activity against prostate cancer cell growth with IC50s around 25-50 M, compared with T1 or T2A. This increased bioactivity of CT may be in part due to its higher bioavailability since it was reported that CT had higher bioavailability than other tanshinones.
- The combination of T1 and T2A did not show further enhanced activity in inhibiting the LNCaP tumor growth, suggesting that the combination may not be synergistic or additive.
- Both T1 and T2A did not show significant effects on inhibiting LN metastasis, but CT inhibited LN metastasis in a dose-dependent manner and the inhibitory effect at 200mg/kg BW was significant. This finding suggests that CT may have potent anti-growth and anti-metastasis activities against LNCaP tumor in vivo.

- The treatments did not significantly alter food intake or body weight, confirming that tanshinones at the efficacious doses do not have significant side effects.

### Administrative Accomplishments

George L. Blackburn, MD, PhD

- Attended the BIDMC MIS\_WLS Research Group, which consisted of monthly meetings with staff and fellows focused on research projects.
- Attended the BIDMC Dietetic Intern Advisory board, which meets semi-annually to review internship objectives and to ensure they are being met.

### Individual Accomplishments

George L. Blackburn, MD, PhD

- Planned and was the co-director of a very well attended symposium jointly sponsored by Harvard Medical School Division of Nutrition and BNORC entitled “Your Brain Can Help You Eat Better” ([www.nutrition.med.harvard.edu/education/edu\\_nut\\_symp13\\_program.html](http://www.nutrition.med.harvard.edu/education/edu_nut_symp13_program.html))
- Completed my 25th year as course director of Harvard Medical School Department of Continuing Education post-graduate course entitled “25th annual International Conference on Practical Approaches to the Treatment of Obesity.”
- Received the Kenneth W. Warren MD lectureship award from New England Baptist Hospital.
- For Weight of the Nation (WON), was invited to be a member of Steering Committee, Chair of Medical Care Committee, and a member of Awards Committee. The Centers for Disease Control and Prevention are planning a WON national conference on obesity prevention and control in Washington, DC on May 7-9, 2012.
- Food Research and Action Center, Washington, D.C. Board of Directors
- Certification of Obesity Medicine Physicians (COMP) ASN Representative
- Stop Obesity Alliance, Steering Committee Member
- The Obesity Society, Member Advocacy Committee
- The Obesity Society, Member Development Committee (Grants Subcommittee)
- Invited to be a grant reviewer for the NIH Loan Repayment program and for Harvard Catalyst.
- Served as a reviewer for the: Annals of Internal Medicine, American Journal of Clinical Nutrition, American Journal of Lifestyle Medicine, American Journal of Preventative Medicine, Archives of Internal Medicine, Diabetes Care (on Editorial Board), Journal of Clinical Oncology, Metabolism, New England Journal of Medicine, and Obesity

George L. Blackburn, MD, PhD

Jin-Rong Zhou, PhD



George L. Blackburn, MD, PhD

Jin-Rong Zhou, PhD

Jin-Rong Zhou, PhD

- Member of the Editorial Board for the *Journal of Single Cell Genomics & Proteomics* and the *Journal of Health Sciences*
- Field Editor for the journal *Functional Foods in Health and Disease*
- Advisory Board Member for Webmed Central
- Served as a reviewer for grant applications submitted to the USDA Agriculture and Food Research Initiative (AFRI) Competitive Grants Program, the James & Esther King Biomedical Research Program, the Bankhead-Coley Cancer Research Program Review Panel, Florida Department of Public Health, the Singapore National Medical Research Council Research Grant Panel, the Singapore National Medical Research Council, the Prevention, Control and Population Sciences P01 Review Panel, NCI/NIH, and the Cancer Therapeutics SEP (ZRG1 OTC-X(90)) Study Section, NIH
- Reviewer for the *Chemical Research in Toxicology*, *International Journal of Cancer*, *Journal of Nutritional Biochemistry*, and *Molecules*

#### Invited Presentations

George L. Blackburn, MD, PhD

“The Lifestyle Change Imperative and Underlying Neurocognitive Mechanisms.” Centers for Obesity Research and Education CORE, Obesity Treatment and Prevention CME. San Francisco, CA. May 6, 2011.

“Metabolic Considerations in the Management of Surgical Patients.” New England Baptist Hospital, Kenneth W. Warren, MD Lecture. Boston, MA. June 15, 2011.

“Introduction to 25th Annual International Conference on Practical Approaches to the Treatment of Obesity.” Harvard Medical School CME. Cambridge, MA. June 16, 2011.

“The Lifestyle Change Imperative and Underlying Neurocognitive Mechanisms.” Harvard Medical School CME, 25th Annual International Conference on Practical Approaches to the Treatment of Obesity. Cambridge, MA. June 16, 2011.

“The Lifestyle Change Imperative and Underlying Neurocognitive Mechanisms.” 43rd Annual Scientific Meeting of the Hungarian Medical Association of America. Sarasota, FL. October 24, 2011.

Jin-Rong Zhou, PhD

“Pharmacogenomic Approaches to Identify Natural Compounds for Cancer Prevention.” Plants for Human Health Institute, Department of Food Science. North Carolina State University.

“Identification of Bioactive Dietary and Natural Components for Cancer Prevention.” Department of Food and Nutrition, Purdue University. Richmond, IN.



## Teaching, Training, and Education

George L. Blackburn, MD, PhD

Graduate School and Graduate Medical Courses

- Continued to be a tutor in the Introduction to Clinical Nutrition Fundamentals of Medicine IN757.NUT, HMS

CME Courses

- Director of the 25th Annual International Conference on Practical Approaches to the Treatment of Obesity” Harvard Medical School CME, Cambridge, MA. June 16-18, 2011.

Other Teaching Contributions

- Co-Director and organizer of the 13th Annual Postgraduate Nutrition Symposium Harvard Medical School Division of Nutrition/Harvard School of Public Health/Boston university School of Medicine “Your Brain Can Help You Eat Better: Do you control your brain or does your brain control you?” July 13-14, 2011 Boston, MA

## Bibliography (January–December 2011)

### Peer-Reviewed Publications in Print or Other Media

Research Investigations

Aronis KN, Joseph RJ, **Blackburn GL**, Mantzoros C. Trans-Fatty acids, insulin resistance/diabetes, and cardiovascular disease risk: should policy decisions be based on observational cohort studies, or should we be waiting for results from randomized placebo-controlled trials? *Metabolism* 2011;60(7):901-5.

Gong Y, Li Y, Lu Y, Li L, Abdolmaleky H, **Blackburn GL** Zhou JR. Bioactive tanshinones in salvia miltiorrhiza inhibit the growth of prostate cancer cells in vitro and in mice. *Int J Cancer* 2011;129(5):1042-52.

Imayama I, Alfano CM, Kong A, Foster-Schubert KE, Bain CE, Xiao L, Duggan C, Wang C, Campbell KL, **Blackburn GL**, McTiernan A. Dietary weight loss and exercise interventions effects on quality of life in overweight/obese postmenopausal women: a randomized controlled trial. *Int J Behav Nutr Phys Act.* 2011;8(1):118.

Joseph RJ, Alonso-Alonso M, Bond DS, Pascual-Leone A, **Blackburn GL**. The neurocognitive connection between physical activity and eating behaviour. *Obes Rev* 2011;12(10):800-12.

Mason C, Foster-Schubert KE, Imayama I, Kong A, Xiao L, Bain C, Campbell KL, Wang CY, Duggan CR, Ulrich CM, Alfano CM, **Blackburn GL**, McTiernan A. Dietary weight loss and exercise effects on insulin resistance in postmenopausal women. *Am J Prev Med* 2011;41(4):366-75.

Mason C, Xiao L, Imayama I, Duggan CR, Bain C, Foster-Schubert KE, Kong A, Campbell KL, Wang CY, Neuhouser ML, Li L, W Jeffery R, Robien K, Alfano CM, **Blackburn GL**, McTiernan A. Effects of weight loss on serum vitamin D in postmenopausal women. *Am J Clin Nutr* 2011;94(1):95-103.

George L. Blackburn, MD, PhD

Jin-Rong Zhou, PhD

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Papageorgis P, Cheng K, Ozturk S, Gong Y, Lambert AW, Abdolmaleky HM, **Zhou JR**, Thiagalingam S. Smad4 inactivation promotes malignancy and drug resistance of colon cancer. *Cancer Res* 2011;71(3):998-1008.

Zerbini LF, de Vasconcellos JF, Czibere A, Wang Y, Paccez JD, Gu X, **Zhou J**, Libermann TA. JunD-mediated repression of GADD45 $\alpha$  and  $\gamma$  regulates escape from cell death in prostate cancer. *Cell Cycle* 2011;10(15):2583-91.

Zerbini LF, Tamura RE, Correa RG, Czibere A, Cordeiro J, Bhasin M, Simabuco FM, Wang Y, Gu X, Li L, Sarkar D, **Zhou JR**, Fisher PB, Libermann TA. Combinatorial effect of non-steroidal anti-inflammatory drugs and NF- $\kappa$ B inhibitors in ovarian cancer therapy. *PLoS One* 2011;6(9):24285.

Research Investigations (Submitted or in Press)

Foster-Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, Kong A, Bain CE, Wang CY, **Blackburn GL**, McTiernan A. Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. *Obesity* 2011; in press.

#### **Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

**Blackburn GL**. Medicalizing obesity: individual, economic, and medical consequences. *Virtual Mentor* 2011;13:890-5. <http://virtualmentortest.ama-assn.org/2011/12/pfor1-1112.html>. Accessed December 2, 2011.

**Blackburn GL**. Metabolic considerations in management of surgical patients. In: Dudrick SJ, Sanchez JA, editors. *Nutrition and metabolism of the surgical patient, part I*. Elsevier, Inc; Surg Clin N AM 91 2011;467- 80.

Kang KH, **Blackburn GL**. Clinical assessment of intestinal failure in adults. In: *Clinical management of intestinal failure*. Duggan CP, Gura KM, Jaksic T, editors. CRC Press 2011;63-73.

Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Williams ME, **Blackburn GL**. Nutritional and metabolic management of obesity and the metabolic syndrome in the chronic kidney disease patient. In: Kopple JD, Massry SG, editors. *Nutritional management of renal disease*. Williams and Wilkins, Baltimore 2011; in press

#### **Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Abbenhardt C, Duggan CR, Foster-Schubert K, Xiao L, Bain C, Mason CE, Campbell K, Kong A, McTiernan A, Potter J, **Blackburn GL**, Alfano C. Effects of individual and Combined diet and exercise intervention in postmenopausal women on adiponectin and Leptin. AACR 10th Annual International Conference on Frontiers in Cancer Prevention Research, October 24, 2011 Boston, MA.

Eskandari M, Abdolmaleky H, Gong Y, **Zhou JR**. Targeting Huntingtin network genes for prevention of breast cancer. *Era of Hope* 2011, August 2-6, 2011, Orlando, FL.

Eskandari MR, Abdolmaleky HM, Gong Y, Li L, **Zhou JR**. Huntingtin associated protein-1 activation for breast cancer therapy. Joint Symposium of the Dana-Farber/Harvard Cancer Center Programs in Breast and Gynecologic Cancer, March 25, 2011, Boston, MA

Gong Y, Abdolmaleky H, Li H, **Zhou JR**. Bioactive tanshinones in Salvia Miltiorrhiza inhibit the growth of breast cancer cells by targeting aurora A and survivin. Joint Symposium of the Dana-Farber/Harvard Cancer Center Programs in Breast and Gynecologic Cancer, March 25, 2011, Boston, MA

Gong Y, Abdolmaleky H, Li H, **Zhou JR**. Synergistic combination between resveratrol and tanshinone I for effective prevention of pancreatic cancer. AACR 10th Annual International Conference on Frontiers in Cancer Prevention Research, October 24, 2011 Boston, MA.

**Zhou JR**, Gong Y, Li L, Li Y, Abdolmaleky H. Bioactive tanshinones as effective therapeutic and preventive agents for prostate cancer progression. 2011 Innovative Minds in Prostate Cancer Today (IMPACT) Conference, March 9-12, 2011, Orlando, FL.

**George L. Blackburn, MD, PhD**

**Jin-Rong Zhou, PhD**



## Research Focus

Our work focuses on outcomes research in high-acuity pancreaticobiliary surgery. Fueled by a robust clinical practice that focuses on treatment of pancreatic malignancies, cystic lesions, pancreatitis, and complex biliary conditions in a multidisciplinary setting, we perform over 200 major pancreaticobiliary operations per annum. A prospective database of over 4000 operations and 750 pancreatic resections 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 for diseases of the pancreas and biliary tree. 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. We are currently building a Quality Scorecard for Pancreatic Surgery that reflects the Institute of Medicine HealthCare Quality Domains.

## Accomplishments in the Past Year

### Research Progress

One of our primary endeavors has been in caring for patients with incidentally identified, asymptomatic pancreatic lesions. This clinical focus by our group has led to a landmark publication that describes the predominance of malignant and premalignant pathologies encountered in this scenario. Other work has contributed to a better understanding of managing cystic lesions of the pancreas – particularly Intraductal Papillary Mucinous Neoplasm (IPMN). We continue to establish parameters of recovery following pancreatic resections. We have defined benchmark outcomes for pancreatic resections in the elderly cohort (> 75 y.o.) featuring our interdisciplinary collaboration with gerontology consultation.

We have also described the importance of optimal operative performance, including minimizing blood loss, as well as the negative influence of preoperative hospitalization for patients requiring pancreatic resection. We are also very interested in the emerging concept of “borderline resectable” pancreatic tumors, and have illustrated the predictive capacity of CT angiograms for this problem. In addition, through collaboration with our Radiology and Oncology consultants, we defined the value of Cyberknife radiotherapy for pancreatic cancer, both on locally advanced disease, as well as the situation of positive margins following resection.

Other investigations have focused on technical approaches to pancreatic surgery, and we have contributed to two Consensus Conference monographs on pancreatic cancer surgery. We are deepening our investigations relating to quality metrics in high-acuity pancreatic surgery including mortality and readmission rates, offering compelling root-cause analyses of each. We remain active in the leadership of all major national and international specialty societies in HPB and GI Surgery.



**Mark P. Callery, MD, FACS**

Chief, Division of General Surgery;  
Associate Professor of Surgery

### Group Members

Jennifer Erdrich, MD  
Satish Nadig, MD  
Wande Pratt, MD  
Teviah Sachs, MD  
Stephen Gondek, MD  
Laura Mazer, MD  
Ammara Abbasi, MD  
David Odell, MD  
Norberto Sanchez, MD  
Charity Glass  
Brian Kalish



**Tara S. Kent, MD**

Instructor in Surgery



**Charles M. Vollmer, Jr., MD, FACS**

Assistant Professor of Surgery;  
Instructor in Surgery

*(Left BIDMC June 2011)*

**Mark P. Callery, MD, FACS**

**Tara S. Kent, MD**

**Charles M. Vollmer, Jr. MD, FACS**

### **Individual Accomplishments**

Mark P. Callery, MD, FACS

- Served as Past-President of the AHPBA for 2010-11
- Elected Secretary/Executive Council, Boston Surgical Society, 2010-present
- Chair, Department of Surgery Leadership Council
- Served as Program Committee Chairman, and on Board of Trustees, Society for Surgery of the Alimentary Tract (SSAT), 2006-2011
- Chair, SSAT Members Needs Assessment Task Force 2011
- Served on Board of Governors, SAGES, 2006-2010
- Serves on Executive Council for the IHPBA (International Hepato-Pancreato-Biliary Association)
- 2010-11 Castle-Connelly USA and Boston Magazine Top Doctor
- Several Invited National and International Lectures
- Serves as Associate Editor for HPB
- Editorial Board Member: *Journal of Gastrointestinal Surgery*

Charles M. Vollmer, Jr, MD, FACS

- Served as Chairman of the Membership Committee and member of the Executive Council for the AHPBA
- Serves as 2012 Program Committee and Annual Meeting Chair for AHPBA
- Serves as parallel AHPBA Program Chair for the 2012 IHPBA Congress
- Served on Program Committee (Pancreatic Subcommittee) for the SSAT
- Elected as new member of the Society of University Surgeons, Surgical Biology Club II, and New England Surgical Society
- Several Invited National and International Lectures
- Editorial Board Member: *HPB*

Tara S. Kent, MD, FACS

- 2011 Recipient HMSOFA Eleanor and Miles Shore 50th Anniversary Fellowship for Scholars in Medicine
- Elected Member of Boston Surgical Society, Association for Surgical Education
- Active Committee assignments w/ AHPBA and SSAT
- 2010 Recipient AHPBA Travel Grant Award
- Department of Surgery Research Fund-Satisfaction and Quality of Life after Pancreatectomy
- Several Invited Regional and National Lectures

- New Ad-Hoc peer-Reviewer: *Journal of the Pancreas (JOP)*, *Annals of Surgery*, *HPB*

### Selected Invited Presentations

Mark P. Callery MD, FACS

“Preventing Bile Duct Injuries Including Dealing with a Difficult Gallbladder.” EHPBA World Congress, Postgraduate Course, Cape Town, South Africa.

“Molecular Diagnosis of Pancreatic Cancer.” EHPBA World Congress, New Technologies Symposium, Keynote Lecture, Cape Town, South Africa.

“Some Things to Consider.” John Warren Surgical Society, Annual Keynote Speaker. Boston, MA.

Charles M. Vollmer, Jr, MD, FACS

“Chemotherapy for Pancreatic Malignancies - Pre or Postoperative?” Society of Surgical Oncology, Annual Scientific Meeting. San Antonio, TX.

“Laparoscopic Pancreatectomy Will NOT Become the Standard of Care.”, American Hepato-Pancreato-Biliary Association (AHPBA) Annual Congress. Miami Beach, FL.

“Surgical Resection of Pancreatic Head Cancer – Review and Interpretation of the Literature.” Pancreas Cancer: Surgical Treatment 2011. Rome, Italy.

“Show Me the Way: Finding the Duct in Surgically Altered Anatomy.” Digestive Disease Week (DDW), ASGE/SSAT Combined Clinical Symposium. Chicago, IL.

“Mortality in for Pancreatic Resection.” Surgical Biology Club II, San Francisco, CA.

Tara S. Kent, MD, FACS

“Autoimmune Pancreatitis.” American Hepato-Pancreato-Biliary Association (AHPBA) Annual Congress. Miami Beach, FL.

“Women in Surgery.” John Warren Surgical Society. Boston, MA.

### Bibliography (January – December 2011)

#### Peer-Reviewed Publications in Print or Other Media

##### Research Investigations

Kent TS, Sachs TE, Callery MP, Vollmer CM. Readmission after major pancreatic resection: a necessary evil? *J Am Coll Surg* 2011;213(4):515-23.

Kent TS, Sachs TE, Sanchez N, Vollmer CM Jr, Callery MP. Conditional survival in pancreatic cancer: better than expected. *HPB (Oxford)* 2011;13(12):876-80.

Mark P. Callery, MD, FACS

Tara S. Kent, MD

Charles M. Vollmer, Jr. MD, FACS



**Mark P. Callery, MD, FACS**

**Tara S. Kent, MD**

**Charles M. Vollmer, Jr. MD, FACS**

Mahadevan A, Miksad R, Goldstein M, Sullivan R, Bullock A, Buchbinder E, Pleskow D, Sawhney M, **Kent T, Vollmer CM, Callery MP**. Induction gemcitabine and stereotactic body radiotherapy (GEM-SBRT-GEM) for locally advanced non-metastatic pancreas cancer. *Int J Radiat Oncol Biol Phys* 2011;81(4):e615-22.

**Vollmer CM, Sanchez NJ, Christein JD, Kent TS, Callery MP**. A root-cause analysis of mortality following major pancreatectomy. *J Gastrointest Surg* 2011;16(1):89-103.

Research Investigations (Submitted or in Press)

**Kent TS, Gautum S, Callery MP, Vollmer CM**. The burden of infection for elective pancreatic resections. *Surgery* 2011; in press

Nadig S, Goldsmith J, Pedrosa I, **Callery MP, Vollmer CM**. Clinical implications of non-neoplastic mucinous cysts of the pancreas. *Pancreas* 2011; in press.

Nimhuircheartaigh J, Sun M, **Callery MP, Sanchez N, Siewert B, Vollmer CM, Kane R**. Value of intra-operative ultrasound for the performance of pancreatic surgery: a multidisciplinary assessment. *Radiology* 2011; in press.

Sachs TE, **Kent TS, Pratt WB, Callery MP, Vollmer CM**. The pancreaticojejunal anastomotic stent: friend or foe? *Surgery* 2011; in press.

#### **Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Books/Textbooks for the Medical or Scientific Community

**Callery MP, Sanchez N, Stewart L**. Cholecystolithiasis and stones in the common bile duct: which approach, when? In: Jarnagin WR et al, editors. *Blumgart's surgery of the liver, pancreas, and biliary tract*, 5th ed. Philadelphia: Elsevier; 2011.

**Callery MP, Stewart L**. Open cholecystectomy with choledochotomy and common bile duct exploration. In: Lillemoe KD, Jarnagin WR, editors. *Master techniques in hepatobiliary and pancreatic surgery*. Wolters Kluwer; 2011.

Nadag S, **Vollmer CM**. Post-cholecystectomy problems. In: Jarnigan W, editor. *Blumgart's surgery of the liver, biliary tract, and pancreas*, 5th ed. Philadelphia: Elsevier; 2011.

#### **Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

**Callery MP, Pratt WB, Sanchez N, Kent TS, Chaikof E, Vollmer CM**. A Prospectively Validated Risk Score Model for Pancreatic Fistula after Pancreaticoduodenectomy. Oral presentation. American College of Surgeons' 97th Annual Meeting; San Francisco, CA October 2011.

**Kent TS, Sachs T, Sanchez N, Vollmer CM, Callery MP**. Conditional Survival for Resected Pancreatic Adenocarcinoma: Better Than Expected. Oral presentation. America's Hepato-Pancreato-Biliary Association Annual Congress. Miami, FL March 11-13 2011.

Sanchez N, Gondek S, **Kent TS, Callery MP, Vollmer CM**. Marked Variance Between Estimated and Calculated Blood Loss for Major Pancreatic Resections. Oral Presentation. America's Hepato-Pancreato-Biliary Association Annual Congress. Miami, FL March 11-13 2011.

**Vollmer CM**, Sanchez NJ, **Kent TS, Callery MP**. A Root-Cause Analysis of Mortality Following Major Pancreatectomy. Plenary Oral Presentation. SSAT 52nd Annual meeting and Pancreas Club meeting for Digestive Disease Week. Chicago, IL. May 2011.

**Mark P. Callery, MD, FACS**

**Charles M. Vollmer, Jr. MD, FACS**

**Tara S. Kent, MD**



## Research Focus

My research focus is in clinical research, with the following ongoing projects:

### 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 3,200 adult women who reside in Accra.

### 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. The study expands to other regions of Ghana for comparative analysis.

We also have two additional clinical studies underway. First is "Knowledge, attitude, and practice: Self-breast examinations as a screening tool in resource poor communities." The second is the Clinical Scholarship Program (in collaboration with Ranjna Sharma, MD, and Ali Links, MD). This study examines atypical hyperplasia of the breast and the role of excision following lesion removal by core biopsy.

## Research Accomplishments

### Individual Accomplishments

- Fulbright Specialist Award
- Treasurer, Board of Directors, Women's Empowerment Network, a not-for-profit organization
- Medical and surgical volunteer - Ghana, Haiti, Nicaragua
- Developing breast cancer program in Matagalpa, Nicaragua
- Forming collaborative research relationship with Cape Coast Hospital, Ghana

### Invited Presentations

"Surgical Service and Public Health." Beth Israel Deaconess Medical Center, Global Health Forum. Boston, MA.

"The Health of the Women in Accra, Ghana: A Double Burden of Disease." Central Regional Hospital. Cape Coast, Ghana.

"An Added Burden of Disease: Cancer in the Caribbean and Central America." Society of Surgical Oncology Annual Meeting. San Antonio, TX.



**Rosemary B. Duda,  
MD, MPH**

Associate Professor of Surgery

## Teaching, Training, and Education

### Other Teaching Contributions

International teaching of professional staff, residents in training, medical students

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## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Bhushan D, Duda RB. Teaching rural women in Nicaragua the principles of breast health. J Cancer Educ 2011;26(3):560-5.

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 2011;26(3):299-314.

## Research Focus

The focus of my laboratory is to understand how *Helicobacter pylori* infection facilitates gastric atrophy, which is an important initiator of cancer development along the gastric cancer cascade (Figure 1). Gastric cancer is the third most common cancer and the second most common cause of cancer deaths worldwide. Despite the global prominence of *H. pylori* infection and gastric cancer, little is known about how this infection-mediated cancer develops.

Gastric atrophy occurs when mature epithelial cells, namely parietal and chief cells, die rapidly during infection. We thus approach our work by studying mechanisms that regulate cell survival and death in gastric epithelial cells. In particular, we are interested in the role of inflammation in parietal and chief cell death that is caused, at least in part, by mucosal barrier dysfunction at tight junctions. Tight junction dysfunction allows the permeation of luminal contents across the mucosa, which is particularly toxic to epithelial cells in the stomach in addition to being essential for perpetuating inflammation. We recently found that pro-inflammatory cytokines increase mucosal permeability by transcriptionally regulating tight junction proteins and that ammonia, a luminal cytotoxin elicited by *H. pylori*, kills gastric epithelial cells by a newly described mechanism (see the Research Progress and Bibliography sections).

In a second approach, we study how survival and death mechanisms are regulated in gastric epithelial cells to gain an understanding of how these pathways are blocked in cancer development. This approach has been challenging, since gastric parietal cells do not express any of the classical BCL-2-family proteins like BCL-2, BAX, BAK, etc. In the past year we identified brain-type N-methyl-D-aspartate channels, which are calcium transport channels, in parietal cells and studied the role of these channels in regulating apoptosis mechanisms. In both cases, we are interested in uncovering therapeutic targets to block gastric atrophy and cancer development during infection.

## Research Support

Departmental Bridge Funding  
 “Biology of alimentary epithelia in health and disease”  
 National Institutes of Health, NIDDK P30 DK034854-12  
 Harvard Digestive Diseases Center Grant  
 Project Period: 2010-2015  
 PI: Wayne Lencer, MD (Boston Children’s Hospital)  
 Subcontract PI and Imaging Core B Director: Susan J. Hagen, PhD

## Research Grants Submitted and Pending Review/Funding

“Gastric Barrier in Health and Disease”  
 National Institutes of Health, NIDDK R01 DK094586-01  
 Project Period: 2012-2017  
 PI: Susan J. Hagen, PhD



## Susan J. Hagen, PhD

Associate Professor of Surgery;  
 Associate Vice-Chair for Research

## Lab, Core, and Administrative Groups

Research Laboratory  
 Ji Hye Seo, PhD

Core Facilities, Microscopy-Confocal  
 Lay-Hong Ang, PhD  
 Yi Zheng, PhD  
 Andrea Calhoun

Core Facilities, Histology  
 Suzanne White  
 Lena Liu

Surgical Research  
 Rachel St. Fort  
 Molly Jay

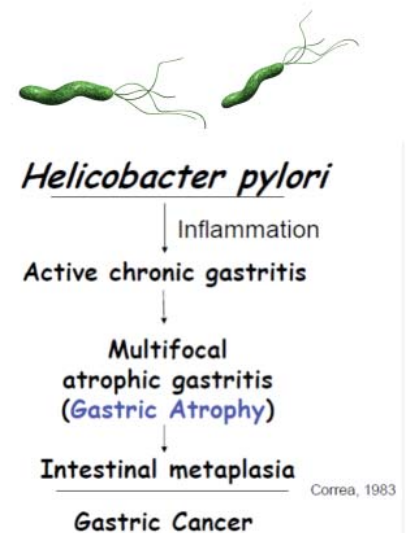


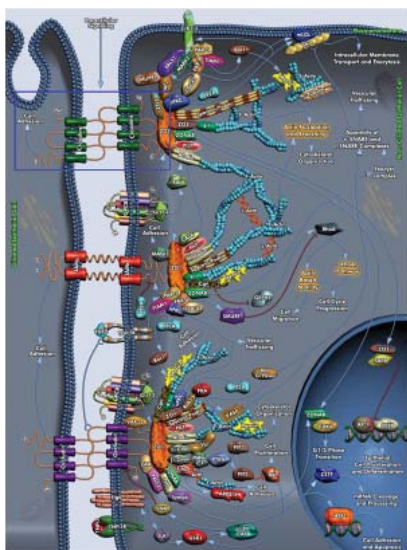
Figure 1



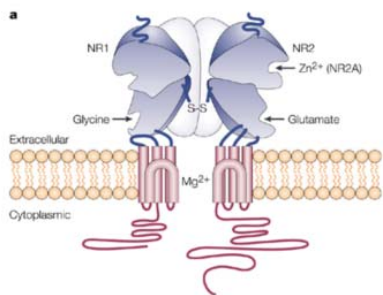
*Dr. Hagen with the laboratory, core groups, and administrative staff*

*Back (from left): Susan Hagen, Ancrea Calhoun, Suzanne White, and JiHye Seo.*

*Front (from left): Lay-Hong Ang, Leena Liu, Yi Zheng, and Rachel St. Fort.*



*Figure 2*  
Copyright 2009 QIAGEN, All Rights Reserved



*Figure 3*

## Accomplishments in the Past Year

### Research Accomplishments

#### Tight Junction Barrier Function in Gastric Cancer Development

We are interested in how pro-inflammatory cytokines, particularly IL-1 $\beta$ , affect tight junction function during *H. pylori* infection. In the past year, we found that IL-1 $\beta$ , via p38 MAPK activation, significantly decreased barrier function in gastric epithelial cells. When we explored the mechanism behind this change in barrier function, we learned that the stomach expresses one particular tight junction protein, claudin-18 (Figure 2, blue box), which is responsible for limiting the paracellular flux of H<sup>+</sup> across the mucosa; when knocked-out, there is severe mucosal injury and gastric atrophy in the stomach within three days of birth due to acid back-diffusion from acid secretion. IL-1 $\beta$  in combination with TNF $\alpha$  and IFN $\gamma$  blocked claudin-18 expression in vitro, which resulted in robust paracellular flux. We found that more than 80% of gastric glands have no claudin-18 in *H. pylori*-infected stomach, suggesting that this important change in tight junction structure alone drives an increase in paracellular flux, mucosal injury, and gastric atrophy during infection. We plan to use the claudin-18 knockout mice to explore the features of infection that are responsible for cancer development.

In addition to important changes in claudin-18 expression we found that claudin-7, which is not normally expressed in the stomach, was highly up-regulated by IL-1 $\beta$  in vivo and in vitro in *H. pylori*-infected mice. While claudin-7 is a tight junction component, the interesting aspect of its localization in *H. pylori* infection is that claudin-7 shows robust apical staining that is similar to the localization of mucins and trefoil factor. This unexpected finding suggests that claudin-7 may be protective in some way, but knockout will be required to understand its role in barrier function. At present, the cytoplasmic localization of claudin-7 suggests that it is an infection-mediated tumor promoter with no role in regulating tight junction function.

The results of our work on IL-1 $\beta$ , claudin-18, and claudin-7 were accepted for presentation at the FASEB meeting in April (2012) and the Digestive Diseases Week meeting in May (2012) as oral presentations.

#### NMDA Channels, Calcium (Ca<sup>2+</sup>) Influx, and Cell Death Mechanisms in Gastric Cells

In the past year, we discovered that gastric epithelial cells express N-methyl D-aspartate (NMDA) channels, which are brain-specific glutamate channels that transport Ca<sup>2+</sup>. NMDA channels consist of two subunits, NR1 and NR2, have glutamate and glycine regulatory binding sites, require zinc, and the open channel is inhibited dose-dependently by magnesium and other pharmacological blockers (Figure 3). We found that ammonium, a cytotoxin liberated by *H. pylori*, reduces epithelial cell viability by excessive Ca<sup>2+</sup> permeation through NMDA channels and concluded that NMDA channels may be essential to regulate cell survival and death pathways in *H. pylori* infection. To examine NMDA channel activation in *H. pylori* infection, we showed that ammonium increased Ca<sup>2+</sup> permeation in gastric epithelial cells in a cAMP-dependent manner, which was blocked by NMDA NR2B receptor, open channel, and cell signaling antagonists. Wild-type *H. pylori* (producing ammonium), but not urease mutant *H. pylori* (no ammonia production), showed extensive Ca<sup>2+</sup> permeation that was blocked when NMDA receptor expression was repressed. The mechanism used to affect cell viability was that Ca<sup>2+</sup> entered cells and activated proteases, including cathepsins and calpain. Later, Ca<sup>2+</sup> was sequestered to cytoplasmic vacuoles



that are dilatations of the endoplasmic reticulum (ER). Inositol-3-phosphate-dependent release of  $\text{Ca}^{2+}$  from ER and protease activity damaged mitochondria, reduced ATP, and transcriptionally up-regulated the expression of cell death effectors—all of which ultimately killed the cells. Additional data showed that NMDA receptor expression is transcriptionally up-regulated in surface epithelial cells by *H. pylori* in vitro, consistent with in vivo expression studies in *H. pylori* infected mice. In parietal cells, however, NMDA receptor expression is down-regulated early in infection before any mucosal changes are evident. We are currently working to understand the role of NMDA channels in parietal cells, which may prove to be essential in regulating their survival program in collaboration with cell signaling pathways activated during acid secretion.

This work was published in December 2011 (see references) and also resulted in an editorial about the importance of this new finding.

### Administrative Accomplishments

I continued to work as Associate Vice-Chair for Research in the Department of Surgery. Accomplishments this year were successful completion of a new administrative infrastructure in my office, which consisted of writing new job descriptions, hiring, and training two new employees. Rachel St. Fort (photo, right) was hired as the new Research Administrative Supervisor for Research and Molly Jay (photo, below) was hired as the new Administrative Assistant for Research. With Wendy Dasgupta, our prior Administrative Coordinator, a mechanism to collect data on scholarly publications by investigators in Surgery was instituted by creating a sophisticated database that is collected by Division in myNCBI.

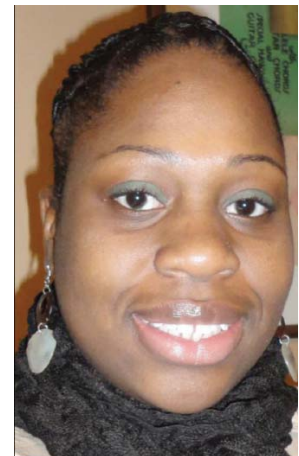
This listing of publications is distributed to the Faculty in Surgery and will be highlighted quarterly in *Surgery Notes*. We better integrated non-clinical and clinical faculty/staff by encouraging participation in Surgical Grand Rounds and departmental faculty meetings. My office assisted with the set-up of Affinity Research Collaboratives (ARCs), headed by Dr. Ferran. I got the T32 (training) grant program up and running with administrative support and the first T32 grant application will be submitted in January 2012. I instituted and the office administratively supported a new seminar series, “Surgical Horizons,” which hosts a research seminar once per month that features an emerging leader in surgery. In 2011, I also organized a series of group meetings for clinical staff, to better support that group in surgery.

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, for which I serve as the imaging core director. I also serve as Director of the Electron Microscopy Core within the BIDMC Microscopy Core Facility and in the past year, developed tomography as a new technique to visualize microscopic structures in 3D.

### Individual Accomplishments

- Served until July 1, 2011 as an elected Councilor for the GI section of the American Physiological Society. This post was for the Steering Committee.
- Invited as a keynote speaker at the Japanese Ulcer Society Meetings in Tokyo, Japan.

**Susan J. Hagen, PhD**

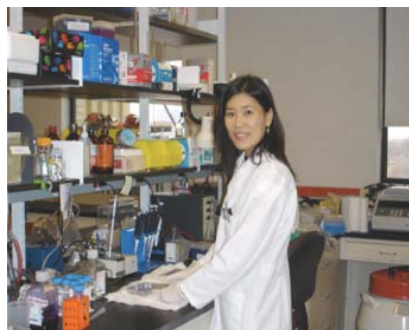


Rachel St. Fort

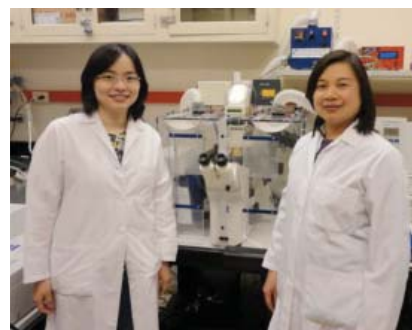


Molly Jay

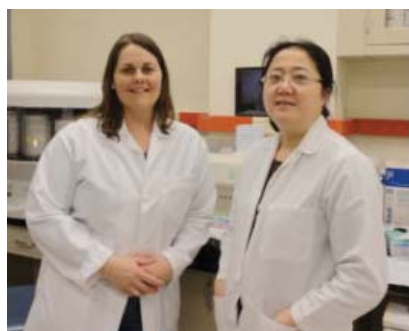
**Susan J. Hagen, PhD**



*Dr. Ji Hye Seo*



*Drs. Lay-Hong Ang and Yi Zheng  
in the confocal core—with the  
live-cell confocal*



*Suzanne White and Leena Liu in  
the Histology Core*

- In addition to the regular reviewer requests I receive, I was asked to review this year by *Plos1*, *Journal of Nutrition*, *BMC Microbiology*, *International Journal of Biochemistry and Cell Biology*, *Nutrients*, and the *Journal of Physiology and Pharmacology*.
- Served as Co-Chair of the Affinity Research Collaborative (ARC), Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School.
- Member of the Search Committee for Chief of Acute Care Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.
- Served as an interviewer for Surgical Resident Applicants in Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.
- Ji Hye Seo, PhD, was awarded a trainee travel award from the American Physiological Society for her work on NMDA channels.
- Dr. Seo's abstract was chosen as a finalist for the internal Surgery Research Abstract competition.

### **Invited Presentations**

“N-methyl-D-aspartate (NMDA) channels: Brain-specific channels in gastric cells that regulate ammonia cytotoxicity.” RIST symposium on Drug Discovery for Gastrointestinal Diseases. Tokyo University of Science, Chiba, Japan. November, 2011.

“Tight junction claudins as novel components of the gastric mucosal defense system.” Japanese Ulcer Society Meeting, Special Symposium in honor of Dr. William Silen. Tsukuba International Congress Center, Tsukuba, Japan. November 2011.

“N-methyl-D-aspartate (NMDA) channels: Brain-specific channels in gastric cells that regulate ammonia cytotoxicity.” Kyoto Pharmaceutical University, Department of Pharmacology, Kyoto, Japan. November, 2011.

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## **Teaching, Training, and Education**

### **Undergraduate and Medical School Courses**

- Taught in the Human Body course (IN753.0) at Harvard Medical School from 10/2011- 11/2011 as Director of the Cannon Society histology laboratory.
  - Mentor for Mr. Siddhartha Jena from the Research Science Institute at Massachusetts Institute of Technology. Siddhartha was from the International Academy in Bloomfield, Michigan and did a 5-week summer project on claudin expression in *H. pylori* infection.
-

## Bibliography (January-December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Seo JH, Fox JG, Peek RM, Jr, **Hagen SJ**. N-methyl-D-aspartate channels link ammonia and epithelial cell death mechanisms in *Helicobacter pylori* infection. *Gastroenterology* 2011;141(6):2064-75.

*With an accompanying editorial by:*

Sachs G, Marcus EA, Scott DR. The role of the NMDA receptor in *Helicobacter pylori*-induced gastric damage. *Gastroenterology* 2011; 141(6):1967-8.

Song P, Groos S, Riederer B, Feng Z, Krabbenhoft A, Manns MP, Smolka A, **Hagen SJ**, Neusch C, Seidler U. Kir4.1 channel expression is essential for parietal cell tubulovesicle recycling and control of acid secretion. *J Biol Chem* 2011;286(16):14120-8.

### Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

Seo JH, Fox JG, Peek RM, Jr, **Hagen SJ**. N-methyl-D-aspartate (NMDA) channels regulate apoptosis in *Helicobacter pylori* infection by ammonia-induced calcium permeation mechanisms. BIDMC Surgery, Clowes Visiting Professor Research Competition, Finalist.

Seo JH, Fox JG, **Hagen SJ**. N-methyl-D-aspartate (NMDA) channel-mediated calcium influx regulates ammonia cytotoxicity in non-transformed gastric epithelial cells. FASEB J, 2011. Dr. Seo was awarded a Postdoctoral Fellow Travel Award from the American Physiological Association.

### Susan J. Hagen, PhD



*Andrea Calhoun at the new JEOL 1400 Electron Microscope*



## Research Focus

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 (*Figure 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/EBP $\beta$  and  $\delta$  and NF- $\kappa$ B as well as the nuclear co-factors p300 and PGC-1 $\alpha$  and  $\beta$  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/GSK3 $\beta$  signaling.

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 *Figure 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 and 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/EBP $\beta$  can be activated by acetylation and phosphorylation. Indeed, recent experiments in our laboratory have provided evidence that C/EBP $\beta$  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. Thus, the regulation of protein degradation in atrophying muscle is complex and factors influencing protein degradation in catabolic muscle are regulated at multiple levels.

## Research Support

“Muscle protein turnover and amino acid uptake in sepsis”  
NIH/NIDDK, R01 DK37908-20  
08/01/2006-06/30/2011  
PI: Per-Olof Hasselgren, MD, PhD



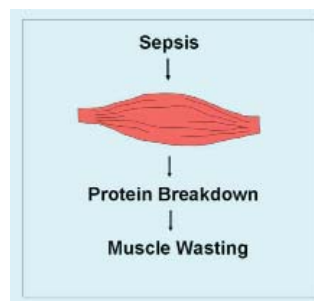
**Per-Olof Hasselgren, MD, PhD**

George H.A. Clowes  
Professor of Surgery

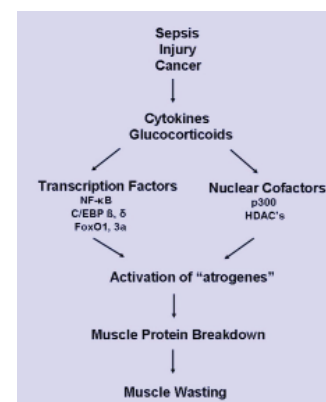
Vice-Chairman for Research,  
Director of Endocrine Surgery

### Lab Members

Nima Alamdari, PhD  
Zaira Aversa, MD  
Estibaliz Castillero, PhD  
Aniket Gurav  
Sally Gwin



*Figure 1*



*Figure 2*



## Applications Submitted and Pending Review/Funding

“Muscle protein turnover and amino acid uptake in sepsis.”

NIH/NIDDK, R01 DK37908-20

PI: Per-Olof Hasselgren, MD, PhD

“Hyperacetylation and muscle wasting”

NIH/NIDDK, R01 AR62869-01

PI: Per-Olof Hasselgren, MD, PhD

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## Accomplishments in the Past Year

### Invited Presentations

“Transcription factors, nuclear cofactors, and muscle wasting.” Fujita Health University School of Medicine, Department of Surgery and Palliative Medicine. Mie, Japan. February 15, 2011.

“Transcription factors, nuclear cofactors, and muscle wasting.” 26th Annual Meeting of the Japanese Society for Parenteral and Enteral Nutrition. Nagoya, Japan. February 17, 2011.

“Muscle wasting in sepsis and critical illness – mechanisms and the potential role of nutritional and metabolic support.” 26th Annual Meeting of the Japanese Society for Parenteral and Enteral Nutrition. Nagoya, Japan. February 17, 2011.

“Transcription factors, nuclear cofactors and muscle wasting.” Vanderbilt University, Collaborative Research Conference. Nashville, TN. February 28, 2011.

“Hyperacetylation and muscle wasting.” Collaborative Research Forum, Annual Meeting. Beaver Creek, CO. March 26, 2011.

Transcription factors, nuclear cofactors, and muscle wasting,” MGH/Shriners Hospital, Research Seminar. Boston, MA. May 13, 2011.

“Transcription factors, nuclear cofactors, and muscle wasting.” Boston University, Boston Claude D. Pepper Older Americans Independence Center (OAIC). Boston, MA. December 6, 2011.

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## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Gonnella P, Alamdari N, Tizio S, Aversa Z, Petkova V, **Hasselgren PO**. C/EBP $\beta$  regulates dexamethasone-induced muscle cell atrophy and expression of atrogen-1 and MuRF1. *J Cell Biochem* 2011;112: 1737-48.

O’Neal P, Mowschenson P, Connolly J, **Hasselgren PO**. Large parathyroid tumors have an increased risk for atypia and carcinoma. *Am J Surg* 2011; 202:146-50.

Smith IJ, Aversa Z, **Hasselgren PO**, Pacelli F, Rosa F, Doglietto GB, Bossola M. Calpain activity is increased in skeletal muscle from gastric patients with no or only minimal weight loss. *Muscle Nerve* 2011;43:410-4.

Tizio SC, Petkova V, **Hasselgren PO**. TNF-alpha potentiates dexamethasone-induced expression and activity of C/EBP-beta in cultured muscle cells. *J Am Coll Surg* 2011;213:S62-3.

Research Investigations (Submitted or in Press)

Alamdari N, Toraldo G, Aversa Z, Smith I, Renaud G, Qaisar R, Larsson L, Jasuja R, **Hasselgren PO**. Loss of muscle strength during sepsis is in part regulated by glucocorticoids and is associated with reduced muscle fiber stiffness. 2011; submitted.

#### **Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

Aversa Z, Alamdari N, **Hasselgren PO**. Molecules modulating gene transcription during muscle wasting in cancer, sepsis and other critical illness. *Crit Rev Clin Lab Sci* 2011;48:71-86.

**Hasselgren PO**. Muscle wasting. In: Vincent JL, Hall JB, editors. *Encyclopedia of intensive care medicine*; 2011.

Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Alamdari N, Aversa Z, Castellero E, **Hasselgren PO**. Acetylation and deacetylation – novel factors in muscle wasting. 2011; submitted.

Goldfarb M, O'Neal P, Osborn C, **Hasselgren PO**, Schwaitzberg S. Endocrine. In: Goldberg M, Gromski MA, Hurst JM, Jones DB, editors. *Pocket Surgery – The Beth Israel Deaconess Medical Center Handbook of Surgery*. Wolters Kluwer/Lippincott Williams & Wilkins, 2011, in press.

**Hasselgren PO**, Cannon JW, Fischer JE. Perioperative management: practical principles, molecular basis of risk, and future directions. In: Fischer JE, Jones DB, Pomposelli FB, Upchurch GR, editors. *Fischer's Mastery of Surgery*, 6th edition. Lippincott Williams & Wilkins, Philadelphia, PA. 2011; in press.

Mele A, **Hasselgren PO**. Adrenalectomy for minimally invasive surgery: laparoscopy, therapeutic endoscopy, and NOTES. In: Jones D et al, editors. 2011; submitted.

**Per-Olof Hasselgren, MD, PhD**



## Research Focus

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

The Section for Minimally Invasive Surgery has trained medical students, residents, research fellows, clinical fellows, and surgeons worldwide in advanced laparoscopic techniques and founded the the Carl J. Shapiro Simulation and Skills Center. Education research is focused on establishing a technical skills laboratory validating new teaching tools and instituting curriculums for Harvard Medical School students and BIDMC residents. Research assesses team simulation 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 2009 BIDMC reaccredited SASC. We continue to collaborate with Nice Medical School Simulation Center in France.

In collaboration with Ram Chuttani, MD, of GI Endoscopy (Department of Medicine at BIDMC) we have developed new natural orifice transluminal endoscopic approaches to pancreatic resection in the animal model. NOTES techniques may achieve comparable outcomes with faster recuperation.

Collaborative efforts have also worked towards developing better simulators. With S. De, PhD at RPI we have been awarded \$10 million of NIH R01 grants to create a virtual reality laparoscopic simulator for teaching laparoscopic procedures, electrosurgical principles, FLS testing, and NOTES. The aim of the NOTES project is to design and simulator to develop NOTES procedures and then use simulator to train surgeons safely.

There are ongoing NIH Collaborative Projects among the Center for Modeling, Simulation and Imaging in Medicine (CeMSIM), Rensselaer Polytechnic Institute (RPI), Carl J. Shapiro Simulation and Skills Center, Beth Israel Deaconess Medical Center (BIDMC), and the Tufts University.

There are three ongoing NIH funded projects (#1–3) and a project on trainer for virtual electrosurgery (#4). The project descriptions follow.

1. Virtual Basic Laparoscopic Skills Trainer (VBLaST)
2. Virtual Natural Orifice Transluminal Endoscopic Surgery (VR-NOTES) simulator
3. Generation (Gen) 2 cognitive simulator
4. Virtual Electrosurgery Trainer (VEST)

### Virtual Basic Laparoscopic Skills Trainer

Fundamentals of Laparoscopic Surgery (FLS), is a set of five basic tasks which has been approved for skills training and credentials in North America. The Virtual Basic Laparoscopic Skills Trainer (VBLaST) is a virtual reality trainer that replicates the FLS tasks for skills training. In this project, a specialized interface with haptic feedback was built at CeMSIM, RPI to replicate the FLS box for the VBLaST. Currently in the project, three tasks of the FLS namely, Peg Transfer, Pattern Cutting and Ligating Loop have been implemented.



**Daniel B. Jones, MD, MS, FACS**

Professor of Surgery

Director, Section of Minimally Invasive Surgery

Vice-Chair, Office of Technology & Simulation

### Group Members

Shapiro Simulation and Skills Center

David Fobert

Darren Tavernelli, RN

Mike McBride, RN

Linda Trainor, RN

Maritza Avendano

Collaborators

Ben Schneider, MD

Robert Andrews, MD

Jonathan Critchlow, MD

Steven D. Schwartzberg, MD

George Blackburn, MD, PhD

Steven Loring, MD, PhD

Stephanie Jones, MD

Ram Chuttani, MD

Christina C. Wee, MD, MPH

Caroline Cao, PhD

Grace Zhou, PhD

Suvranu De, Sc.D.

MIS Fellows (BIDMC)

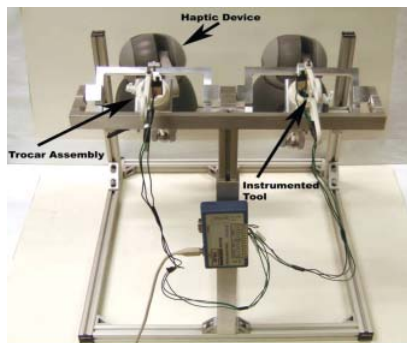
Raul Gupta, MD

Arpan Goel, MD

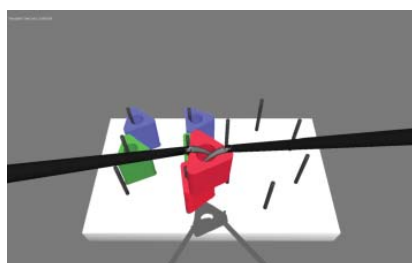
Abe Frech, MD

Yusef Kudsi, MD

**Daniel B. Jones, MD, MS, FACS**



*VBlaST Haptic Interface*



*VBlaST Peg Transfer*



*VBlaST Ligating Loop Task*



*VBlaST Pattern Cutting Task*

Construct and convergent validity for the Peg Transfer task have also been completed with subject pool of medical students, residents, Fellows and attendings from Beth Israel Deaconess Medical Center.

Validation study for the Pattern Cutting and Ligating Loop simulations are planned to be undertaken in early December of 2011.

### **Virtual Natural Orifice Transluminal EndoScopic Surgery (VR-NOTES) simulator**

NOTES is an emerging technology which is currently undergoing FDA approved clinical trials in U.S. The surgery has also been performed at many places around the world. Due to its experimental nature, NOTES requires extensive testing/training in animal or virtual simulator models before successfully transitioning to humans. The instrumentation used for NOTES is derived from traditional endoscopic surgery and may require changes for which a realistic test bed is needed. Animal models are expensive and have to be replenished after each procedure.

In order to provide a training and testing platform for NOTES, the VR-NOTES simulator is being developed at CeMSIM, RPI. A need analysis study was performed at the 2011 Annual NOSCAR conference to identify, the procedure that should be simulated for NOTES along with the possible routes, type and number of channels of the scope for interaction. NOTES–Cholecystectomy was chosen as the target procedure based on the overwhelming response from the study participants. Both transgastric and transvaginal approaches are being modeled in the VR-NOTES simulator.

Currently, the VR-NOTES simulator has virtual organ models through which a fly through simulation can be done along the predetermined path for transgastric approach. A haptic interface with realistic flexible endoscope is being developed to interact with the VR-NOTES simulator.

### **Generation (Gen) 2 cognitive simulator**

The virtual reality simulators that have been developed so far have been focused on either part-task or procedural simulations with an overall goal of increasing the psychomotor skills of the trainees. Though there are some simulators that can give you evaluations at the completion of the procedure, no real-time feedback systems exist for giving feedback to the trainee on the fly. Moreover, creating an environment as close to real surgery as possible including, the operating room environment, devices, and noises in the room, would make the training very realistic. To test this hypothesis, the Gen 2 simulator is being currently developed at the CeMSIM, RPI. The simulator will train on the LAGB procedure using SILS technique.

The models and simulation that was developed for our previous simulator for LAGB using multi-port laparoscopic technique (Gen 1) is being used for the Gen2 simulator. In addition, a virtual operating room is being currently modeled to provide a realistic environment for the trainee and increase the cognitive fidelity of the simulator. A cognitive feedback module will be developed in 2012 and validation studies are planned for the end of 2012.

## Virtual Electrosurgery Trainer (VEST)

Electrosurgery is an important technique that needs to be mastered. Training in electrosurgery is difficult since using in vitro models produce dangerous smoke and active energy should be used at all times. Moreover, clear understanding of the principles of electrosurgery is needed to effectively operate the devices. A virtual reality simulator for electrosurgery will be a valuable tool since the procedure can be repeated any number of times without the need to change the models, clearing smoke or using an actual energy source. The virtual electrosurgery trainer (VEST) is an ongoing project at the CeMSIM, RPI, that currently includes basic modules to teach possible ways of patient injury during an electrosurgery procedure. VEST can simulate, insulation failure, capacitive and direct coupling.

An interface with two ports for trocar and tool placement whose motion are captured by optical and gyroscope sensors was built to interface the VEST for testing. The system was successfully demonstrated to the expert surgeons during the SAGES meeting in Boston this year.

Collaborative studies with Christina Wee, MD, study risk assessment among patients considering weight loss operations. This NIH RO1 funded project assembles a racially diverse cohort of 650 patients recruited from two bariatric centers and a cross-sectional sample of 600 primary care patients from the community in order to examine the perspectives and experiences of patients seriously contemplating weight loss surgery and those who are less likely to undergo surgery.

Goals of the project are to better understand patients' preferences and value for weight loss and outcomes of bariatric surgery, identify factors and patient characteristics that predict greatest value and benefit from surgery, and identify barriers and factors that influence decision-making among those not already committed to this treatment. An important overarching aim of the project will be to better understand the factors and barriers that might explain current observed racial variation in the use of bariatric surgery and after several years this ongoing data base will provide a robust tool for clinical investigation.

Robert Andrews, MD, heads basic science efforts in collaboration with Nicholas Stylopoulos, MD, at Boston Children's Hospital to study the physiology of gastric bypass, gastric sleeve and band procedures. Ben Schneider, MD, is collaborating with scientists to understand hormonal changes with weight loss surgery.

## Research Support

"Physically realistic virtual surgery"

NIH/NIBIB, R01 EB005807-01

06/01/2006-03/31/2010

PI: Suvranu De, PhD

Collaborator: Daniel Jones, MD

"Understanding how patients value bariatric surgery"

NIDDK, R01 DK073302-01

2007-2009

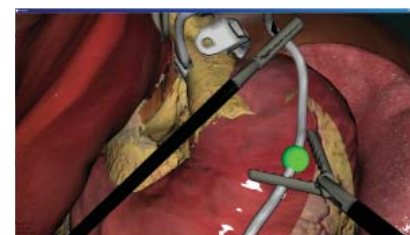
PI: Christina Wee, MD

Collaborator: Daniel Jones, MD

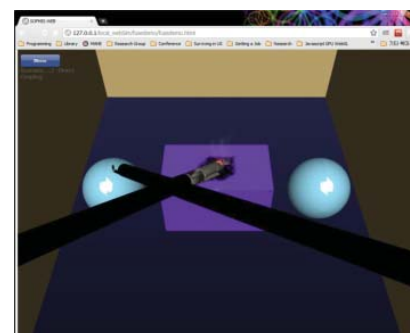
Daniel B. Jones, MD, MS, FACS



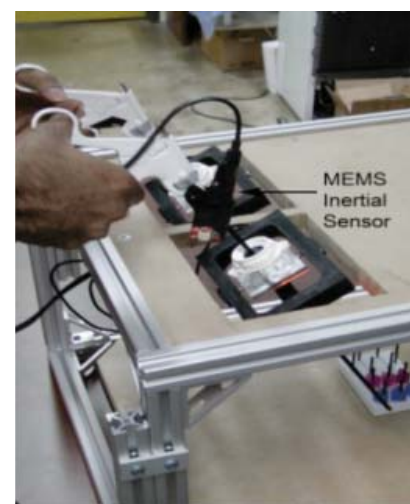
*VR-NOTES simulation environment*



*The Gen1 LAGB simulator*



*VEST Interface with optical and MEMS sensors*



*VEST simulator showing direct coupling failure*

**Daniel B. Jones, MD, MS, FACS**

CRICO-Simulation  
2009-2010  
PI: Daniel Jones, MD

“Development and validation of a virtual basic trainer (VBLAST)”  
NIH, R01 EB010037-01  
PI: Suvranu De, PhD  
Collaborator: Daniel Jones, MD

“High Fidelity reconstruction of human anatomy using 3 dimensional printing”  
Harvard Medical School - Milton Grant  
2010-2011  
PI: Daniel Jones, MD  
Collaborator: Robert Andrews, MD

“Developing physics-based virtual simulation technology for NOTES”  
NIH, Ro1 EB009362-o1A2  
PI: Suvranu De, PhD  
Collaborator: Daniel Jones, MD

“Development and validation of a virtual electrosurgical skill trainer (VEST)”  
NIH, RO1  
PI: Suvranu De, PhD  
Collaborator: Daniel Jones, MD

**Applications Submitted and Pending Review/Funding**

“Development and validation of a virtual electrosurgical skill trainer (VEST)”  
NIH, RO1  
PI: Suvranu De, PhD  
Collaborator: Daniel Jones, MD

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**Accomplishments in the Past Year**

Currently all surgical residents must pass the Fundamentals of Laparoscopic Surgery exam prior to taking Board exams. This is done in a box trainer. Our group is developing a simulator so that this test can be administered easier, quicker and faster. This year we have been validating the VBLAST simulator at BIDMC.

**Administrative Accomplishments**

- Daniel Jones, MD, was promoted to Professor, Harvard Medical School, and to Vice Chair in Surgery, Office of Technology & Simulation.
- Ben Schneider, MD, assumed role as Director, MIS Fellowship

**Individual Accomplishments**

- Co-Chair, ACS-ASE Skills-based Simulation Curriculum for Medical School Year 1-3
- Chair, SAGES Fundamentals of Surgical Energy (FUSE) Task Force
- Chair, SAGES Quality Outcomes and Safety Committee



- Program Chair, SAGES Annual Meeting
- Chair, SSAT Public Policy and Advocacy Committee
- American Society of Metabolic and Bariatric Surgery representative to Fellowship Council Board
- Member American Surgical Association
- Hasson Naama Memorial Lecture, Weill Cornell Medical College
- Associate Professor of France
- Boston Red Sox Medical All Star
- Top Doctors, *Boston Magazine*

#### Invited Presentations

- “Surgical Approaches to the Treatment of Obesity.” The Egyptian Society of Laparoscopic Surgery (ESLS). Cairo, Egypt. January 20, 2011.
- “Safer Surgery with Simulation.” The Egyptian Society of Laparoscopic Surgery (ESLS). Cairo, Egypt. January 21, 2011.
- “Opportunities and Challenges in Surgical Robotics Workshop.” Beth Israel Deaconess Medical Center, Innovation, Design, and Emerging Alliances in Surgery (IDEAS). Boston, MA. April 9, 2011.
- “Bariatric Centers of Excellence: The Right Thing for Patients.” Society for Surgery of the Alimentary Tract Annual Meeting. Chicago, IL. May 10, 2011.
- “Changing the Safety Culture.” American Society Metabolic and Bariatric Surgery 28th Annual Meeting, A System Approach to Patient Safety. Orlando, FL. June 14, 2011.
- “GI Interventions.” American Society Metabolic and Bariatric Surgery 28th Annual Meeting, Moderator: ASMBS/TOS Medical Specialties Track. Orlando, Florida, ASMBS/TOS Medical Specialties Track. June 16, 2011.
- “Debates: Is Bypass Passe? ” and “Top 5 Posters.” American Society Metabolic and Bariatric Surgery 28th Annual Meeting, Moderator. Orlando, Florida. June 16, 2011.
- “Complications After Weight Loss Surgery: What Every Caregiver Should Know.” 25th International Conference on Practical Approaches to the Treatment of Obesity. Cambridge, MA. June 18, 2011.
- “Gastric Bypass, Band and Sleeve and What the American Surgeon is Doing Next.” Chichester Bariatric 2011: Controversies in Quality in Bariatric Surgery Conference. Chichester, England. September 26, 2011.
- “Bariatric Surgery.” American College of Surgeons, 97th Clinical Congress, Facilitator: Meet the Expert Luncheon. San Francisco, CA. October 23-27, 2011.
- “Indications and Contraindications for Revision Surgery.” 7th International Bariatric Endoscopic Surgical Trends Congress. New York City, New York. November 4, 2011.

**Daniel B. Jones, MD, MS, FACS**

“Men, Obesity and Nutrition.” Harvard Medical School, Men’s Health: Opening a New Frontier. Boston, MA.

“Weight Loss Options.” Association of Perioperative Registered Nurses (AORN) Massachusetts, Current Advances in Weight Loss Surgery, Boston, MA.

“Weighing in on Obesity Surgery and Training.” University of Nevada School of Medicine, Visiting Professor. Las Vegas, NV.

“Bariatric Surgery.” The National Academies, Roundtable on Biomedical Engineering Materials and Applications: Effects of Obesity and Gender on Medical Device Therapies. Washington, D.C.

“Obesity Surgery in the United States.” University Hospital Munich, Campus Grosshadern. Munich, Germany.

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### Teaching, Training, and Education

- Course co-director, American Society Metabolic and Bariatric Surgery 28th Annual Meeting, Kissimmee, FL “A system approach to patient safety.”
- Course director, 97th Annual Clinical Congress, American College of Surgeons. “Bariatric and Metabolic Surgery”, San Francisco, CA CRICO/ Harvard Operating Room Team Training with Simulation Pilot
- Site PI for Harvard wide initiative to introduce simulation to General Surgery to promote safer practices. Team based training included anesthesiologist and nurses.

### Undergraduate Courses

HMS CME Courses, 2011

- 25th Annual Practical Approaches to the Treatment of Obesity

Role: Associate Course Director  
200 surgeons, internists and dieticians  
Preparation/Contact 30 hours

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### Bibliography (January – December 2011)

#### Peer-Reviewed Publications in Print or Other Media

##### Research Investigations

Gould J, Ellsmere J, Fanelli R, Hutter M, Jones S, Pratt J, Schauer P, Schirmer B, Schwaitzberg S, **Jones DB**. Panel report: best practices for the surgical treatment of obesity. Surg Endosc 2011;25:1730-40.

Hutter MM, Schirmer BD, **Jones DB**, Ko CY, Cohen ME, Merkow RP, Nguyen NT. First report from the ACS-Bariatric Surgery Center Network: laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and bypass. Ann Surg 2011; 254(3):410-20.

Matthes K, Thakkar SJ, Lee S, Gromski M, Lim RB, Janschek J, Derevianko A, Jones SB, **Jones DB**, Chuttani R. Development of a pancreatic tumor animal model and evaluation of NOTES tumor enucleation. Surg Endosc 2011; 25(10): 3191-7.

Roberts DH, Kane EM, **Jones DB**, Almeida JM, Bell SK, Weinstein AR, Schwartzstein RM. Teaching medical students about obesity: A pilot program to address an unmet need through longitudinal relationships with bariatric surgery patients. *Surg Innov* 2011;18(2):176-83.

Roberts D, Kane EM, Almeida JA, **Jones DB**, Schwartzstein RM. The longitudinal bariatric surgery patient elective. A model for obesity education in the third year of medical school. *Surg Innov* 2011;18(2):176-83.

Sankaranarayanan G, Adair J, Halic T, Gromski M, Lu Z, Woojin A, Dargar S, **Jones DB**, De S. Validation of a novel laparoscopic adjustable gastric band simulator. *Surg Endosc* 2011;25(4):1012-8.

#### Research Investigations (Submitted or in Press)

Conrad C, Konuk Y, Werner PD, Cao CG, Warshaw A, Rattner W, Stangenberg L, Ott HC, **Jones DB**, Miller DL, Gee DW. A quality study on avoidable stressors and countermeasures affecting surgical motor performance and learning. *Ann Surgery* 2011; in press.

Wee CC, Davis RB, Huskey KW, **Jones DB**, Hamel MB. Quality of life among obese patients: the role of obesity-related social stigma and functional status. *JAMA* 2011; submitted.

#### Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media

##### Reviews, Chapters, Monographs, and Editorials

Adair JD, Gromski MA, Sankaranarayanan G, De S, **Jones DB**. Simulation in laparoscopic bariatric surgery. *Bariatric Times* 2011;7(6):1-13.

**Jones DB**. The current role of simulators in teaching surgical techniques. *J Gastrointest Surg* 2011;15:1718-21.

Joseph RJ, Blackburn GL, **Jones DB**. Updating criteria for weight loss surgery. *Bariatric Times* 2011; 8(4):12-14.

##### Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Jones SB, **Jones DB**. Perioperative management of morbid obesity. In: Fischer JE, Jones DB, Pomposelli FB, Upchurch GR, editors. *Fischer's Mastery of Surgery*, 6th edition. Lippincott Williams & Wilkins, Philadelphia, PA. 2011; in press.

##### Books/Textbooks for the Medical or Scientific Community (Submitted or in Press)

Goldberg M, Gromski MA, Hurst JM, **Jones DB**, editors. *Pocket Surgery – The Beth Israel Deaconess Medical Center Handbook of Surgery*, 1st edition. Wolters Kluwer/Lippincott Williams & Wilkins, 2011, in press.

Tsuda S, Scott DJ, **Jones DB**. Textbook of simulation: skills & team training. *CineMed* 2011, in press.

#### Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

Andrews R, Adair J, Kurcharzyk J, **Jones DB**. Learning what we don't know: an initial step to assuring competency. American College of Surgeons, October 24, 2011.



**Daniel B. Jones, MD, MS, FACS**

Stefanidis D, Arora S, Parrack D, Hamad G, Capella J, Grancharov T, Urbach D, Scott Dm **Jones DB**, ASE Simulation Committee, A prioritized research agenda for Surgical simulation using Delphi methodology, ASE Annual Meeting, Boston, March 2011.

## Research Focus

My clinical research interests include oncoplastic reconstruction of partial mastectomy defects, evaluating clinical outcomes in the octogenarian patient population diagnosed with invasive carcinoma, and identifying radiologic and pathologic features that contribute to an upgrade of common breast atypias to carcinoma.

My translational research interests include breast cancer stem cell identification to elucidate diagnostic and therapeutic strategies, and evaluating the clinical efficacy of a breast cancer targeted vaccine.

## Accomplishments in the Past Year

### Research Progress

Our group has developed a protocol to retrospectively study prospectively collected patient data examining the oncoplastic reconstruction of partial mastectomy defects. To date, approximately 10 patients have undergone oncoplastic reconstruction under the direction of our Plastic Surgery colleagues.

Our Group has developed a database to retrospectively review the upgrade rate from atypia to carcinoma in patients with atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS).

### Administrative Accomplishments

- Joined the BIDMC Cancer Committee.
- Joined the BIDMC Breast Center Executive Committee.
- Sat on the National Accreditation Program for Breast Centers (NAPBC) BIDMC Executive Sponsor Steering Committee.
- BIDMC General Surgery Residency Applicant Interviewer.
- Joined the DFCI/HCC DCIS Task Force.
- Became a member of the DFCI/HCC parp inhibitor working group.
- Remained an active member of the Society of Surgical Oncology, American Society of Breast Surgeons, American Society of Clinical Oncology, American College of Surgeons, Association of Women Surgeons, Massachusetts Medical Society, Boston Surgical Society, Chief Administrative Fellow, Breast Surgical Oncology, MD Anderson Cancer Center.

### Individual Accomplishments

- I was a Peer-reviewer for the following journals: *Journal of Anesthesia & Clinical Research*, *Association of Radiologic and Imaging Nursing Core Curriculum*, and the *Cardiovascular & Interventional Radiology Journal*.
- I was an Editor for Dynamed, <http://www.ebscohost.com/dynamed>, Breast Cancer in Women, Sentinel Lymph Node Biopsy, and Tumor Markers in Breast Cancer.



**Ranjna Sharma, MD**

Instructor in Surgery

## Teaching, Training, and Education

### Graduate School and Graduate Medical Courses

- Delivered lectures “Surgery as a career” ( Harvard Medical School John Warren Surgical Society) and “Breast Cancer” (BIDMC Resident Lecture Series).
- BIDMC Department of Surgery faculty mentor to Ali Linsk, MD, a general surgery resident in the Clinical Scholarship Program. We are retrospectively studying the upgrade rate of atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ.

### Other Teaching Contributions

- Faculty Advisor, BIDMC General Surgery Residents, Department of Surgery
- Faculty Mentor, BIDMC Department of Surgery Clinical Scholarship Program (CSP)
- BIDMC Department of Surgery Rotation Specific Education Committee
- Harvard Medical School, Fourth Year Medical Student Comprehensive Clinical Exam Examiner
- BIDMC General Surgery Residency Mock Oral Exam Examiner
- BIDMC/Harvard Medical Student Surgery Clerkship Oral Examiner
- BIDMC Speaker’s Bureau: Breast Cancer

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## Bibliography (January–December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

**Sharma R**, Rourke LL, Kronowitz SJ, Oh JL, Lucci A, Litton JK, Robb GL, Babiera GV, Mittendorf EA, Hunt KK, Kuerer HM. Management of local-regional recurrence following immediate breast reconstruction in patients with early breast cancer treated without post-mastectomy radiotherapy. *Plast Reconstr Surg* 2011; 127(5):1763-72.

### Other Peer-Reviewed Publications in Print or Other Media

#### Case Reports (Submitted or in Press)

Saied A, Bhati C, **Sharma R**, Garrean S, Salti G. Small bowel obstruction from breast cancer metastasis: A case report and review of the literature. *Breast Dis* 2011; in press.

### Non Peer-Reviewed Scientific or Medical Publications/Materials in Print or Other Media

#### Reviews, Chapters, Monographs, and Editorials

**Sharma R**, Wagner JL, Hwang RF. Ablative therapies of the breast. In: Curley SA, editor. *Surgical oncology clinics of North America: ablative procedures in surgical oncology*. Philadelphia, PA: Elsevier. 2011; 20(2): 317-40.

## Division of Ophthalmology members

Frank G. Berson, MD	Chief, Division of Ophthalmology; Associate Professor of Ophthalmology
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Jorge G. Arroyo, MD, MPH	Associate Professor of Ophthalmology; Director, Retina Service Retina Research Center
Thomas O'Day	Ophthalmic Technician
Carole Uminski	Administrative Assistant II
Sushant Wagley, BA	Clinical Research Assistant and Coordinator

Don C. Bienfang, MD	Assistant Professor of Ophthalmology
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Michele Coleman, OD	Lead Optometrist
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Kevin Hart	Operations Manager
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Dianna Iandolo, OD	Optometrist
--------------------	-------------

Mark C. Kuperwaser, MD	Instructor in Ophthalmology
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Paul Murray, OD	Optometrist
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Timothy J. Murtha, MD	Clinical Instructor in Ophthalmology
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Jessica Poscover, OD	Optometrist
----------------------	-------------

Eileen Rose	Administrative Director
-------------	-------------------------

Nurhan Torun, MD	Instructor in Ophthalmology
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Olga Zeldin, OD	Optometrist
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## Division of Ophthalmology

*Longwood Medical  
Eye Center*



## Research Focus

At the Retina Research Center, I am committed to excellence in teaching and continued scholarship in ophthalmic research. Our areas of research focus include retinal imaging and treatment of age-related macular degeneration (AMD), diabetic retinopathy, neovascular glaucoma, epiretinal membranes, and retinal detachments. In addition, I am also dedicated to collaborative projects with Joslin Diabetes Center and the Scepens Eye Institute.

## Research Support

“A randomized, double masked, active controlled phase III study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF trap in subjects with neovascular age-related macular degeneration”

Regeneron Pharmaceuticals Inc.

12/2007 – 12/2011

Site PI: Jorge G. Arroyo, MD, MPH

“Vitreous and serum pharmacokinetic study of posterior sub-tenon’s injection of triamcinolone acetonide”

Macula Society Research Grant

01/2006 – 07/2011

PI: Jorge G. Arroyo, MD, MPH

“Evaluation of triple combination therapy in patients with wet AMD”

Investigator Initiated Novartis AMD Clinical Research Grant

12/2008 -1/2011

PI: Jorge G. Arroyo, MD, MPH

## Accomplishments in the Past Year

### Research Progress

During the past year, we completed three investigator initiated clinical investigations and one industry-sponsored Phase-III clinical trial of an anti-VEGF drug designed for wet AMD. We initiated two clinical studies and one epidemiologic study examining AMD.

### Current Unfunded Research Projects

“Apolipoprotein A1-Milano in AMD”

Investigating the role of apolipoprotein A1-Milano in subjects in Limone sul Garda, Italy to better understand the underlying pathophysiology of AMD and identify a novel treatment approach for this disease.

PI: Jorge G. Arroyo, MD, PhD

“Endoscopic Retinal and Ciliary Body Photocoagulation (ECP) for Treatment of Neo-vascular Glaucoma”

Outcomes comparison of ECP versus standard treatment for neo-vascular glaucoma.

PI: Jorge G. Arroyo, MD, PhD

“AMD in the American population—Results from the National Health and Nutrition Examination Survey”

Examination of trends and associations at the population level between various social, behavioral, and biologic markers/risk factors and AMD.

PI: Jorge G. Arroyo, MD, PhD



**Jorge G. Arroyo,  
MD, MPH**

Associate Professor of  
Ophthalmology

Research Staff  
Sushant Wagley  
Carole Uminski  
Thomas O'Day



*Sushant Wagley in the lab, analyzing data.*

## Invited Presentations

“Endoscopy in Vitreoretinal Surgery.” Second Annual Massachusetts Eye and Ear Infirmary Vitrectomy Course. Boston, MA. July 2011.

“History of Retinal Detachment Surgery.” Boston University School of Medicine, Department of Ophthalmology, Resident Lecture Series. Boston, MA. November 2011.

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## Teaching, Training, and Education

Medical school advanced clerkship in Ophthalmology –  
Harvard Medical School  
Massachusetts Eye and Ear Infirmary Resident Rotation  
Joslin Diabetes Center Fellow Rotation

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## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Kinoshita T, Kovacs KD, Wagley S, **Arroyo JG**. Morphological differences in epiretinal membranes on ocular coherence tomography as a predictive factor for surgical outcome. *Retina* 2011;31(8):1692-8.

Kovacs KD, Quirk MT, Kinoshita T, Gautam S, Ceron OM, Murtha TJ, **Arroyo JG**. A retrospective analysis of triple combination therapy with intravitreal bevacizumab, posterior sub-tenon's triamcinolone acetonide, and low-fluence verteporfin photodynamic therapy in patients with neovascular age-related macular degeneration. *Retina* 2011;31(3):446-52.

#### Research Investigations (Submitted or in Press)

Kovacs KD, Wagley S, Quirk MT, Ceron OM, Silva PS, Singh RJ, Gukasyan HJ, **Arroyo JG**. Pharmacokinetic study of vitreous and serum concentrations of triamcinolone acetonide after posterior sub-tenon's injection. *Am J Ophthalmol* 2011; in press.

Krishnan S, Wagley S, **Arroyo JG**. Effects of egg consumption on macular pigment concentration and serum cholesterol. *Surv Ophthalmol* 2011; in press.

Wagley S, Yuan J, Hoffert DS, **Arroyo JG**. Postoperative choroidal hemorrhage shows elevated concentration of tissue plasminogen activator (tPA). *Retin Cases Brief Rep* 2011; in press.

### Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

Wagley S, Kinoshita T, Kovacs KD, **Arroyo JG**. Morphological differences in epiretinal membranes on ocular coherence tomography as a predictive factor for surgical outcome. Presented (as a poster) at ARVO (The Association for Research in Vision and Ophthalmology). Fort Lauderdale, FL, April, 2011.

Wagley S, Kinoshita T, Kovacs KD, **Arroyo JG**. Morphological differences in epiretinal membranes on ocular coherence tomography as a predictive factor for surgical outcome. Presented (as a poster) at Harvard Medical School and Massachusetts Eye and Ear Infirmary Department of Ophthalmology Annual Meeting, Boston, MA, June, 2011.



## Division of Plastic and Reconstructive Surgery members

Robert A. Frankenthaler, MD	Acting Chief, Division of Plastic and Reconstructive Surgery; Chief, Division of Otolaryngology; Assistant Clinical Professor of Surgery
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Geoffrey Brahmer, MDiv	Educational and Research Coordinator
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Peter S. Kim, MD	Instructor in Surgery
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Bernard T. Lee, MD John T. Nguyen, MD	Assistant Professor of Surgery Research Fellow
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Samuel J. Lin, MD Ahmed Ibrahim, MD Amr Rabie, MD	Assistant Professor of Surgery Research Fellow in Surgery International Collaborator, Ain Shams University
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Donald Morris, MD	Assistant Clinical Professor of Surgery
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Maria Semnack, RN	Nurse Manager
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Sumner A. Slavin, MD	Associate Clinical Professor of Surgery
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Adam M. Tobias, MD	Instructor in Surgery
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Joseph Upton, MD	Professor of Surgery
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### *Other Faculty/Staff/Students*

Olubimpe Ayeni, MD	Aesthetic Plastic Surgery Fellow
Reena Bhatt, MD	Hand/Microsurgery Fellow
Ian Buchanan	Student Researcher
Daniel Gittings	Student Research Fellow
Aldebarani Gonzalez	Student Research Fellow
Ken Hughes	Aesthetic Plastic Surgery Fellow
Ibrahim Khansa	Research Fellow
Adeyiza Momoh, MD	Clinical Fellow
Priti Patel, MD	Clinical Fellow
Sashank Reddy, MD, PhD	Research Fellow
Hani Sinno, MD	International Collaborator
Simon Talbot, MD	Hand/Microsurgery Fellow
Jacob Zhang	Student Intern

## Division of Plastic and Reconstructive Surgery



## Research Focus

### Basic Research

The Division of Plastic and Reconstructive Surgery focused on these primary basic research projects in 2011:

#### 1. Electrochemical Activation and Inhibition of Neuromuscular Systems through Modulation of Ion Concentrations with Ion-Selective Membranes

This is a collaborative project with the Han group at Massachusetts Institute of Technology and is focused on innovation in basic neuroscience. We are developing a electrochemical nerve stimulation and blocking method using a microelectromechanical systems device (*Figure 1*), which modifies local ion concentrations at the peripheral nerve surface (*Figure 2*).

#### 2. Perforator Identification Using Near-Infrared Imaging

Using a real time, light emitting diode-based imaging system to exploit invisible near-infrared (NIR) light for assessment of flap physiology, the perforator flaps were assessed with NIR fluorescence angiography using indocyanine green, an FDA-approved NIR fluorophore. This process permits patient-specific planning, image-guided creation, and intraoperative assessment without the need for lasers or ionizing radiation.

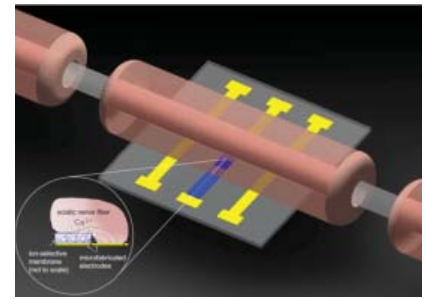
We are currently looking at ways to quantify perforator flap perfusion and identifying vascular compromise. We have created two indices for arterial occlusion and venous congestion in which we are able to perform a cutaneous assessment that will provide information about vascular status. In addition, we are completing projects looking at the importance of perforator number, dominance, and location to flap perfusion. This collaborative large animal project is conducted by Bernard T. Lee, MD, and John V. Frangioni, MD, PhD, (Medicine, BIDMC).

#### *Near-Infrared Imaging For Intra-operative Assessment of Perfusion in Vascularized Bone Flaps*

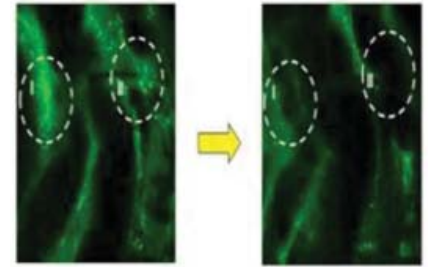
Free vascularized bone transfers are a versatile and valued technique for reconstructing large bone defects resulting from post oncologic resections, trauma, infections, and congenital defects. However, vascularized bone transfers carry significant risks. Estimates in the literature of total flap loss after reconstruction are as high as 14%, with complication rates of 21-43%. Therefore, it is imperative that techniques are established to effectively monitor viability of vascularized bone grafts to improve surgical outcomes. NIR fluorescence imaging provides a composite intraoperative evaluation of perfusion in real time. This study was designed to investigate the ability of NIR fluorescence imaging to assess perfusion and viability of vascularized bone flaps.

#### *Assessment of Perfusion in a Partial Face Transplantation Model with a Near-Infrared Imaging System*

Composite tissue allografts (CTAs) have many applications in microsurgery including partial face composite tissue allotransplantation. Partial face CTA has recently been achieved in human subjects with success; however, significant risk of complications still exists with major concerns of tissue ischemia and rejection. As a result, it is imperative to establish techniques to effectively



*Figure 1. Microelectromechanical systems device.*



*Figure 2. Confocal microscopy showing decreased ion concentration around nerves (green signal outlined by the hashed oval).*

monitor the viability of transplanted microsurgical grafts in order to decrease the failure rate of composite tissue flaps. NIR fluorescence imaging system is capable of providing a composite intra-operative evaluation of perfusion in real time and has been shown to assess tissue perfusion. This study was designed to investigate the ability of NIR fluorescence imaging to effectively monitor and assess perfusion and viability on harvested partial face CTAs.

### *Spatial Frequency Domain Imaging to Effectively Monitor Viability of Composite Tissue Facial Flaps*

New techniques are required to effectively monitor the viability of transplanted microsurgical grafts. Because NIR photons travel deep into tissues (up to 1cm), optical imaging is capable of providing an intra-operative evaluation of CTA status in real time. Our team has developed and validated a novel NIR optical imaging technique using spatial frequency domain imaging for effectively monitoring oxygenation and assessing tissue perfusion and viability over a large field of view (18 x 14 cm).

### *Clinical Pilot Study Using Spatial Frequency Domain Imaging to Assess Oxygenation of Perforator Flaps during Breast Reconstructive Surgery*

There currently exists no reliable method for passively monitoring tissue oxygenation and perfusion during reconstructive surgery. Standard of care still relies on the surgeon's experience to assess flap viability based on clinical signs, such as color, temperature, capillary refill, and bleeding. It has been shown that early detection of vascular complications improves the rate of flap salvage; therefore, newer methods that allow for a reliable objective measurement of flap viability are desperately needed. Our team has developed a novel imaging system using spatial frequency domain imaging to measure oxygenation over a large field of view (18 x 14 cm). Following validation on large animals approaching the size of humans, this imaging system has been translated to a clinical pilot study where perforator flap oxygenation was assessed intraoperatively.

## Clinical Research

In 2011, the Division of Plastic and Reconstructive Surgery worked on several clinical research projects, which focused on craniofacial and breast reconstructive surgery.

### Head, Neck, and Face Surgery

#### *1. Real-time Intraoperative Computed Tomography Monitoring of Fracture Reduction*

The aim of this exploratory study was to assess the potential impact of real-time intraoperative CT scanning (xCAT® ENT) during surgical reduction of fractures (Figure 3).

#### *2. Outcomes Following Surgery for Skin Cancer of the Head and Neck*

The aim of this study is to evaluate contributing factors related to the development, diagnosis, and management of patients with skin cancer of the head and neck. A retrospective analysis of patients with skin cancer of the head and neck is being done. Skin cancer rate, clinical outcomes, and the various

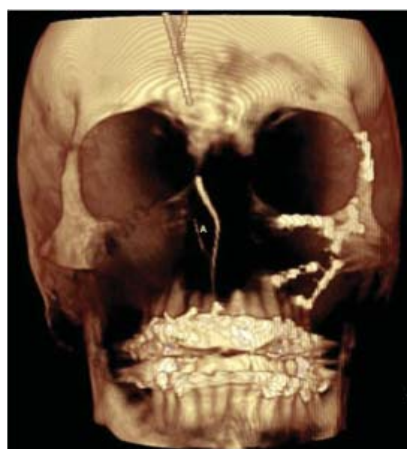


Figure 3. 3-D reconstruction using intraoperative CT scanning.

contributing factors related to development, diagnosis and management of skin cancer will be analyzed.

### 3. Evaluation of the Nasal Airway Using an Acoustic Rhinometer

The aim of this study is to compare patency of the nasal airway before and after a procedure of the nose in patients complaining of nasal obstruction and in patients not complaining of nasal obstruction, and to correlate this with the patients' symptoms and data gathered from acoustic rhinometry.

## Breast Surgery

### 1. *Evaluation of Plastic Surgery Outcomes in an Academic Medical Center*

In recent years, a significant body of research in the United States has focused on measuring clinical outcomes and improving quality of care in surgery. Such work is receiving heightened attention in our increasingly value-driven healthcare system. In this context, establishment of an institutional database for plastic surgery outcomes would be a valuable tool in assisting surgeons, patients and payers in choosing safe, effective, and efficient interventions.

### 2. The Outcomes of a DIEP Flap Program

The newly developed DIEP flap program at the BIDMC is a financially viable program that increases utilization of breast reconstruction and improves outcomes and patient satisfaction. Specific aims of the study include:

- Analyzing the breast reconstruction rate before and after the institutionalization of a sub specialized DIEP flap program at an academic medical center.
- Comparing clinical outcomes and patient satisfaction with breast reconstruction, before and after the institutionalization of a sub specialized DIEP flap program.
- Calculating both the overhead costs of starting a DIEP flap program and the average cost of a DIEP flap.
- Comparing costs of implant, TRAM, and DIEP flaps and analyzing the reimbursement schema for DIEP flaps.
- Breast Anatomy and DIEP Flap Analysis

A recent published paper suggested that the incidence of complications resulting from DIEP flap reconstruction of the left breast differed from that that of the right. This may be attributed to variations in their anatomy. The team will investigate and analyze factors that cause differences and variations in breast anatomy. The research will also assess the harvest times of the recipient vessels in the right breast compared to the left, as well as a comparison of the operating times for performing the microsurgery on each breast.

### 3. *Post-mastectomy Breast Reconstruction after Previous Lumpectomy and Radiation Therapy: Analysis of Complications and Satisfaction*

This is an ongoing study in post-mastectomy breast reconstruction. Few studies have looked at the effect of prior radiation in the setting of breast-conservation therapy (BCT) on surgical complications and patient satisfaction with breast reconstruction after a salvage mastectomy. Our studies examine

whether a history of BCT leads to higher rates of complications and dissatisfaction with subsequent breast reconstruction. As this topic is complex and ongoing, we continue to monitor and develop new research projects in this evolving clinical area.

#### *4. The Outcomes of Breast Reconstruction following Partial Mastectomy*

This study aims to analyze breast reconstruction rates following partial mastectomy, comparison of clinical outcomes and evaluation of patient satisfaction as well as calculation of the cost of using different reconstructive techniques. A retrospective cohort analysis of breast reconstruction procedures following partial mastectomy is being undertaken.

#### *5. Breast Cancer Recurrence Following Post mastectomy Reconstruction Compared to Mastectomy with no Reconstruction*

Continuing advances in breast reconstruction have provided surgeons with a multitude of reconstructive options. Concerns remain, however, about the effects of the various reconstructive methods on the ultimate oncologic outcomes. This study compares incidence, detection, and the management of recurrent breast cancer in a large series of patients treated with mastectomy alone or with mastectomy and various forms of reconstruction.

#### *6. Impact of Complications on Patient Satisfaction in Breast Reconstruction*

The development of a complication after surgery can be difficult for both the patient and the surgeon. There is a growing body of literature that evaluates patient satisfaction after breast reconstruction; however, few studies directly focus on the impact of surgical complications on satisfaction. This study analyzes the effect of complications on general and aesthetic satisfaction after breast reconstruction.

#### *7. The Impact of Nipple Reconstruction on Patient Satisfaction in Breast Reconstruction.*

Nipple reconstruction is an integral part of the breast reconstruction process. This study evaluates the effect of nipple reconstruction on patient satisfaction. We found that patients with breast reconstruction who undergo nipple reconstruction have a higher general and aesthetic satisfaction compared to having breast reconstruction alone. Patients should be fully counseled about the potential benefits of nipple reconstruction when undergoing breast reconstruction.

#### *8. Complications in a Large Series of Breast Reductions*

Though there are currently hundreds of articles about breast reduction, there are no single group series of approximately 1000 patients. This will be one of the largest single group series ever analyzed. The study assesses complications and their associated comorbidities. It focuses upon which comorbidities increase the risk of complications in this very commonly performed plastic surgical operation.

### 9. “AirXpanders Patient Activated Controlled Tissue Expander System for Breast Reconstruction”

The research project evaluates the safety and performance of the AirXpander™ Tissue Expanders System in women who are having or have had a mastectomy and plan to have immediate or delayed breast reconstruction surgery, and require tissue. The study is designed to demonstrate that the AirXpander™ Tissue Expander System will perform the same function as saline expanders, stretching the skin and/or tissue of the chest wall to provide for permanent breast implants following mastectomy. Under guidance, it is hoped that the Expanders system will allow the patient to complete the expansion process at home. In addition, it will attempt to eliminate the connection between the external environment and the implanted device, and may reduce the risk of infection from repeated needle injections.

### 10. Silicone Gel-Filled Mammary Prosthesis Clinical Study

In November of 2006, the FDA approved the use of silicone gel-filled implants with the stipulation that all currently enrolled patients continued to be followed through their five year cycle. The IRB-Approved “Inamed Corporation Silicone-Filled Breast Implant Adjunct Clinical Study” involves the collection of clinical data regarding the use of silicone mammary implants for reconstruction in both cancer and non-cancer patients. The studies have been closed to enrollment since November of 2006 and in September of 2011, we completed the follow up of all patients enrolled in the Mentor study. The Inamed Study is nearly its completion and should be closed by the beginning of 2012.

## Research Support

“Electrochemical activation and inhibition of neuromuscular systems with modulation of ion concentrations using ion-selective membranes.”

Affinity Research Collaborative Grant, Department of Surgery, BIDMC  
2011-2012

PI: Samuel Lin, MD

“Aesthetic and reconstructive plastic surgery fellowship”

Synthes Corporation  
7/2007-07/2012

PI: Samuel Lin, MD

“Aesthetic plastic and reconstructive surgery fellowship”

Mentor Corporation  
2011-2012

PI: Samuel Lin, MD

“Perforator identification using near-infrared imaging (NIR)”

NIH/NCI, R01 CA115296  
2010-2015

PI: John Frangioni, MD, PhD

Co-I: Bernard Lee, MD

“Peter Jay Sharp program for aesthetic and reconstructive breast surgery”

Peter Jay Sharp Foundation  
2005-2012

PI: Adam Tobias, MD



“AirXpander patient activated controlled tissue expander system for breast reconstruction”

AirXpander Corporation

2012-2013

PI: Donald Morris, MD

Co-I: Terri Halperin, MD

## Accomplishments in the Past Year

### Research Progress

Research efforts in the Division of Plastic and Reconstructive 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. Members of both Samuel Lin, MD, and Bernard Lee, MD, research teams meet weekly to evaluate and report on current projects, to brainstorm new potential studies, and to develop research time-lines and strategies in moving the projects forward, including the formulation of presentations, abstracts, and original articles.

Over the course of the year, research in plastic surgery has taken major strides in both organizing and participating in collaborative projects. Lin is now closely linked with scientists at the Massachusetts Institute of Technology (see paragraph below) and Lee is working closely with John Frangioni, MD, PhD, and members of his research laboratory (Medicine, BIDMC). Both ongoing projects are attempting to solve major clinical problems by applying basic scientific principles in order to develop new and innovative clinical applications.

Samuel Lin, MD, as Co-Principal Investigator of the project, with Ahmed Ibrahim, MD, and collaborators at MIT published an article about electrochemical nerve stimulation and blocking in *Nature Materials* (right). Dr. Lin and this group were awarded an Affinity Research Collaborative (ARC) Grant by Surgery at BIDMC to foster this collaboration.

Dr. Bernard Lee and team members, John Nguyen, MD, and Ahmed Ibrahim, MD, continue to work as a project team dedicated to research on reconstructive microsurgery. Throughout 2011, the team has particularly focused upon near-infrared imaging to assess preoperative assessment of perfusion in reconstructive surgical flaps, flap viability, as well as oxygenation of perforator flaps in breast reconstructive surgery. This work, as it evolves, may lead to surgical breakthroughs in reconstructive microsurgery and surgical transplantations, including face transplants.

Donald Morris, MD, completed two 5 year long IRB approved studies of silicone gel breast implants utilized in both aesthetic and reconstructive breast surgery. Over 300 patients were enrolled during the life of the study.

One of the major ongoing accomplishments as a Division is our ongoing ability and commitment to recruit and work with young residents, medical students, and researchers. All faculty members are gifted mentors who are able to motivate, inspire and involve younger learners in both basic scientific and clinical research. This collaborative model extends to all of our work in the Division, including our ongoing fellowship programs: body contouring, aesthetic and reconstructive breast surgery, and hand/microsurgery fellowships.



## Administrative Accomplishments

### 1. The Annual Walk in Boston for Breast Cancer.

For the past two years, Maria Semnack, RN, has supported, worked with, and recruited families for the Annual Walk in Boston for Breast Cancer which occurs every October. The walk, “Making Strides Against Breast Cancer,” is sponsored by the American Cancer Society. During the walk, Semnack took a special photo of the pink ribbons (*Figure 4*). Each ribbon represents someone who died from breast cancer, and the sayings are what the walkers wrote to remember them. “The names and ribbons signify all of the people that we are walking for and working for; they are the real inspiration and purpose of our work,” said Semnack.



Figure 4

### 2. Terri Halperin, MD, was named the Chief of Plastic Surgery at Cambridge Health Alliance, Cambridge, MA.

Bernard Lee, MD, co-chaired a Task Force on Immediate Implant Based Reconstruction sponsored by the Massachusetts Registration in Medicine. The year-long task force gathered over 40 multi-disciplinary specialists in the state of Massachusetts and used evidence based medicine approaches to examine practices in implant based reconstruction. The Task Force culminated in an executive summary found on the Board of Medicine website and also a publication in the Journal of the American College of Surgeons.

Adam Tobias, MD, obtained another year of funding for the Breast Reconstructive Surgery Fellowship Program through the Peter Jay Sharp Foundation. The fellowship program has now graduated five fellows, all of whom obtained academic appointments in breast reconstructive surgery at reputable academic medical centers. All of these fellows, utilizing the Tobias-Lee Pathway Model for Autologous Breast Reconstruction, established breast reconstruction programs in their respective medical centers.

## Individual Accomplishments

### Robert Frankenthaler, MD

- Served as Acting Chief, Division of Plastic Surgery.
- Actively involved in giving presentations and writing original articles and book chapters in Otolaryngology.

### Geoffrey Brahmer, MDiv

- Invited to participate in an international collaborative project to write a UNESCO Handbook on the Bioethics of the Holocaust. The handbook will be used to teach bioethics to law students and medical students from around the world.
- Trained and invited to participate in the Ethics Liaison Committee, Beth Israel Deaconess Medical Center.

### Terri Halperin, MD

- Participated in Task Force on Immediate Implant Based Reconstruction sponsored by the Massachusetts Registration in Medicine.

Ahmed Ibrahim, MD

- Participated in and coauthored an article on Electrochemical Activation and Inhibition of Neuromuscular systems Through Modulation of Ion Concentrations with Ion-Selective Membrane. The article was published in Nature Materials.
- Served as Managing Editor for Pearls of Wisdom: Plastic and Reconstructive Surgery, 2nd Edition.
- Co-authored grant submission for ARC grant, awarded by Department of Surgery, BIDMC.
- Served as Reviewer for the On-Line Journal, PLoS ONE.

Peter Kim, MD

- Obtained 1st place for the best resident paper competition at Northwestern University Feinberg School of Medicine, in Chicago, 2nd place for his best resident paper competition at the Illinois Society of Plastic Surgeons, and 2nd place for best poster at the American Association of Plastic Surgeons, 90th Annual Meeting, Boca Raton, FL. The topic of the project was HMG-CoA reductase inhibitors (Statins): A novel approach to preventing hypertrophic scar formation.
- Graduated from the Hand/Microsurgery Program, University of Washington Sports Medicine and Orthopaedics, Seattle, WA.
- Obtained faculty position in the Division of Plastic Surgery, set up an office practice in plastic surgery and hand surgery, BIDMC.
- Obtained academic position, Instructor in Surgery, HMS.
- Joined faculty for the BIDMC orthopedic and plastic surgery hand fellowships and now serves as supervising attending surgeon at the weekly combined plastic and orthopedic hand clinic.

Bernard Lee, MD

- Co-chaired a Task Force on Immediate Implant Based Reconstruction sponsored by the Massachusetts Registration in Medicine.
- Completed his Masters of Business Administration
- Served as Co-Director for the Peter Jay Sharp Reconstructive & Aesthetic Breast Surgery Program.
- Served as primary academic and clinical mentor to the Peter Jay Sharp Aesthetic & Reconstructive Breast Surgery Fellows.
- Served as Faculty Advisor for Harvard Medical School, Holmes Society.
- Served as 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*.
- Served as Member, National In-service Examination Committee, American Society of Plastic Surgeons / Plastic Surgery Educational Foundation.

## Samuel Lin, MD

- Served as BIDMC Residency Site Director for the Harvard Plastic Surgery Residency Program.
- Lead investigator for Neural Prosthetics with Chemical Harvesting and Stimulation for Facial Nerve Reanimation, a project in collaboration with investigators from MIT.
- Co-authored and serves as PI for ARC grant, awarded by the Department of Surgery, BIDMC.
- Served as Director of the Aesthetic Plastic Surgery Fellowship.
- Established and mentored an International Research Fellow within the Division.
- Edited, 1) *Plastic and Reconstructive Surgery Pearls of Wisdom* – 2nd edition, 2) *An Aesthetic Atlas of the Head and Neck*, and wrote a chapter on Minimally Invasive Techniques, for a book entitled, *Aesthetic Head and Neck Surgery*.
- Served as Editor for the On-Line Journal, *PLoS ONE*.
- Served as Associate Editor for *Pearls of Wisdom: Plastic and Reconstructive Surgery*, 2nd Edition.
- Served as reviewer for the *Journal of Plastic and Reconstructive Surgery*.

## Donald Morris, MD

- Became a contributing author to UpToDate for a chapter on “Skin Grafts and Flaps.”
- Participated in Task Force on Immediate Implant Based Reconstruction sponsored by the Massachusetts Registration in Medicine.
- Served for a second year as a member of the Academy of Medical Educators, BIDMC.

## Sumner Slavin, MD

- Served as Chairman for International Symposium, Plastic Surgery at the Red Sea, Eilat, Israel, March, 2011.
- Served as the Co-Director of the Aesthetic Plastic Surgery Fellowship.
- Listed by 2011 *Boston Magazine* as one of the Top Plastic Surgeons in Boston.
- Served as Associate Editor for *Plastic and Reconstructive Surgery* (Journal).

## Maria Semnack, RN

- For the past two years, Maria Semnack, RN, has supported, worked with, and recruited families for the Annual Walk in Boston for Breast Cancer which occurs every October. The walk, “Making Strides Against Breast Cancer,” is sponsored by the American Cancer Society.

Adam Tobias, MD

- 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 intra-operative pathways, and the ongoing education of residents and medical students. Over the course of the year, Dr. Tobias has also been active in research and in the mentoring of fellows, residents, and medical students.

Joseph Upton, MD

- 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 in the integration of the plastic surgery and orthopedic surgery hand fellowships.
- Recipient of the Rofeh International Award, for his surgical work providing medical care and surgical services to children, the poor, and indigents from around the world.
- Actively involved in giving presentations and the writing of original articles and book chapters on hand and microsurgery.

**Invited Presentations**

Geoffrey Brahmer, MDiv

“Kovno Ghetto: Stories of Light and Darkness in a Lithuanian Ghetto.” Congregation Eitz Chayim. Cambridge, MA. January 9, 2011.

“Kovno Ghetto: Stories of Light and Darkness in a Lithuanian Ghetto.” Glasgow Reform Synagogue. Glasgow, Scotland. January 19, 2011.

“In Remembrance: Journey to the Ghetto of Łód .” Arlington High School. February 7, 2011.

“In Remembrance: The Armenian Genocide.” New Bridge on the Charles. Dedham, MA. February 16, 2011.

“In the Eye of the Storm: 6 Photographers in the Nazi Era.” Temple Shir Tikvah, German Jewish Dialogue of Newton. March 6, 2011.

“The Ghetto of Łód.” Boston Psychoanalytic Institute, Panel Speaker: Fecallists in the Ghetto of Łód: Integrity and Moral Decision Making Amidst Mortal Danger. Boston, MA. March 7, 2011.

“The Ghetto of Łód.” Annual Meeting Eastern Psychological Association, Panel Speaker: Fecallists in the Ghetto of Łód: Integrity and Moral Decision Making Amidst Mortal Danger. Boston, MA. March 11, 2011.

“In the Eye of the Storm: 6 Photographers in the Nazi Era.” Hebrew College, German Jewish Dialogue of Newton. Newton, MA. April 12, 2010.

“Health Care Workers in the Ghetto of Łód: Care, Compliance, Conscience and Resistance.” Temple Tifereth Israel. Malden, MA. April 28, 2011.

“You Can Kill Us But You Can’t Humiliate Us: How Do People Survive with Integrity In the Face of Humiliation and Terror?” Boston Psychoanalytical Institute, Open Members Session, with Bursztajn H, Haque OS, Orenstein A. Boston, MA. May 2, 2011.

“Kovno Ghetto: Stories of Light and Darkness in a Lithuanian Ghetto.” Beth Israel Deaconess Medical Center, General Surgery Grand Rounds. Boston, MA. May 11, 2011.

“In the Eye of the Storm: 6 Photographers in the Nazi Era.” Temple Emunah, German Jewish Dialogue of Newton. Lexington, MA. June 18, 2011.

“Kovno Ghetto: Stories of Light and Darkness in a Lithuanian Ghetto.” Congregation Agudas Achim & Eretz Israel. June 26, 2011.

“In the Eye of the Storm: 6 Photographers in the Nazi Era.” German-Jewish Dialogue of Belmont, Belmont, MA. June 28, 2011.

“Health Care in the Ghetto of Łódź.” Stiftung Neve Synagogue Berlin, Centrum Judaicum, Sponsored by German Medical Society, Panel Speaker: The Forgotten Doctors of the Holocaust: Making Tragic Ethical Choices in the Midst of Terror. Berlin, Germany. July 18, 2011.

“Kovno Ghetto: Stories of Light and Darkness in a Lithuanian Ghetto.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. August 2, 2011.

“Lamentation for Łódź.” Jewish Synagogue. Bethlehem, NH. August 26, 2011.

Peter Kim, MD

“Contemporary Rehabilitation of Upper Extremity Amputees.” Beth Israel Deaconess Medical Center, Department of Surgery Grand Rounds. Boston, MA.

“Compressive Neuropathies and Dupuytren’s Disease.” Fenway Health. Boston, MA.

“Reconstruction, Restoration and Replacement: Contemporary Rehabilitation of Upper Extremity Amputees.” Beth Israel Deaconess Medical Center, Division of Plastic Surgery. Boston, MA. December 13, 2011.

Bernard Lee, MD

“Designing Clinical Pathways in Breast Reconstruction.” Beth Israel Deaconess Medical Center, Department of Pathology and Breast Surgery Institute, Breast Tumor Board Multidisciplinary Conference. Boston, MA. October 26, 2011.

Samuel Lin, MD

“Tumors of The Parotid Gland/Head and Neck Cancer.” Shriners Burn Hospital, Plastic Surgery Grand Rounds (Core Curriculum). Boston, MA. March 23, 2011.

“Graded Modulation Using a BioMEMBs Device.” Plastic Surgery Research Council, 56th Annual Meeting. Louisville, KY. April 28-30, 2011.

“Orthopaedic PGY-1’s Minimal Goals and Objectives.” Massachusetts General Hospital, Orthopedic Intern Orientation for Plastic Surgery. Boston, MA. June 22, 2011.

“In-service Review for Plastic Surgery Residents.” Beth Israel Deaconess Medical Center. Boston, MA. July 5, 2011.

“Electrochemical Prosthesis Using a BioMEMS Device.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Meeting. Boston, MA, November 1, 2011.

“Development of a Facial Nerve Neuroprosthetic Device.” Shriners Burn Hospital, Plastic Surgery Grand Rounds. Boston, MA. November 9, 2011.

“Electrochemical Prosthesis Using a BioMEMS Device. Advanced Nerve Stimulation and Inhibition by Ion Selective Membrane (ISM) Electrodes.” Massachusetts Institute of Technology (MIT), Cellular Biophysics: Special Lecture. Cambridge, MA, December 9, 2011.

“Annual Residency Advisor.” Harvard Medical School, Third Year Medical Student Reception. Boston, MA.

“Practical Approaches to the Treatment of Obesity.” 25th Annual International Conference on Obesity. Boston, MA.

Donald Morris, MD

“Complications of breast reconstruction following radiation therapy.” The Israeli Society of Plastic & Aesthetic Surgery, International Conference, Plastic Surgery at the Red Sea. Eilat, Israel. March 23-25 2011.

Maria Semnack, RN

“A Nurse’s Life and Practice.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. December 6, 2011.

Sumner Slavin, MD

“Telemedicine in Plastic Surgery: Perils, Pitfalls and Benefits in the Post Operative Care of the Plastic Surgery Patient.” 25th Annual Virgin Island Workshop in Plastic Surgery. St. John, USVI. January 25-28, 2011.

“Dermal Matrix in the Correction of Secondary Deformities After Breast Augmentation.” 25th Annual Virgin Island Workshop in Plastic Surgery. St. John, USVI. January 25-28, 2011.

“Approaches to Oncoplastic Surgery (Moderator).” Breast Cancer Coordinated Care, Washington, DC. February, 3-5, 2011.

“Timing of Autologous Reconstruction in the Patient Receiving Post-Mastectomy Radiation: The Harvard Perspective.” Washington, DC. February, 3-5, 2011.

“Immediate and Late Reconstruction of the Lumpectomy Defect with Flaps.” Washington, DC. February, 3-5, 2011.

“Correction of Secondary Deformities After Breast Augmentation.” American Association of Plastic Surgeons, 90th Annual Meeting. Boca Raton, FL. April, 9-12, 2011.



“New Lymphatic Pathways in the Breast and Axilla.” American Association of Plastic Surgeons, 90th Annual Meeting. Boca Raton, FL. April, 9-12, 2011.

Jospeh Upton, MD

“Pollicization.” The Israeli Society of Plastic & Aesthetic Surgery, International Conference, Plastic Surgery at the Red Sea. Eilat, Israel. March 23-25, 2011.

“Common Pediatric Hand Problems.” Indiana University, Department of Surgery, Visiting Professor. Bloomington, IN. June 1-2, 2011.

“Pediatric Microsurgery.” Indiana University, Department of Surgery, Visiting Professor. Bloomington, IN. June 1-2, 2011.

“Pollicization.” Indiana University, Department of Surgery, Visiting Professor. Bloomington, IN. June 1-2, 2011.

“Congenital Anomalies.” International Federation of Societies for Surgery of the Hand, Congress Meeting. Las Vegas, NV. September 8-10, 2011.

“Syndactyly.” International Federation of Societies for Surgery of the Hand, Congress Meeting. Las Vegas, NV. September 8-10, 2011.

“What is Your Surgical IQ?” Beth Israel Deaconess Medical Center, Department of Surgery Grand Rounds. Boston, MA. November 16, 2011.

#### **Invited Presentations by Research Fellows**

Reena Bhatt, MD

“Nerve Compression and Neuropathy of the Hand.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Meeting. Boston, MA. July 19, 2011.

“Wrist Anatomy: Bones and Ligaments.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Meeting. Boston, MA. August 16, 2011.

“Hand Jeopardy I.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Meeting. Boston, MA, October 11, 2011.

“Hand Jeopardy II.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Meeting. Boston, MA, December 20, 2011.

Ken Hughes, MD

“Safety in Office-Based Practice.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. February 15, 2011.

“Review of Aesthetic Plastic Surgery Fellowship.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. July 5, 2011.

Ahmed Ibrahim, MD

“Tumors of The Parotid Gland/Head and Neck Cancer.” Shriners Burn Hospital, Plastic Surgery Grand Rounds (Core Curriculum). Boston, MA. March 23, 2011.

“Graded Modulation Using a BioMEMBs Device.” Plastic Surgery Research Council, 56th Annual Meeting. Louisville, KY. April 28-30, 2011.

“Orthopaedic PGY-1’s Minimal Goals and Objectives.” Massachusetts General Hospital, Orthopedic Intern Orientation for Plastic Surgery. Boston, MA. June 22, 2011.

“Electrochemical Prosthesis Using a BioMEMS Device.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Meeting. Boston, MA, November 1, 2011.

“Development of a Facial Nerve Neuroprosthetic Device.” Shriners Burn Hospital, Plastic Surgery Grand Rounds. Boston, MA. November 9, 2011.

“Electrochemical Prosthesis Using a BioMEMS Device. Advanced Nerve Stimulation and Inhibition by Ion Selective Membrane (ISM) Electrodes.” Massachusetts Institute of Technology (MIT), Cellular Biophysics: Special Lecture. Cambridge, MA, December 9, 2011.

### Adeyiza Momoh, MD

“Challenging Breast Reconstructive Cases.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. March 22, 2011.

“Review of Breast Reconstructive Surgery Fellowship.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. June 21, 2011.

### Amr Rabie, MD

“Tumors of The Parotid Gland/Head and Neck Cancer.” Shriners Burn Hospital, Plastic Surgery Grand Rounds (Core Curriculum). Boston, MA. March 23, 2011.

“Graded Modulation Using a BioMEMBs Device.” Plastic Surgery Research Council, 56th Annual Meeting. Louisville, KY. April 28-30, 2011.

“Electrochemical Prosthesis Using a BioMEMS Device.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Meeting. Boston, MA, November 1, 2011.

“Development of a Facial Nerve Neuroprosthetic Device.” Shriners Burn Hospital, Plastic Surgery Grand Rounds. Boston, MA. November 9, 2011.

### Simon Talbot, MD

“Flexor Tendon Injuries.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. January 4, 2011.

“Inservice Hand Review.” Beth Israel Deaconess Medical Center, Plastic Surgery Division Rounds. Boston, MA. February 8, 2011.

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## Teaching, Training, and Education

### Undergraduate and Medical School Courses

The Division of Plastic Surgery was active in teaching student clerkships and 4th year medical students for HMS course, SU514M.1, a course that

was directed by Bernard Lee, MD, and Samuel Lin, MD. In 2011, we had 11 HMS student clerks rotate through the Division. Each student spent one month in the Division. We had hosted three international medical students who were on observational rotations.

The Division was part of the Dept. of Surgery's elective rotation for two-week rotations of Harvard Medical Students, HMS III's. In 2011, we helped mentor three students. In addition to mentoring ongoing students, the Division sponsored several hour-long wound healing and suturing training seminars for each group of rotating students assigned to the BIDMC.

Sponsored three postgraduate Clinical Fellows, four student clinical fellows and one high school summer research intern.

Reena Bhatt, MD, 2011-2012, gave a talk on medical careers in plastic surgery to medical students at HMS.

Peter Kim, MD, presented two formal lectures for second year medical students at Harvard Medical School. The presentations included one on "Hand Anatomy" and a second on "Performing a Hand Consultation."

### **Graduate School and Graduate Medical Courses**

All faculty members introduced plastic surgery residents and fellows, as well as surgical interns special challenges and approaches in microsurgery and working with surgical flaps. Residents, fellows and medical students are invited to participate on papers, abstracts and presentations.

Drs. Lin, Lee, Miller and Tobias sponsored two educational sessions on non-surgical fillers.

Drs. Lee and Lin sponsored and taught two head and neck cadaver labs.

Peter Kim, MD, taught a hand and upper extremity cadaver lab, which included a practicum on Femoral Free Flap Cadaver Dissection.

Peter Kim, MD, presented three one-hour lectures to Emergency Medicine Residents at Harvard Medical School. The lectures included: 1) Hand Anatomy and Performing a Hand Examination in the ER; 2) Upper Extremity Splinting Workshop; 3) Treatment of Facial Abscesses

Drs. Lin, Lee, Morris, Tobias, Slavin and Upton all participated in the Core Curriculum and Journal Club of the Combined Harvard Plastic Surgery Residency Program.

Simon Talbot, MD, while a BIDMC Hand / Microsurgery Fellow, provided weekly tutoring sessions for three month to doctoral students in the development of biomedical devices, Harvard School of Engineering and Applied Sciences ES227.

In 2011, faculty members helped mentor thirteen EMED, interns, fourteen General Surgery Interns, six orthopedic interns, two podiatry residents, and 21 plastic surgery residents. We also sponsored four fellows: aesthetic and reconstructive breast surgery, body contouring, hand/microsurgery, and a post-graduate hand preceptor. In addition, we were also actively involved in training the BIDMC Orthopedic Hand Fellow and seven PGY 2 Orthopedic residents who were assigned to the hand services.

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Bar-Meir ED, Lin SJ, Momoh AO, Tobias AM, Colakoglu S, Yueh JH, Slavin SA, Lee BT. The lateral chest wall: a separate aesthetic unit in breast surgery. *Plast Reconstr Surg* 2011;128(6):626e-34e.

Colakoglu S, Khansa I, Curtis MS, Yueh JH, Ogunleye A, Han CH, Tobias AM, Lee BT. Impact of complications on patient satisfaction in breast reconstruction. *Plast Reconstr Surg* 2011;127(4):1428-36.

Craft RO, Colakoglu S, Curtis MS, Yueh JH, Lee BS, Tobias AM, Lee BT. Patient satisfaction in unilateral and bilateral breast reconstruction. *Plast Reconstr Surg* 2011;127(4): 1417-24.

Curtis MS, Arslanian B, Colakoglu S, Tobias AM, Lee BT. Immediate micro-surgical breast reconstruction and simultaneous lymph node dissection: issues with node positivity and recipient vessel selection. *J Reconstr Microsurg* 2011;27(7):445-8.

deBlacam C, Momoh AO, Colakoglu S, Tobias AM, Lee BT. Evaluation of clinical outcome and aesthetic results after autologous fat grafting for contour deformities of the reconstructed breast. *Plast Reconstr Surg* 2011;128(5):411e-8e.

Gioux S, Mazhar A, Lee BT, Lin SJ, Tobias AM, Cuccia DJ, Stickdale A, Oketokoun R, Ashitate Y, Kelly E, Weinmann M, Durr NJ, Moffitt LA, Durkin AJ, Tromberg BJ, Frangioni JV. First-in-human pilot study of a spatial frequency domain oxygenation imaging system. *J Biomed Opt* 2011;16(8):086015.

Ibrahim AM, Rabie AN, Lee BT, Lin SJ. Intraoperative CT: A teaching tool for the management of complex facial fracture fixation in surgical training. *J Surg Educ* 2011;68(5):437-41.

Khansa I, Colakoglu S, Tomich D, Nguyen MD, Tobias AM, Lee BT. Factor V Leiden associated with flap loss in microsurgical breast reconstruction. *Microsurgery* 2011;31(5):409-12.

Khansa I, Colakoglu S, Curtis MS, Yueh JH, Ogunleye A, Tobias AM, Lee BT. Post-mastectomy breast reconstruction after previous lumpectomy and radiation therapy: analysis of complications and satisfaction. *Ann Plast Surg* 2011;66(5):444-51.

Ko JH, Kim PS, O'Shaughnessy KD, Kuiken TA, Dumanian GA. A quantitative evaluation of gross versus histologic neuroma formation in a rabbit forelimb amputation model: potential implications for the operative treatment and study of neuromas. *J Brachial Plex Peripher Nerve Inj* 2011;6:8.

Lin SJ, Nguyen MD, Chen C, Colakoglu S, Curtis MS, Tobias AM, Lee BT. Tissue oximetry monitoring in microsurgical breast reconstruction decreases flap loss and improves rate of flap salvage. *Plast Reconstr Surg* 2011;127(3):1080-5.

Pomahac B, Nowinski D, Diaz-Siso JR, Bueno EM, Talbot SG, Sinha I, Westvik TS, Vyas R, Singhal D. Face transplantation. *Curr Probl Surg* 2011;48(5):293-357.

**Rabie A, Ibrahim AM, Lee BT, Lin SJ.** Use of intraoperative CT in complex facial fracture reduction and fixation: an early report. *J Craniofac Surg* 2011;22(4):1466-7.

**Reddy SK, Colakoglu S, Curtis MS, Tobias AM, Lin SJ, Lee BT.** Bilateral autologous reconstruction from different sites: indications and outcomes after DIEP and SGAP flaps. *Plast Reconstr Surg* 2011;127(6):151e-3e

Song YA, Melik R, **Rabie AN, Ibrahim AM, Moses D, Tan A, Han J, Lin SJ.** Electrochemical activation and inhibition of neuromuscular systems through modulation of ion concentrations with ion-selective membranes. *Nat Mater* 2011;10(12):980-6.

**Talbot SG, Rogers GF.** Compartment syndrome caused by intravenous infiltration. *Ann Plast Surg* 2011;67(5):531-3.

**Talbot SG, Upton J, Driscoll DN.** Changing trends in pediatric upper extremity electrical burns. *Hand* 2011;6(4):394-8.

Yueh JH, Bar-Meir ED, Liao EC, **Lee BT.** Major limb replantation. *ePlasty* 2011;11:ic1.

Research Investigations (Submitted or in Press)

*\*Co-first author on the publication.*

Ashitate Y, **Lee BT\***, Laurence RG, Lunsford E, Hutteman M, Oketokoun R, Choi HS, Frangioni JV. Intraoperative prediction of post-operative flap outcome using the near-infrared fluorophore methylene blue. *Ann Plast Surg* 2011; in press.

Ashitate Y, **Lee BT\***, Ngo LH, Laurence RG, Hutteman M, Oketokoun R, Lunsford E, Choi HS, Frangioni JV. Quantitative assessment of nipple perfusion with near-infrared fluorescence imaging. *Ann Plast Surg* 2011; in press.

**de Blacam C, Momoh AO, Colakoglu S, Slavin SA, Tobias AM, Lee BT.** Cost analysis of implant-based breast reconstruction with acellular dermal matrix. *Ann Plast Surg* 2011; in press.

**de Blacam C, Ogunleye AA, Momoh AO, Colakoglu S, Tobias AM, Sharma R, Houlihan MJ, Lee BT.** High BMI and smoking predict morbidity in breast cancer surgery: a multivariate analysis of 26,988 patients from the NSQIP database. *Ann Surg* 2011; in press.

Gioux S, Mazhar A, **Lee BT**, Cuccia DJ, Stockdale A, Oketokoun R, Ashitate Y, Durr N, Durkin AJ, Tromberg BJ, Frangioni JV. Preclinical and clinical validation of a novel oxygenation imaging system. *Proc SPIE* 2011; in press.

**Ibrahim AMS, Rabie A, Lee BT, Lin SJ.** Intraoperative CT: A teaching tool for the management of complex facial fracture fixation in surgical training. *J Surg Educ* 2011; in press.

Kasper EM, Ridgway EB, **Rabie A, Lee BT, Chen C, Lin SJ.** Staged scalp soft tissue expansion prior to delayed allograft cranioplasty: a technical report. *Neurosurg* 2011; in press.

**Momoh AO, Colakoglu S, de Blacam C, Gautam S, Morris DJ, Tobias AM, Lee BT.** Delayed autologous breast reconstruction after postmastectomy radiation therapy: is there an optimal time? *Ann Plast Surg* 2011; in press.

**Momoh AO, Colakoglu S, de Blacam C, Yueh JH, Lin SJ, Tobias AM, Lee BT.** The impact of nipple reconstruction on patient satisfaction in breast reconstruction. *Ann of Plast Surg* 2011; in press.

**Momoh AO, Colakoglu S, Westvik TS, Curtis MS, Yueh JH, de Blacam C, Tobias AM, Lee BT.** Analysis of complications and patient satisfaction in pedicled TRAM and DIEP flap breast reconstruction. *Ann Plast Surg* 2011; in press.

**Momoh AO, Colakoglu S, de Blacam C, Curtis MS, Lee BT.** The forked liposuction cannula: a novel approach to the correction of cicatricial contracture deformities in breast reconstruction. *Ann Plast Surg* 2011; in press.

**Ogunleye AA, de Blacam C, Curtis MS, Colakoglu S, Tobias AM, Lee BT.** An analysis of delayed breast reconstruction outcomes as recorded in the American College of Surgeons National Surgical Quality Improvement Program. *J Plast Reconstr Aesthet Surg* 2011; in press.

**Rabie AN, Chang J, Ibrahim AM, Lee BT, Lin SJ.** Use of Tragal cartilage grafts in rhinoplasty: an anatomic study and review of the literature. *Ear Nose Throat J* 2011; in press.

**Sinno H, Ibrahim AM, Izadpanah A, Thibaudeau S, Christodoulou G, Youssef T, Slavin SA, Lin SJ.** Utility outcome assessment of the aging neck following massive weight loss. *Otolaryngol Head Neck Surg* 2011; in press.

**Sinno H, Thibaudeau S, Izadpanah A, Tahiri , Christodoulou G, Slavin S, Lin SJ.** The impact of living with a functional and aesthetic nasal deformity following primary rhinoplasty: a utility outcomes score assessment *Ann of Plast Surg* 2011; in press.

**Sinno H, Thibaudeau S, Izadpanah A, Tahiri , Christodoulou G, Zuker R, Lin SJ.** Utility outcome scores for unilateral facial paralysis. *Ann of Plast Surg* 2011; in press

**Sinno H, Thibaudeau S, Tahiri Y, Mok E, Christodoulou G, Lessard L, Williams B, Lin SJ.** Utility assessment of body contouring after massive weight loss. *Aesthetic Plast Surg* 2011; in press.

**Song YA, Rabie AN, Ibrahim AM, Han J, Lin SJ.** Graded nerve modulation using a BioMEMS device. *Plast Reconstr Surg* 2011; in press.

**Talbot SG, Rogers GF.** Muenke syndrome associated with multiple osteochondromas. *Craniofacial Surg* 2011; in press.

#### **Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

**Hughes K, Lee BT.** Injectable Fillers. In: **Lin SJ, Hijjawi JB**, editors. *Plastic and reconstructive surgery board review: pearls of wisdom*. New York, NY: McGraw-Hill/Appleton & Lange; 2011.

**Lin S, Hijjawi J.** *Plastic and reconstructive surgery board review: pearls of wisdom*. 2nd ed. McGraw-Hill Professional Publishing; 2011.

**Lin SJ, Mustoe TA**, editors. *An aesthetic atlas of the head and neck*. 2nd ed. McGraw-Hill Publishing; 2011.

**Talbot SG, Taghinia AH.** Diagnosis and treatment of hand and upper extremity injuries. In: *Global Surgery*; 2011

Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

**Ayeni OA, Lin SJ.** Chemical Peels. In: **Lin SJ, Mustoe TA**, editors. *An aesthetic atlas of the head and neck*. New York, NY: McGraw-Hill. 2011; in press.

**Cooper JS, Lee BT.** Fillers. In: **Mustoe TA, Lin SJ**, editors. *Aesthetic head and neck: an operative atlas*. New York, NY: McGraw-Hill. 2011; in press.

**Ibrahim AM, Lin SJ, Lee BT.** Autologous dermal-fat flaps for breast reshaping after weight loss. In: **Herman CK, Strauch B**, editors. *Encyclopedia of aesthetic rejuvenation through volume enhancement*. 2011; in press.

**Kim PS, Friedrich JB.** Upper extremity compartment syndrome. American society for surgery of the hand, *ASSH Hand Manual*. Lippincott. 2011; in press.

**Kim PS & Hanl DP.** Management of carpal malunions and onunions. American society for surgery of the hand, *ASSH Hand Manual*. Lippincott. 2011; in press.

**Lau F, Przylecki W, Lee BT, Slavin SA.** Plastic Surgery. In: **Goldfarb M, Gromski MA, Hurst JM Jones DB**, editors. *Pocket surgery: the Beth Israel Deaconess Medical Center handbook of surgery*. Philadelphia, PA: Lippincott, Williams, and Wilkins. 2011; in press.

**Lee BT, Lin SJ.** Lip reconstruction. In: **Fischer JE, Bland KI, Callery MP, Clagett GP, Jones DB, Moneta GB, Seeger JM**, editors. *Fischer's mastery of surgery*. Philadelphia, PA: Lippincott, Williams, and Wilkins. 2011; in press.

**Lin SJ, Mustoe TA**, editors. *An aesthetic atlas of the head and neck*. 2nd ed. New York, NY: McGraw-Hill Publishing. 2011; in press.

**Lin SJ, Ayeni OA.** Neck Lift. In: **Lin SJ, Mustoe TA**, editors. *An aesthetic atlas of the head and neck*. New York, NY: McGraw-Hill Publishing; in press.

**Lin SJ, Butler CE.** Myocutaneous flaps in abdominal hernia repair. In: **Jones D**, editor. *Master of abdominal hernia repair*.

**Lin SJ, Lee BT.** Lip Reconstruction. In: **Fischer J**, editor. *Fischer's Mastery of Surgery*. 2011; in press.

**Rabie AN, Ibrahim AM, Lin SJ.** Eyebrow anatomy. In: **Lin SJ, Mustoe TA**, editors. *An aesthetic atlas of the head and neck*. New York, NY: McGraw-Hill. 2011; in press.

**Rabie AN, Ibrahim AM, Lin SJ.** Forehead anatomy. In: **Lin SJ, Mustoe TA**, editors. *An aesthetic atlas of the head and neck*. New York, NY: McGraw-Hill; in press.



## Clinical Guidelines and Reports

Lee BT, Duggan MM, Keenan MT, Kamatkar S, Quinlan RM, Hergrueter CA, Hertl MC, Shin JH, Truppin NB, Chun YS, and the Massachusetts Board of Registration in Medicine Expert Panel on Immediate Implant Based Breast Reconstruction following Mastectomy for Cancer. Commonwealth of Massachusetts Board of Registration in Medicine expert panel on immediate implant-based breast reconstruction following mastectomy for cancer: executive summary, June 2011. J Am Coll Surg 2011;213(6):800-5.

## Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

**Brahmer G, Bursztajn H, Chelouche T, Holzer J.** The Forgotten Doctors of the Holocaust: Making Tragic Ethical Choices in the Midst of Terror, Panel Presentation, 32nd Congress of the International Academy of Law and Mental Health, Humboldt University, Berlin, Germany, July 19, 2011.

**De Blacam C, Momoh AO, Colakoglu S, Slavin SA, Tobias AM, Lee BT.** Cost Analysis of Implant-based Breast Reconstruction with Acellular Dermal Matrix/ Plenary Presentation (abstract), Annual Meeting, Plastic Surgery Research Council, Louisville, KY, April 28-30, 2011.

**De Blacam C, Momoh AO, Colakoglu S, Tobias A, Lee BT.** Evaluation of Clinical Outcomes and Aesthetic Results after Autologous Fat Grafting for Contouring Deformities of the Reconstructed Breast, Plenary Presentation, European Plastic Surgery Research Council, Hamburg, Germany, August 26, 2011.

**Khansa I, Colakoglu S, Curtis MS, Yueh JH, Ogunleye A, Tobias AM, Lee BT.** Breast Cancer Recurrence following Postmastectomy Reconstruction compared to Mastectomy with no Reconstruction, Plenary Presentation, Annual Meeting, Plastic Surgery Research Council, Louisville, KY, April 28-30, 2011.

**Khansa I, Colakoglu S, Curtis MS, Yueh JH, Ogunleye A, Tobias A, Lee BT.** Post-mastectomy Breast Reconstruction after Previous Lumpectomy and Radiation Therapy: Analysis of Complications and Satisfaction/ Plenary Presentation (abstract). Annual Meeting, Plastic Surgery Research Council, Louisville, KY, April 28-30, 2011.

**Kim PS, Ko JH, O'Shaughnessy KD, Kuiken TA, Dumanian GA.** Targeted muscle reinnervation of a pedicled rabbit rectus abdominis flap: The demonstration of a cure for the common neuroma? Plenary Presentation (Abstract). 1st Targeted Muscle Reinnervation (TMR) Conference, Chicago, IL. October 7, 2011.

**Kim PS, Lohse G, Moon E, Huang JI.** Bier block intravenous regional anesthesia for the operative treatment of adult distal radius fractures. Poster Presentation (Abstract). American Society for Surgery of the Hand, Annual Meeting, Las Vegas, NV. September 2011.

**Ko JH, De la Garza M, Kim PS, Kuiken TA, Dumanian GA.** Topographic distribution of sensory and motor axons in the human brachial plexus. Plenary Presentation (Abstract). 1st Targeted Muscle Reinnervation (TMR) Conference, Chicago, IL. October 7, 2011.

**Ko JH, Kim PS, Zhao Y, Hong SH, Mustoe TA.** HMG-CoA reductase inhibitors (Statins): A novel approach to preventing hypertrophic scar formation. Plenary Presentation (Abstract). Illinois Society of Plastic Surgeons, Annual

Senior Resident Paper Competition, Chicago, IL. June 3, 2011. Received 2nd Place, 2011 Senior Resident Paper Competition.

Ko JH, Zhao Y, Hong SH, Ding XZ, **Kim PS**, Agnew SP, De la Garza M, Mustoe TA. HMG-CoA reductase inhibitors (Statins): A novel approach to preventing hypertrophic scar formation. Plenary Presentation (Abstract) Midwestern Association of Plastic Surgeons, 50th Annual Meeting, Chicago, IL. May 14, 2011.

Ko JH, Zhao Y, Hong SH, Ding XZ, **Kim PS**, Agnew SP, De la Garza M, Mustoe TA. HMG-CoA reductase inhibitors (Statins): A novel approach to preventing hypertrophic scar formation. Poster Presentation (Abstract). American Association of Plastic Surgeons, 90th Annual Meeting, Boca Raton, FL. April 9-12, 2011. Received 2nd Place, 2011 Resident Poster Competition.

Ko JH, **Kim PS**, Zhao Y, Hong SH, Mustoe TA. HMG-CoA reductase inhibitors (Statins): A novel approach to preventing hypertrophic scar formation. Plenary Presentation (Abstract). 1st Annual Resident and Alumni Day, Division of Plastic and Reconstructive Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL. June 10, 2011. Received 1st Place, Paper Competition.

**Lee BT**, Early Evaluation of Barbed Sutures for Abdominal Closure in DIEP Flap Breast Reconstruction, Plenary Presentation (abstract). New England Society of Plastic and Reconstructive Surgeons meeting; Brewster, MA, Proceedings of the New England Society of Plastic and Reconstructive Surgeons, Inc. 52nd Annual Meeting, Brewster, MA, June 3-5, 2011.

**Lee BT**, Impact of Nipple Reconstruction on Patient Satisfaction in Breast Reconstruction, Plenary Presentation, Annual Meeting, Northeastern Society of Plastic Surgeons meeting; Amelia Island, FL, October 23, 2011.

**Lin SJ**, Curtis M, **Tobias A**, **Lee BT**. Tissue Oximetry Monitoring in Microsurgical Breast Reconstruction Decreases Flap Loss and Improves Rate of Flap Salvage. American Society of Reconstructive Microsurgery, Cancun, Mexico, January, 2011.

**Momoh AO**, **Colakoglu S**, **deBlacam C**, **Morris DJ**, **Tobias AM**, **Lee, BT**. Delayed autologous breast reconstruction in patients receiving postmastectomy radiation therapy: is there an optimal time? Proceedings of the New England Society of Plastic and Reconstructive Surgeons, Inc. 52nd Annual Meeting, Brewster, MA, June, 3-5, 2011.

**Reddy SK**, **Colakoglu S**, Curtis MS, Tobias AM, Lin SJ, Lee BT. Delayed Autologous Breast Reconstruction after Postmastectomy Radiation Therapy: Is There an Optimal Time?, Plenary Presentation, Annual Meeting, Plastic Surgery Research Council, Louisville, KY, April 28-30, 2011.

**Sinno H**, Thibaudeau S, Tahiri Y, Mok E, Christodoulous G, Lessard L, Williams B, Lin SJ, Utility Assessment of Body Contouring after Massive Weight Loss, 6th Congress of the International Confederation for Plastic Reconstructive and Aesthetic Surgery (IPRAS), Vancouver, BC, May 22-27, 2011.

**Sinno H**, Tahiri Y, Thibaudeau S, Izadpanah A, Christodoulou G, Lin SJ, Williams BH, Gilardino M. Living with Cleft Lip and Palate: An Objective Assessment. 2nd H. Bruce Williams Research Day. Montreal Children's Hospital. Montreal, Quebec. June 2nd 2011

**Sinno H**, Tahiri Y, Thibaudeau S, Izadpanah A, Christodoulou G, Slavin S, Lin SJ. Annual Meeting, The Impact of Living with Functional Nasal Asymmetry Following Prior Rhinoplasty: A Utility Score Assessment, Northeastern Society of Plastic; Amelia Island, FL, October 23, 2011.

**Sinno H**, Tahiri Y, Thibaudeau S, Izadpanah A, Christodoulou G, Zuker R, Lin SJ. Annual Meeting, Utility Score for Facial Paralysis Requiring Facial Reanimation, Northeastern Society of Plastic; Amelia Island, FL, October 23, 2011.

Song YA, **Ibrahim A**, Melik R, **Rabie A**, Lin S, Han J. Microfabricated ion-selective micro electrodes for enhanced neuromuscular stimulation. BioMethods Boston Conference, Boston, MA, July 14-15, 2011.

Song YA, **Ibrahim A**, **Rabie A**, Lin S, Han J. A New Neuroprosthetic Device for Electrochemical Activation and Inhibition of Neuromuscular Systems. 4th Massachusetts Life Sciences Innovation (MALSI) Day, Boston, MA, June 2, 2011.

Song YA, **Ibrahim A**, **Rabie A**, Lin S, Han J. Ion-Specific Membranes: A New Neuroprosthetic Device for the Treatment of Neurological Diseases. Massachusetts Biotechnology Council (MassBio) Annual Meeting, Cambridge, MA, March 21-22, 2011.

Song YA, **Rabie AN**, **Ibrahim AM**, Han J, Lin SJ. Graded Nerve Modulation Using a BioMEMS Device. Plastic Surgery Research Council Annual Meeting, Louisville, KY, April 28-30, 2011.

## Division of Podiatry members

John M. Giurini, DPM

Dafny Suazo

Chief, Division of Podiatry;  
Associate Clinical Professor of  
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Administrative Assistant

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Jeremy Cook, DPM, MPH

Clinical Instructor in Surgery

Tranh Dinh, DPM

Clinical Instructor in Surgery

Thomas E. Lyons, DPM

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Clinical Instructor in Surgery

Aristidis Veves, MD, DSc

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Sarada Kuchibhotla  
Ermelindo Leal, PhD  
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Xingzi Shanguan  
Francesco Tecilazich, MD  
Ana Tellechea

Associate Clinical  
Professor of Surgery  
Research Assistant  
Research Assistant  
Research Fellow  
Research Coordinator  
Research Coordinator  
Research Fellow  
Visiting Graduate Student

## Division of Podiatry



## Research Focus

I am mainly involved in “bench to bedside” research. My main research focus is diabetes and its complications, with particular emphasis on wound healing and cardiovascular disease. Approximately 90% of my effort is dedicated to research, 5% for teaching, and an additional 5% for administrative and other relevant professional activities.

I run my own basic research laboratory that mainly explores the findings of the translational research and tries to identify mechanisms that are related to the observed results. My laboratory works closely with Dr. Frank LoGerfo’s laboratory and other laboratories in the Beth Israel Deaconess Medical Center and is funded by NIH grants. I also collaborate with Dr. Mooney’s laboratory at the Wyss Institute and Harvard Engineering School; the main aim of our collaboration is the development of new wound-healing products. This collaboration has resulted in grant applications that are currently being considered for funding by NIH.

## Clinical (Translational) Research

Translational research is the major part of my research activities. My work mainly focuses on the interaction between neuropathy and microvascular disease in the development of diabetic foot ulceration and the subsequent wound healing impairment. This work has been supported by NIH funding and nonprofit organizations. I collaborate with investigators from various departments of my hospital, the Beth Israel Deaconess Medical Center, and investigators from other institutions, such as the Brigham and Women’s Hospital and the McLean Hospital, to conduct additional translational research.

I conduct investigator-initiated research studies that examine the effects of various FDA-approved medications on cardiovascular function. These studies, although funded by the industry, have been conceived, designed and executed by my unit and focus on possible new mechanisms through which these medications exert their beneficial effects. Finally, in the past I have served as the leading investigator and the leading author in industry sponsored multicenter trials that investigated the efficacy of new therapeutic interventions for the management of diabetic foot ulceration.

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 Atul Malhotra, MD, from the Harvard Center on Sleep Neurobiology and Sleep Apnea, to examine the effects of sleep apnea on vascular reactivity.



**Aristidis Veves, MD, DSc**

Associate Professor of Surgery

### Lab Members

Ermelindo Leal, PhD  
 Francesco Tecilazich, MD  
 Xingzi Shangguan  
 Mary Lauren Magargee  
 Michael Auster  
 Sarada Kuchibhotla  
 Ana Tellechea

## Research Support

“Impaired wound healing in diabetic foot ulceration”

NIH, R01DK076937-01

01/01/06-12/31/10

PI: Aristidis Veves, MD

“Metabolic MRI of diabetic lower extremity disease”

NIH, R01 DK071569-01

12/1/06-11/30/11

PI: Greenman

Co-I: Aristidis Veves, MD

“The effect of diabetes, neuropathy and arterial disease in lower extremity energy”

NIH, R21 DK82987-01

09/01/2009-08/31/2011

PI: Aristidis Veves, MD

“The effect of aliskiren on endothelial function in pre-diabetes and diabetes”

Novartis Pharma Inc.

09/01/09-08/31/11

PI: Aristidis Veves, MD

“Role of neuropeptides in diabetic foot problems”

NIH, R01NS066205-01

07/01/10-06/30/15

MPI: Aristidis Veves, MD, Leena Pradhan-Nabzdyk, PhD

“Contractile hydrogel dressing for primary wound closure”

NIH, R41DK089789-01

09/01/10-08/31/11

MPI: Aristidis Veves, MD, Anjal C. Sharma, PhD

“Stimuli responsive topical gels for mechanically assisted wound debridement”

NIH, R41GM096535-01

09/30/10-09/29/11

MPI: Aristidis Veves, MD, Anjal C. Sharma, PhD

“Repeated challenge of insufficient sleep: Effects on endothelial function”

NIH, R01HL106782-01

12/01/10-11/30/15

PI: Janet Mullington, PhD

Co-I: Aristidis Veves, MD

“Mechanisms of neuropeptides action in diabetes”

NIH, R01DK091949

09/30/11-09/29/15

MPI: Aristidis Veves, MD, Janice Zabolotny, PhD

“Obstructive sleep apnea increases cardiovascular risk in type 2 diabetes”

NIH, R01HL110350-01

12/01/2011-11/30/2016

MPI: Aristidis Veves, MD, Atul Malhotra, MD



**Applications Submitted or Pending Review/Funding****Aristidis Veves, MD, DSc**

“Novel therapeutic approaches for the management of diabetic foot ulceration”

NIH, R24DK091210-01

MPI: Aristidis Veves, MD, Frank LoGerfo, MD, David Mooney, PhD,  
William Shih, PhD

Score 25, pending council review

“Spatially dependent measurement of phosphocreatine  
recovery kinetics in diabetes”

NIH, R21DK094064-01A1

PI: Robert L.Greenman, PhD

Co-I: Aristidis Veves, MD

“iPSC-derived repair-responsive fibroblasts to heal refractory venous ulcers”

NIH, R01 AR062394-06-A1

Garlick (PI) Role: Co-Investigator, Subcontract PI

“Contractile hydrogel dressing for primary wound closure”

NIH, R41DK089789-01

MPI: Aristidis Veves, MD, Anjal C. Sharma, PhD

“Novel, effective topical treatment for diabetic ulcer”

NIH, R42

06/01/2012-05/31/2013

PI: Gyula Varadi, PhD

Site PI: Leena Pradhan-Nabzdyk, PhD

Co-I: Aristidis Veves, MD

**Accomplishments in the Past Year****Research Progress**

During the past year we initiated studies that are funded by the two new NIH R01 grants. We also continued our work on projects that are funded by previous NIH R01, R21, and STTR grants. We also continue to enroll subjects in an investigator initiated study funded by Novartis Pharma.

**Individual Accomplishments**

- 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 ad hoc member for ACTS Study Section panel.
- I was a member of the Neurodiab Consensus Workshop on Diabetic Neuropathy, October 2009, Toronto, Canada.
- I continue to serve as an Associate Editor for the journal: *Wounds: A Compendium of Clinical Research and Practice* (2000-).
- I was asked to act as a peer reviewer for the journals including *Diabetes*, *Diabetologia*, *Diabetes Care*.
- I continue as the Series Editor, *Contemporary Diabetes*, Humana Press, Totowa, NJ.

### Invited Presentations

“Role of Inflammation and Vascular Dysfunction in Diabetes Complications.” 25th Annual Meeting of the Northern Greece Diabetes Association.

“Mechanisms of Impaired Wound Healing in Diabetes.” Sanofi-Aventis Wound and Fibrosis Team. Bridgewater, NJ.

“Mechanisms of Impaired Wound Healing in Diabetes.” Wound Healing Society Meeting. Dallas, TX.

“Ultrasound and Dopplers: From Diagnosis to Treatment.” Session Moderator. Spring Symposium on Advanced Wound Care and Wound Healing Society (SAWC/WHs) Meeting. Dallas, TX.

“Ultrasound and Dopplers: From Diagnosis to Treatment.” Diagnostic Techniques. Spring Symposium on Advanced Wound Care and Wound Healing Society (SAWC/WHs) meeting. Dallas, TX.

“What is the Hype and What is the Science of Wound Debridement? Innovations in Complex Vascular & Endovascular Interventions: Special Sessions: Management of Non-Healing Wounds & Vascular Lab Evaluation.” Columbia University College of Physicians and Surgeons, Weill Cornell Medical College. New York, NY.

“Inflammation and Wound Healing in Diabetes. Innovations in Complex Vascular & Endovascular Interventions: Special Sessions: Management of Non-healing Wounds & Vascular Lab Evaluation.” Columbia University College of Physicians and Surgeons, Weill Cornell Medical College. New York, NY.

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### Teaching, Training, and Education

In the past year I was involved in the following teaching responsibilities:

- Ermelindo Leal, PhD, post doc research fellow worked directly under me in basic research.
- Francesco Tecilazich, MD, is a research fellow working directly under me in clinical research.
- Ana Tellechea is a PhD student working directly under me in basic research.

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### Bibliography (January – December 2011)

#### Peer-Reviewed Publications in Print or Other Media

Research Investigations (Submitted or in Press)

Gibbons CH, Freeman R, Tecilazich F, Dinh T, Lyons TE, Veves A. Natural history of neurophysiologic function in patients with stable diabetes. 2011, in press.

Malik RA, Veves A, Tesfaye S, Smith G, Cameron N, Zochodne D, Lauria G, on behalf of the Toronto Consensus Panel on Diabetic Neuropathy. Small fiber neuropathy: role in the diagnosis of diabetic sensorimotor polyneuropathy. Diabetes Metab Res Rev 2011; in press.

Pradhan-Nabzdyk L, Kuchibhotla S, Guthrie P, Chun M, Deso S, Anderson N, Nabzdyk C, LoGerfo FW, Veves A. Expression of neuropeptides and cytokines in a novel rabbit model of diabetic neuroischemic wound healing. 2011, in press.

Tecilazich F, Dinh T, Lyons TE, Guest J, Villafuerte R, Sampanis C, Gnardellis C, Zuo C, Veves A. Mitochondrial dysfunction in diabetic patients with neuropathy and peripheral arterial disease. 2011, in press.

### **Non-Peer Reviewed Publications in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

Tecilazich F, Dinh T, Veves A. Treating diabetic ulcers. *Expert Opin on Pharmacother* 2011;12(4):593-606.

Veves A. Discussion. Bioengineered skin constructs and their use in wound healing. *Plast Reconstr Surg* 2011;127(Suppl 1):91S-92S.

### **Abstracts, Poster Presentations and Exhibits Presented at Professional Meetings**

Gibbons CH, Freeman R, Lyons TE, Tecilazich F, Dinh T, Veves A. Longitudinal changes to neurophysiologic function in diabetes: a required reassessment? *Neurology* 2011;76(9):A524.

Kafanas A, Zabolotny JM, Tellechea A, Tecilazidh F, Pradhan L, Veves A. Inflammation and PTP1B expression is increased in diabetic patients and is associated with impaired wound healing. *Wound Repair and Regeneration* 2011;19(2):A30.

Pradhan L, Kuchibhotla S, LoGerfo FW, Veves A. Plasmid cytokine and growth factor expression in a rabbit model of diabetic wound healing. *Wound Repair and Regeneration* 2011;19(2):A44.

Tecilazich F, Dinh T, Lyons T, Gnardellis C, Zuo C, Veves A. Muscle energy reserves changes during exercise. *Diabetes* 2011;60(Suppl 1):A38. (American Diabetes Association Young Investigator Travel Grant Award)

Tellechea A, Zabolotny JM, Pradhan L, Leal E, Kafanas A, Kuchibhotla A, Carvalho E, Veves A. Impaired masT-cell function affects wound healing in diabetes. *Diabetologia* 2011;54(Suppl 1):S471.

Zabolotny JM, Tellechea A, Leal EC, Kontoes I, Kuchibhotla S, Pradhan L, Carvalho E, Veves A. Protein tyrosine phosphatase 1B (PTP1B) deficiency promotes wound healing. *Diabetologia* 2011;54(Suppl 1):S471.

**Aristidis Veves, MD, DSc**



## Division of Surgical Oncology members

Jennifer F. Tseng, MD, MPH

Sing Chau, MS  
Zeling Chau, MD  
Linda Gallagher  
April Isaac Jefferson

Chief, Division of Surgical  
Oncology; Visiting  
Associate Professor of Surgery,  
Harvard Medical School  
Biostatistician  
Research Fellow (Resident)  
Administrative Coordinator  
Administrative Director

*In January of 2012, the Division additionally  
included the following Faculty:*

Rosemary Duda, MD

Associate Professor of Surgery

Per-Olof Hasselgren, MD, PhD

George H.A. Clowes Professor of  
Surgery; Director of Endocrine  
Surgery, Vice-Chairman for  
Research

Mary Jane Houlihan, MD

Assistant Professor of Surgery

A. James Moser, MD

*As of May 2012*

Susan Pories, MD

Assistant Professor of Surgery

Ranjna Sharma, MD

Instructor in Surgery

Nicholas E. Tawa, MD, PhD

Assistant Professor of Surgery

Michael D. Wertheimer, MD

Associate Professor of Surgery

## Division of Surgical Oncology

*New Division in Surgery as  
of December 2011*



## Research Focus

The overall focus of my research is predicting risk for hepatopancreaticobiliary (HPB) and upper GI malignancy and related diseases, as well as assessing the risks and benefits of various modalities employed in the treatment of these conditions. To achieve that end, I have pursued several complementary avenues of investigation including: (1) health services research, including large administrative databases, registries, and institutional databases; (2) biobanking and biomarker discovery for pancreatic malignancy; and (3) decision analysis and decision modeling.

My investigative achievements have centered on building predictive models for pancreatic cancer and related diseases. Using large national databases, I have led research on current perioperative morbidity and mortality for pancreatic cancer and for pancreatectomy that are widely cited in the surgical and pancreatic cancer fields. Disparities in diagnosis, receipt of care, and outcome are among my active areas of inquiry. We have also used national data to build simple, widely applicable risk scores for pancreatic and liver surgery that can be easily calculated by hand or on a computer or handheld device (e.g. <http://www.umassmed.edu/surgery/toolbox>).

We have used institutional data to explore predictors of receiving all components of care; the learning curve in pancreatic surgery; the effect of sequencing options such as neoadjuvant therapy prior to surgical resection on pancreatic cancer outcome; and the application of major vascular resection in order to allow for more patients to have potentially curative surgery. With the eventual goal of integrating molecular information in risk prediction and determining best strategies for individual patients, I have established a novel pancreatic biobank, with whole blood, serum, plasma, and patient tissues, together with potentially biomarker-rich fluids such as pancreatic juice and cystic fluid. In collaboration with basic scientists, we have embarked on microRNA and proteomic profiling of these fluids to identify markers of malignancy as well as response to therapy.

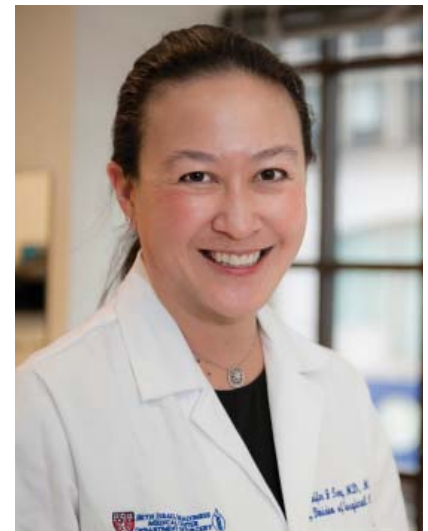
With Drs. Marc Schermerhorn (Chief, Vascular Surgery) and James Rodrigue, PhD, (Transplant Institute), I have been charged by our Chair, Elliot Chaikof, MD, PhD, to build a collaborative Health Services Research effort in the BIDMC Department of Surgery beginning in 2012.

## Research Support

“Decision analysis models for cystic and indeterminate lesions of the pancreas”  
Howard Hughes Medical Institute – Early Career Award  
2006-2012  
PI: Jennifer Tseng, MD

“Proteomic and microRNA biomarkers for malignancy prediction in cystic pancreatic lesions”  
National Institutes of Health, 1 UL1RR031982-01  
2009-2011  
Overall PI: John Sullivan, PhD  
Project PI: Jennifer Tseng, MD

“Determining the optimal sequencing strategies for pancreatic cancer treatment”  
American Cancer Society CPHPS Mentored Research Scholar Grant, MSRG-10-003-01  
2010-2014  
PI: Jennifer Tseng, MD



**Jennifer Tseng,  
MD, MPH**

Visiting Associate  
Professor of Surgery

Group Members  
Sing Chau Ng, MS  
Zeling Chau, MD  
Courtney Collins, MD  
April Issac Jefferson  
Linda Gallagher



## Research Accomplishments over the Past Year

### Invited Presentations

- “Decision modeling for pancreatic cancer.” Institute for Technology Assessment, Massachusetts General Hospital / Harvard Medical School, Boston, MA
- “Cancer and wellness.” East Hawaii IPA Association, Kona, Hawaii, scheduled for August 22, 2011.
- “Mentors and mentoring.” Association for Academic Surgery 7th Annual Career Development Course, San Francisco, CA, scheduled for October 21, 2011.
- “How to EXCEL at starting and maintaining your own database.” AAS 22nd Annual Fundamentals of Surgery Course, San Francisco, CA, scheduled for October 22, 2011.
- “Hepatobiliary-pancreatic disasters for the GI Surgeon.” Cochair (with Michael Sarr), American College of Surgeons Postgraduate Course, scheduled for October 23, 2011.

### Administrative Accomplishments

- Recruited as Chief, Division of Surgical Oncology, BIDMC.
- Appointed clinical Co-Director of the Cancer Center at BIDMC.
- Served as Co-Chair of the Massachusetts Pancreatic Collaborative.
- Served as Co-chair of the American College of Surgeons Postgraduate Course, “HPB Disasters for the General Surgeon.” This course was given at the American College of Surgeons Clinical Congress in October of 2011.
- Chaired of the Pilot Grant Selection Committee for the Pancreatic Cancer Alliance Pilot grant program.
- Continued to review scholarly articles as an ad hoc reviewer for *Annals of Surgery*, *Annals of Surgical Oncology*, *Archives of Surgery*, *Cancer*, *Digestive Diseases and Sciences*, *HPB*, *Journal of the American College of Surgeons*, *Journal of Clinical Oncology*, *Journal of Gastrointestinal Surgery*, *The New England Journal of Medicine*, *Pancreas*, and *Surgery*.
- Served on the editorial board of the *Annals of Surgical Oncology* and the *Journal of Gastrointestinal Surgery*.

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## Teaching, Training, and Education

### Graduate School and Graduate Medical Courses

In 2011, the teaching I did was at the University of Massachusetts Medical School.

- Core surgical clerkship, 3rd year medical students.
- Organ System Disease, 1st year medical students.

- Surgical Education Series (CASS); lectures about The Pancreas; The Stomach; Skin and Soft Tissue Cancers; Tumor Biology. This course was for PGY 1-8 General Surgical Residents.

**Jennifer Tseng, MD, MPH**

## **Bibliography (January-December 2011)**

### **Peer-Reviewed Publications in Print or Other Media**

#### **Research Investigations**

Burr AT, Csikesz NG, Gonzales E, **Tseng JF**, Saidi RF, Bozorgzadeh A, Shah SA.. Comparison of right lobe donor hepatectomy with elective right hepatectomy for other causes in New York. *Dig Dis Sci* 2011;56(6):1869-75.

Burr AT, Li Y, **Tseng JF**, Saidi RF, Bozorgzadeh A, Shah SA. Survival after liver transplantation using hepatitis C virus-positive donor allografts: case-controlled analysis of the UNOS database. *World J Surg*. 2011;35(7):1590-5.

Manasanch EE, Smith JK, Bodnari A, McKinney J, Gray C, McDade TP, **Tseng JF**. Tumor registry versus physician medical record review: A head-to-head comparison of pancreatic neuroendocrine tumor cases. *J Oncol Pract* 2011;7(2):111-6.

Ozhathil DK, Li YF, Smith JK, **Tseng JF**, Saidi RF, Bozorgzadeh A, Shah SA. Impact of center volume on increased risk liver transplant outcomes. *Liver Transpl* 2011;17(10):1191-9.

Ozhathil DK, Li YF, Smith JK, **Tseng JF**, Saidi RF, Jabbour N, Bozorgzadeh A, Shah SA. Effect of center volume and high donor risk index on liver allograft survival. *HPB (Oxford)* 2011;13(7):447-53.

Shah SA, Li YF, Ng SC, Burr A, **Tseng JF**. Underutilization of surgical treatment of hepatocellular carcinoma in the Medicare population. *Cancer* 2011;117(5):1019-26.

Singla A, Hart J, Li YF, **Tseng JF**, Shah SA. Hospitalization for complications of cirrhosis: does volume matter? *J Gastrointest Surg* 2011;15(2):330-5.

#### **Research Investigations (Submitted or in Press)**

Dudeja V, Gay G, Havermann EB, Tuttle TM, **Tseng JF**, Feig BW, Al-Refaie WB. Do hospital attributes predict guideline-recommended gastric cancer care in the United States? *Ann Surg Onc* 2011; in press.

Dudeja V, Havermann EB, Abraham A, Zhong A, Parsons HM, **Tseng JF**, Al-Refaie WB. Is there a role for surgery with adequate nodal evaluation alone in gastric adenocarcinoma? *J Gastrointest Surg* 2011; in press.

Ozhathil DK, Li Y, Smith JK, Witkowski E, Coyne ER, Alavi K, **Tseng JF**, Shah SA. Colectomy performance improvement within NSQIP 2005-2008. *J Surg Res* 2011; in press.

Witkowski EM, Smith JK, Ragulin-Coyne E, Ng SC, Shah SA, **Tseng JF**. Is it worth looking? Abdominal imaging after pancreatic cancer resection: a national study. *J Gastrointest Surg* 2011; in press.

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

**Tseng JF.** Is risk calculation risky? Arch Surg 2011; 146(8): 964-5.

Simons JP, Ng SC, Shah SA, McDade TP, Whalen GF, **Tseng JF.** Malignant intraductal papillary mucinous neoplasm: are we doing the right thing? J Surg Res 2011;167(2):251-7.

**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Smith JK, Witkowski ER, Murphy MM, Ng SC, Shah SA, **Tseng JF.** “Minimally invasive surgery for resectable pancreatic cancer in the US: From staging tool to treatment strategy.” Poster presentation at the American Society of Clinical Oncology 2011 Gastrointestinal Cancers Symposium, San Francisco, CA, January 2011.

Witkowski ER, Smith JK, Ng SC, McDade TP, Shah SA, Al-Refaie WB, **Tseng JF.** “Nationwide trends in diagnosis and outcomes of gastrointestinal stromal tumors in the era of targeted therapy.” Poster presentation at the American Society of Clinical Oncology 2011 Gastrointestinal Cancers Symposium, San Francisco, CA, January 2011.

Ragulin-Coyne E, Smith JK, Ng SC, McDade TP, Shah SA, **Tseng JF.** “Potential predictors of pancreatic cancer: a population-based screen.” Poster presentation at the American Society of Clinical

Smith JK, Ng SC, Hill JS, McDade TP, **Tseng JF.** “The impact of health insurance coverage on outcomes for U.S. gastric cancer patients.” Brief oral presentation at the Association for Academic Surgery 6th Annual Academic Surgical Congress, Huntington Beach, CA, February 2011.

Skinner SJ, Smith JK, **Tseng JF,** McDade, TP. Preoperative biliary drainage for the jaundiced pancreatic cancer patient: a decision analysis.” Brief oral presentation at the Association for Academic Surgery 6th Annual Academic Surgical Congress, Huntington Beach, CA, February 2011.

Ozhathil DK, Li Y, Hudlin MM, Smith JK, **Tseng JF,** Shah SA. Improving Outcomes at National Surgical Quality Improvement Program Utilizing Centers, 2005-2008. Brief oral presentation at the Association for Academic Surgery 6th Annual Academic Surgical Congress, Huntington Beach, CA, February 2011.

Ozhathil DK, Li Y, Burr AT, **Tseng JF,** Saidi RF, Bozorgzadeh A, Shah SA. Expanded Criteria Donor Allografts and Effects of Center Volume on Liver Transplantation. Brief oral presentation at the Association for Academic Surgery 6th Annual Academic Surgical Congress, Huntington Beach, CA, February 2011.

Hill JS, Smith JK, Ng SC, Lambert L, Mansfield, Royal, Fournier, Cormier J, **Tseng JF.** “The surgical treatment of appendiceal cancer in the modern era.” Poster presentation at the Society of Surgical Oncology 64th Annual Cancer Symposium, San Antonio, TX, March 2011.

Witkowski ER, Smith JK, Ng SC, McDade TP, Shah SA, Al-Refaie WB, **Tseng JF**. “Nationwide trends in diagnosis and outcomes of gastrointestinal stromal tumors in the era of targeted therapy.” Poster presentation at the Society of Surgical Oncology 64th Annual Cancer Symposium, San Antonio, TX, March 2011.

Smith JK, Li Y, Ng SC, Witkowski ER, **Tseng JF**, Shah SA. “Recommendations and performance of resection for localized hepatocellular carcinoma in the Medicare population.” Mini-oral presentation at the American Hepatopancreatobiliary Association 11th Annual Meeting, Miami, FL, March 2011.

Witkowski ER, Smith JK, Ragulin Coyne E, Ng SC, McDade TP, Shah SA, **Tseng JF**. “Nationwide patterns in resection for distantly metastatic pancreatic cancer.” Oral poster presentation at the American Hepatopancreatobiliary Association 11th Annual Meeting, Miami, FL, March 2011.

Ragulin-Coyne E, Smith JK, Witkowski ER, Ng SC, McDade TP, Shah SA, **Tseng JF**. “Pancreatic cancer following diagnosis of new-onset diabetes: a population-based study.” Poster presentation at the American Hepatopancreatobiliary Association 11th Annual Meeting, Miami, FL, March 2011.

Ozhathil DK, Li Y, Smith JK, Saidi RF, Bozorgzadeh A, **Tseng JF**, Shah SA. “Effect of Donor Risk Index (DRI) and Center Volume on Liver Transplantation Outcomes.” Oral presentation at the American Hepatopancreatobiliary Association 11th Annual Meeting, Miami Beach, FL, March 2011.

Ragulin-Coyne E, Smith JK, Witkowski ER, Ng SC, McDade TP, Shah SA, **Tseng JF**. Is pancreatic cancer palatable? A national study. Poster presentation, Pancreas Club, Chicago, IL, May 6-7, 2011.

Arous EJ, Smith JK, Ng SC, **Tseng JF**, McDade TP. Tales from the EMR: does a 21st-century data warehouse facilitate clinical research for pancreatic cancer? Poster presentation, Pancreas Club, Chicago, IL, May 6-7, 2011.

Smith JK, Simons JP, Witkowski ER, Ragulin-Coyne E, Ng SC, Valliere SA, Shah SA, **Tseng JF**. Pancreatic cystic lesions: assessing quality of life. Short oral presentation, Pancreas Club, Chicago, IL, May 6-7, 2011.

Witkowski ER, Smith JK, Ragulin-Coyne E, Ng SC, Shah SA, **Tseng JF**. Is it worth looking? Abdominal imaging after pancreatic cancer resection: a national study. Plenary oral presentation and selected for Residents and Fellows Conference, Society for Surgery of the Alimentary Tract, Chicago, IL, May 6-10, 2011.

Ragulin-Coyne E, Witkowski ER, Smith JK, Hill JS, McPhee JT, Al-Refaie W, Ng SC, Shah SA, **Tseng JF**. Are body/tail pancreatic cancers really worse per se? A population-based study. Poster presentation, Society for Surgery of the Alimentary Tract, Chicago, IL, May 6-10, 2011.

Smith JK, Simons JS, Witkowski ER, Bodnari A, Curnen MB, Ng SC, Sullivan ME, Valliere SA, Shah SA, **Tseng JF**. Assessing quality of life in pancreatic cancer: a shifting landscape. Poster presentation, Society for Surgery of the Alimentary Tract, Chicago, IL, May 6-10, 2011.

Arous EJ, McDade TP, Smith JK, Ng SC, Zottola RJ, Ranauro PJ, **Tseng JF**. Tales from the EMR: does a 21st-century data warehouse facilitate clinical research for pancreatic cancer? Podium Presentation at the NESS 92nd Annual Meeting, Bretton Woods, New Hampshire, September 23-25, 2011.

**Jennifer Tseng, MD, MPH**

Ragulin-Coyne E, Santry H, Smith JK, Witkowski ER, Psoinos C, Ng SC, Shah SA, **Tseng JF**. Pancreaticoduodenal trauma in the 21st century: a current view. Brief Oral Presentation at the NESS 92nd Annual Meeting, Bretton Woods, New Hampshire, September 23-25, 2011.

## Transplant Institute members (Department of Surgery\*)

Douglas W. Hanto, MD, PhD*	Clinical Director, The Transplant Institute; Lewis Thomas Professor of Surgery; Associate Surgeon-in-Chief
Helen Snook	Administrative Coordinator
Amy R. Evenson, MD*	Instructor in Surgery
Teresa Williams	Administrative Assistant
Wenda Gao, PhD	Assistant Professor of Medicine
Scott R. Johnson, MD*	Assistant Professor of Surgery
Lynne Mosher	Administrative Associate
Maria Koulmanda, MSc, PhD*	Associate Professor of Surgery
Zhigang Fan MD, PhD	Research Fellow in Surgery
Nipun Goel, PhD	Research Fellow in Surgery
Dusan Hanidziar, MD	Research Fellow in Surgery
Lan Jiang	Research Assistant
Ramandeep Kaur, MB, BS	Research Fellow in Surgery
Derek Liu, MD	Research Fellow in Surgery
Naved Munir, MSc	Research Assistant
Ki-Soo Park, DVM	Research Fellow in Surgery
Rebecca S. Sampathkumar, PhD	Research Fellow in Surgery
Gurbakhshish Singh, MD	Research Fellow in Surgery
Xinju (Joan) Zhang	Research Assistant
Keren Ladin, MSc*	Senior Research Associate in Surgery
Erica Langnas	Research Assistant, Interview Coordinator
Rui Wang	Research Assistant
Xian C. Li, MD, PhD	Associate Professor of Medicine
Dieder A. Mandelbrot, MD	Associate Professor of Medicine
Ajay Kher, MD	Renal Transplant Fellow
Anthony P. Monaco, MD*	Peter Medawar Professor of Surgery
Clare Sullivan	Administrative Assistant
Leo E. Otterbein, PhD*	Associate Professor of Surgery
Beek Yoke Chin, PhD	Instructor in Surgery
Kellie Cunningham	Research Assistant
David Gallo	Senior Research Associate
Andreas Hedblom	Graduate Student

## Division of Transplantation

*Transplant Institute*

Mailin Li  
Lanjuan Wang, MD

Undergraduate Student  
Research Fellow in Surgery

**Martha Pavlakis, MD**

**Associate Professor of Medicine**

**Simon C. Robson, MB ChB, PhD**

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Eva Csizmadia  
Maggie Ham, MD  
Alan Moss, MD  
Martina Nowak, MD  
Moritz Schmelzle, MD  
Xiaofeng Sun, MD  
Yan Wu, PhD

**Professor of Medicine**  
Research Fellow in Medicine  
Sr. Research Associate  
Clinical Fellow in Medicine  
Assistant Professor of Medicine  
Instructor in Anesthesia  
Research Fellow in Medicine  
Instructor in Medicine  
Instructor in Medicine

**James R. Rodrigue, PhD\***

Jonathan Berkman  
Lauren B. Finnigan  
Aaron Fleishman  
Denny Tsai  
Teresa Williams

**Associate Professor of Psychology  
and Surgery, Departments of  
Psychiatry and Surgery; Director,  
Center for Transplant Outcomes and  
Quality Improvement**  
Research Assistant  
Research Assistant  
Research Assistant  
Research Assistant  
Administrative Assistant

**Terry B. Strom, MD\***

Brunilda Ramos-Perez

**Professor of Medicine and Surgery;  
Scientific Co-Director,  
The Transplant Institute**  
Administrative Coordinator

**Hongying Tang, MSc**

**Transplant IS Administrator**

**Laurence A. Turka, MD\***

Alex Huynh  
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Jihoon Chang, PhD  
Weihua Gong, MD, PhD  
Alex Huynh  
Yu Lu, PhD  
Sachin Malhotra, PhD  
Jennifer Mason  
Ryan Newton, PhD  
Natavudh Townamchai, MD  
Greg Whitcher  
Ruan Zhang, PhD

**Professor of Medicine; Scientific  
Co-Director, The Transplant Institute**  
Graduate Rotation Student  
Graduate Rotation Student  
Research Fellow  
Research Fellow  
Graduate Rotation Student  
Research Fellow  
Programs Manager  
Administrative Coordinator  
Research Fellow  
Research Fellow  
Research Assistant  
Research Fellow



<b>M. Todd Valerius, PhD*</b> Daniel Blackler	<b>Instructor in Surgery</b> Research Assistant
<b>Yael Vin, MD*</b>	<b>Instructor in Surgery</b>
<b>Barbara Wegiel, PhD*</b> Kellie Cunningham David Gallo	<b>Assistant Professor of Surgery</b> Research Assistant Senior Research Associate



## Research Focus

I am developing a program in clinical outcomes research in the areas of abdominal transplantation, hepatobiliary surgery, and dialysis access. We have been working to create research databases in these areas and, in collaboration with the medical and radiation oncology services, additional programs for hepatocellular carcinoma and cholangiocarcinoma. I am also interested in applying tools from decision analysis to determine the best treatment options for patients with early-stage hepatocellular carcinoma.

## Accomplishments in the Past Year

### Research Progress

In conjunction with staff from the Transplant Institute, we have been working to convert our current clinical patient management system to a research-friendly data repository. We are also working with an industry sponsor to investigate a novel antibody that may aid in the prevention of delayed graft function in high-risk deceased donor renal transplant recipients.

### Individual Accomplishments

During the summer and fall academic terms, I completed 25 credits toward my Masters in Public Health at the Harvard School of Public Health. I was also asked to review abstract submissions for the annual American Transplant Congress in the category of deceased donor kidney transplantation. I continue to serve as an ad hoc reviewer for a number of transplant publications.

### Invited Presentations

I presented talks to the BIDMC Gastroenterology and Medical Oncology Divisions on the topics of liver transplantation and surgical management of hepatobiliary malignancies.

## Teaching, Training, and Education

### Undergraduate Courses

I continue to lecture to the HMS2 class during their Gastroenterology Section on liver transplantation. Additionally, I hold a weekly tutorial session for a small group of HMS3 students during their general surgery rotation. We discuss core topics in general surgery, transplantation, and related specialties during a weekly case-based conference.

### Graduate Medical Courses

I am responsible for the weekly transplant surgery rotation-specific lecture for medical students, residents, and fellows on our service. Lectures I have created or revised include kidney, liver, and pancreas transplantation, living and deceased donors, acute liver failure, hemodialysis-access techniques, peritoneal dialysis, management of hepatocellular carcinoma, and management of bile duct injuries. I created a lecture for the general surgery resident curriculum on cirrhosis and portal hypertension.



**Amy R. Evenson, MD**

Instructor in Surgery

Staff Member  
Teresa Williams

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Karp SJ, Johnson S, **Evenson A**, Curry MP, Manning D, Malik R, Lake-Bakaar G, Lai M, Hanto D. Minimising cold ischaemic time is essential in cardiac death donor-associated liver transplantation. *HPB (Oxford)* 2011;13:411-6.

#### Research Investigations (Submitted or in Press)

Francis JM, Palmer MR, Donohoe KJ, Curry M, Johnson S, Karp S, **Evenson A**, Pavlakis M, Hanto D, Mandelbrot DA. Evaluation of native kidney recovery after simultaneous liver-kidney transplant. *Transplantation* 2011; in press.

### Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media

#### Reviews, Chapters, Monographs, and Editorials

**Evenson AR**. Utilization of kidneys from donation after circulatory determination of death. *Curr Opin Organ Transplant* 2011;16(4):385-9.

#### Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Hamdan A, **Evenson, A**, Fischer JE, Jones DB, Pomposelli FB, Upchurch GR, Klimberg VS, Schwaitzberg SD. Hemorrhagic risk and blood components. In: Fischer JE, Jones DB, Pomposelli FB, Upchurch GR, editors. *Fischer's Mastery of Surgery*, 6th edition. Lippincott Williams & Wilkins, Philadelphia, PA.; 2011, in press.

Hamdan A, **Evenson A**, Fischer JE, Jones DB, Pomposelli FB, Upchurch GR, Klimberg VS, Schwaitzberg SD. Alternative vein bypass. In: Fischer JE, Jones DB, Pomposelli FB, Upchurch GR, editors. *Fischer's Mastery of Surgery*, 6th edition. Lippincott Williams & Wilkins, Philadelphia, PA; 2011, in press.

## Research Focus

### Basic Research

My current laboratory research effort 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 (IRI) and delayed graft function (DGF), allograft rejection and survival, and in hepatic regeneration. This work is in collaboration with Leo E. Otterbein, PhD, in the Transplant Institute, one of the foremost experts on the biologic effects of CO.

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. DGF is a common complication of kidney transplantation, occurring in 20%-50% of deceased donor kidneys, and is associated with decreased short-term and long-term function, decreased graft survival, increased risk of rejection, and increased costs. We have developed a novel kidney allograft model of DGF in swine that allows us to examine the ability of CO to prevent IRI and the resulting DGF, as well as acute and chronic rejection.

We have shown that treatment of the recipient with intra-operative inhaled CO using a novel CO gas delivery system is effective in restoring kidney function more rapidly than in non-CO treated animals and accelerating the recovery of renal function post-transplant. We are currently determining the optimal treatment regimen (dose, duration, timing), studying whether CO treatment will allow longer cold storage time, what role O<sub>2</sub> plays in the efficacy of CO, and importantly, whether treatment of the donor and the allograft will further limit DGF.

We believe the mechanisms of protection in the recipient and donors are different with regard to the innate immune response to IRI. We are currently investigating the molecular mechanisms by which CO decreases DGF utilizing immunopathology and gene expression profiling using highly sensitive RT-PCR and Affymetrix gene arrays. Data has shown decreased cell death and enhanced epithelial cell repair in CO treated animals with a likely component being more rapid recruitment and differentiation of stem cells. We have also shown that CO enhances rapid and early hepatocyte proliferation in mice after hepatectomy and importantly helps preserve synthetic function. We have shown that the mechanism appears to involve a CO mediated increase in hepatocyte growth factor (HGF) secretion from stellate cells. The HGF generated binds to and activates cMet receptors on hepatocytes to accelerate hepatocyte proliferation through an Akt-cyclin dependent pathway. Further studies in a cirrhotic liver resection model have shown CO is able to down-regulate the increase in fibrosis that occurs in cirrhotic mice subjected to hepatectomy. These findings have obvious clinical application.

### Clinical Research

The Center for Transplant Outcomes and Quality Improvement within the Transplant Institute has, as part of its strategic plan, decided to focus a significant portion of its resources and efforts on examining the role that health care inequalities play in determining access to treatment for chronic kidney disease and kidney transplantation (both living- and deceased-donor transplants) and how they influence post-transplant outcomes. We have reviewed health care inequalities in transplantation and, in fact, have identified areas where the field had overlooked areas of inequality heretofore not recognized.



**Douglas W. Hanto,  
MD, PhD**

Clinical Director,  
The Transplant Institute  
Lewis Thomas Professor of Surgery  
Associate Surgeon-in-Chief

Staff Member  
Helen Snook

We found that there was significant information documenting the pervasiveness of racial and socioeconomic disparities in transplantation, but data regarding other high-risk populations remained elusive. For example, there have been relatively few articles published reflecting age- and gender-based disparities. We found that additional criteria such as religion, housing status, immigration status, geography, and literacy should also be considered in future research of disparities in transplantation.

Finally, while data surrounding kidney transplantation are sparse, the study of disparities in other fields of transplantation such as liver and pancreas has largely been neglected and we believe that future research should aim to paint a more comprehensive picture of disparities across the transplantation landscape, highlighting the most vulnerable populations and procedures. An important original observation is that one must design intervention trials that target not just one stage along the pathway to transplantation, but many different stages to have a significant impact.

We are currently utilizing social network analysis to examine shared risk between potential donors and recipients in a given network, clarifying the likelihood of finding an appropriate match through either direct donation or paired exchange. A detailed hypothesis paper was published in 2011 (see Ladin K; bibliography.). We are studying whether network factors explain low living-donor kidney transplantation among African-American patients.

A second major project has been to better understand why blacks, who represent over a third of patients needing transplants, receive just 13.4% of living donor kidney transplants. We have examined whether age, gender, marital status, family size, employment, education, functional limitations, blood type, hypertension, BMI, diabetes, health behaviors, psychiatric history, and dialysis type explain racial disparities in the rate of living-donor presentation and transplantation using a single-center (BIDMC) sample of 752 potential kidney recipients and 654 potential donors evaluated between the years 2004-2009.

We found that black patients had a significantly lower number of potential donors evaluated and their rate of living-donor transplant or any transplant was lower than white patients. After 18 months, 47%, 21%, and 27% of white patients had at least one potential donor evaluated, received a living-donor transplant, or had undergone any transplant, respectively, compared to 31%, 6%, and 13% of black patients ( $p < 0.001$ ). Prior studies have suggested that if patient characteristics and distribution of commonly cited risk factors were similar for blacks and whites, disparities in transplantation would diminish significantly. This hypothesis, however, had not been tested in the past.

Using statistical methods not previously applied to this question that computed the counterfactual outcomes (if white patients had the distribution of covariates observed in black patient and vice versa), we have been able to show that 46% of white patients and 32% of black patients would have had a potential living donor evaluated within 18 months if the covariate distribution were reversed by race. This suggests to us that lower rates of donor presentation cannot be explained by differences in typical socio-demographic or medical variables and that donor factors may be more important than previously thought. This paper was submitted for publication in 2011 (see Ladin K; bibliography).

## Research Support

“Solid organ transplantation in HIV: Multi-site study”

NIH/NIAID AI052748

2004-2012

PI: Peter G. Stock, MD, PhD (University of California San Francisco)

Site Principal Investigator: Douglas W. Hanto, MD, PhD

“Placebo-controlled, safety and tolerability study of the effects of carbon monoxide for inhalation in patients receiving kidney transplantation”

Ikaria C201

2008-2011

Site Principal Investigator: Douglas W. Hanto, MD, PhD

“Neoadjuvant sorafenib prior to RFA in HCC, a randomized controlled phase II trial”

Bayer/Onyx

2008-

Co-Investigator: Douglas W. Hanto, MD, PhD

“Predicting outcomes with marginal livers after transplantation”

Roche Organ Transplantation Foundation

2011-

Site Principal Investigator: Douglas W. Hanto, MD, PhD

## Research Accomplishments in the Past Year

### Abstracts Presented at Local, National, and International Meetings

Kuramitsu K, Sverdlov D, Csizmadia E, Burkly LC, Schuppan D, Hanto DW, Otterbein LE, Popov Y. Failure of fibrotic liver regeneration in mice is linked to a severe fibrogenic response driven by hepatic progenitor cell activation. 62nd Annual Meeting of the American Association for the Study of Liver Diseases, San Francisco, CA, November 4-8, 2011, abstract #1811 (Presidential Poster of Distinction - poster presentation November 8, 2011).

### Invited Presentations

“Beneficial Biologic Effects of Inhaled Carbon Monoxide (CO) in Transplantation.” Albany Medical College, Department of Surgery and Division of Transplantation, The Neil Lempert, MD. Visiting Professorship Lecture. Albany, NY. June 2, 2011.

“Experience with Carbon Monoxide (CO): from Animals to Humans.” Animal Models of IRI, DGF, SGF Session, FDA Workshop: Ischemia reperfusion injury and down stream effects of delayed graft function, other short term and long term outcomes in kidney transplantation. Silver Spring, MD. September 9, 2011.

“Transplant Centers of Excellence.” Beth Israel Deaconess Medical Center, Chinese Executive Hospital Management Leadership Program 2011 (CEHMLP); Xuejun Kong, MD, Co-Director. Boston, MA. November 3, 2011.

Douglas W. Hanto, MD, PhD



## Teaching, Training, and Education

### Graduate School and Graduate Medical Courses

- At Harvard Medical School (HMS), I participated in the Core Clerkship in Surgery, Transplant elective, and student tutorial as an Attending.
- I participated in the Transplant Fellowship program as an Instructor for pre- and post-operative care and operative technique to Transplant fellows.

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## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Goldfarb-Rumyantzev AS, Sandhu GS, Khattak M, Barenbaum A, **Hanto DW**. Social adaptability index predicts access to kidney transplantation. Clin Transplant 2011; 25:834-42.

Karp SJ, Johnson S, Evenson A, Curry MP, Manning D, Malik R, Lake-Bakaar G, Lai M, **Hanto D**. Minimising cold ischaemic time is essential in cardiac death donor-associated liver transplantation. HPB (Oxford) 2011; 13:411-6.

Kuramitsu K, Csizmadia E, Gallo, D, **Hanto DW\***, Otterbein LE\*. Carbon monoxide enhances early liver regeneration in mice after hepatectomy. Hepatology 2011;53:2016-26. \*These authors contributed equally to this study.

Ladin K, **Hanto DW**. Rational rationing or discrimination: balancing equity and efficiency considerations in kidney allocation. Am J Transplant 2011; 11:2317-21.

Rodrigue JR, Dimitri N, Reed A, Antonellis T, **Hanto DW**, Curry M. Quality of life and psychosocial functioning of spouse/partner caregivers before and after liver transplantation. Clin Transplant 2011;25: 239-47.

Rodrigue JR, **Hanto DW**, Curry MP. Patients' expectations and success criteria for liver transplantation. Liver Transpl 2011;17:1309-17.

Rodrigue JR, **Hanto DW**, Curry MP. Patients' willingness to accept expanded criteria donor liver transplantation. Am J Transplant 2011; 11:1705-11.

Rodrigue JR, Mandelbrot DA, **Hanto DW**, Johnson SR, Karp SJ, Pavlakis M. A cross-sectional study of fatigue and sleep quality before and after kidney transplantation. Clin Transplant 2011; 25:E13-21.

Rodrigue JR, Nelson DR, Reed AI, **Hanto DW**, Curry M. Is model for end-stage liver disease score associated with quality of life after liver transplantation? Progr Transplant 2011; 21:207-14.

Sandhu GS, Khattak M, Woodward R, **Hanto DW**, Dimitri N, Goldfarb-Rumyantzev A. Impact of substance abuse on access to renal transplantation. Transplantation 2011;91:86-93.

Stock PG, Barin B, Murphy B, **Hanto DW**, Diego JM, Light J, Davis C, Blumberg E, Simon D, Subramanian A, Harland R, Lyon GM, Brayman K, Slakey D, Shapiro R, Melancon J, Kumar A, Stosor V, Stablein DM, Roland ME. Kidney transplant outcomes in one hundred and fifty HIV-infected recipients. N Engl J Med 2010;363:2004-14. Erratum in : N Engl J Med 2011; 364:1082.

**Research Investigations (Submitted or in Press)**

Garg J, Karim M, Tang H, Gurprataap SS, DeSilva R, Rodrigue J, Pavlakis M, **Hanto DW**, Goldfarb-Rumyantzev AS. Social adaptability index predicts kidney transplant outcomes; a single-center retrospective analysis. *Nephrol Dial Transplant* 2011; in press.

Pavlakis M, **Hanto DW**. Clinical pathways in transplantation: a review and examples from Beth Israel Deaconess Medical Center. *Clin Transplant* 2011; in press.

Pruett TL, Blumberg EA, Cohen DJ, Crippin JS, Freeman RB, **Hanto DW**, Mulligan DC, Green MD. A consolidated biovigilance system for blood, tissue, organs: One size does not fit all? *Am J Transplant* 2011; in press.

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

## Reviews, Chapters, Monographs, and Editorials

**Hanto DW**, Veatch RM. Uncontrolled donation after circulatory determination of death (UDCDD) and determination of death. *Am J Transplant* 2011;11:1351-2.

Ladin K, **Hanto DW**. Informed consent and living kidney donation: more (information) is not always better. [Editorial] *Am J Transplant* 2011; 11:2547-8.

## Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Robson SC, **Hanto DW**, Otterbein O, Ferran C. Fritz H. Bach MD, April 5, 1934-August 14, 2011. [Memorial] *Xenotransplantation* 2011; in press.

Wegiel B, **Hanto DW**, Otterbein L. The social networking of carbon monoxide in innate immunity. *Trends in Immunology* 2011; in press.

## Books, Monographs, and Text Books

**Hanto DW**. Perspective on biliary disease. In: Zinner MJ, Ashley SW, editors. *Maingot's Abdominal Operations*. 12th Edition. New York, NY. McGraw Hill: 2011; in press.

## Case Reports

**Hanto DW**, Kane RA, Raven K. Acute rise in creatinine in a long-term kidney transplant recipient. *Images in Transplantation*. *Am J Transplant* 2011; 11:2771-3.

**Douglas W. Hanto, MD, PhD**



## Research Focus

The focus of my group is the study of allogeneic and xenogeneic (both fetal and conventional) islet transplants placed into cynomolgus monkey (macaque, *Macaca fascicularis*) recipients. We are particularly interested in novel anti-inflammatory (cytoprotective) strategies as a means to enable immune tolerance and nurture resilient (“cytoprotected”) islets to cure Type 1 Diabetes Mellitus (T1DM) in new-onset diabetics or in recipients of islet transplants.

The major project in my group is to understand the molecular and cellular basis of tolerance to islet allograft and xenograft rejection. By necessity this includes an understanding of the molecular and cellular basis of diabetogenic autoimmunity. In particular, we pursue a promising new area for translational application to understand the mechanism and role of inflammation in transplants. Our aim is to design new therapeutic and diagnostic approaches and test them in animal models. It is necessary to understand the overall effects of inflammation from pro- to anti-inflammatory models as a means to establish tolerance to islets in an autoimmune host. Thus we aim to follow extremely exciting data, concentrating efforts to cure diabetes through the prevention of islet graft rejection or recurrence of autoimmune disease. Inflammation plays a critical role in determining the fate of allografts.

To unravel the roles of graft infiltrating hematopoietic stem cells (HSCs) and innate lymphoid cells (ILCs) should provide a new understanding of the biology of the allograft response given the knowledge concerning the crucial role of ILCs in governing inflammation in other systems. There is essentially a “mirror image” system of helper T-cells and ILCs (including ILC1, ILC2, ILC17, and ILC22). As our preliminary data suggests, HSCs, particularly HSCs positive for the orphan nuclear hormone receptor ROR gamma t (RORgt+), are closely related to graft infiltration by ILCs, at least RORgt+ ILCs.

We know exactly when a transplant is placed and can detect the rapid appearance of intra-graft HSCs. For this we utilized RORgt indicator mice, giving us an unexpected view of LSK HSCs, including esoteric RORgt graft infiltrating non-T-cells. Yet the fate of graft infiltrating HSCs and the role or even presence of graft infiltrating ILCs has not been well established. Our studies have focused upon RORgt+ HSCs, but we have yet to establish the exact phenotype of these RORgt+ILCs. Moreover, RORgt negative ILCs almost certainly will be found within these allografts. In essence, we will obtain a database that may allow us to characterize and then dampen detrimental inflammation in its earliest stage before the advent of adaptive immunity and significant tissue damage. The knowledge and perspective to be obtained may provide invaluable basic and clinical guidance in the field of transplantation.

One new, unfunded project in the lab aims to image islet transplants using “color-coded” T-cells. In this system, T-cell subsets express different colors and can be followed in vivo after islet transplantation. Using this system we have identified important characteristics of graft infiltrating HSCs and ILCs.

The following represents a list of funded projects:

1. Tolerance induction for primate islet transplantation.
2. New strategy of tolerance induction in non-human primate islet allograft model.
3. Tolerance induction for primate islet.
4. Thoracic allograft tolerance in non-human primates.
5. Human islet transplant center – a pipeline to induce tolerance.



**Maria Koulmanda, MSc, PhD**

Associate Professor of Surgery

### Lab Members

Zhigang Fan MD, PhD  
 Nipun Goel, PhD  
 Dusan Hanidziar, MD  
 Ramandeep Kaur, MB, BS  
 Derek Liu, MD  
 Ki-Soo Park, DVM  
 Rebecca S. Sampathkumar, PhD  
 Gurbakhshish Singh, MD  
 Lan Jiang  
 Naved Munir, MSc  
 Xinju (Joan) Zhang

**Maria Koulmanda, MSc, PhD**

6. A new approach to reverse the onset of autoimmune diabetes.
  7. Inflammation and T-cell memory: inter-related barriers to allograft tolerance.
  8. On the role of regulatory T-cells in transplantation.
  9. To test new  $\alpha$ -1-antitrypsin products on the role of inflammation and autoimmunity in the NOD mouse.
- 

### Research Support

“Inflammation and T-cell memory: inter-related barriers to allograft tolerance.”  
National Institutes of Health 1-U19 DK080652  
2007-2012

PI: Maria Koulmanda, PhD

“On the role of regulatory T-cells in transplantation.”  
National Institutes of Health PO1 AI041521  
2007-2012

PI: Terry Strom, MD

Co-Investigator: Maria Koulmanda, PhD

“The autoimmunity/inflammation connection in type-1 diabetes”  
Juvenile Diabetes Research Foundation Center on Immunological Tolerance in Type 1 Diabetes at Harvard Medical School (response to RFA)  
Juvenile Diabetes Research Foundation, 4-2007-1057: Project 8  
2008-2013

Co-Investigators: Terry B. Strom, MD and Maria Koulmanda, PhD

“To test new strategies of tolerance induction in non-human primate allograft model.”  
Juvenile Diabetes Foundation (Corporate)  
2009-2012

PI: Maria Koulmanda, PhD

“Role of the CD226 pathway in Type 1 diabetes.”  
Juvenile Diabetes Research Foundation 4-2007-1057 Juvenile Diabetes Research Foundation Center on Immunological Tolerance in Type 1 Diabetes at Harvard Medical School (response to RFA)  
2010-2013

PI: Laurence A. Turka, MD

Co-Investigator: Maria Koulmanda, PhD

“CI1NH treatment of new onset Type 1 Diabetic NOD mice.”  
Viropharma, Inc.  
2011-2013

PI: Maria Koulmanda, PhD

### Applications Submitted and Pending Review/Funding

“Taming inflammation to create tolerance.”  
National Institute of Health 5 P01 AI041521-17: Project 3 (Competing Renewal)

MPI: Terry B. Strom, MD and Maria Koulmanda, PhD

“Approaches to tolerance of renal and islet allografts.”  
National Institute of Health U19

MPI: Terry B. Strom, MD and Maria Koulmanda, PhD

“Taming inflammation to create tolerance”

National Institute of Health 1R01DK091285-01A1

MPI: Terry B. Strom, MD and Maria Koulmanda, PhD

“Taming inflammation to create transplant tolerance.”

National Institute of Health U01

MPI: Terry B. Strom, MD and Maria Koulmanda, PhD

“Role of TIM-4 in regulating Type 1 Diabetes.”

National Institute of Health R01 DK096138

MPI: Terry B. Strom, MD and Maria Koulmanda, PhD

“Visualizing and analyzing the restoration of tolerance to beta cells.”

American Diabetes Association

Co-Investigators: Terry B. Strom, MD and Maria Koulmanda, PhD

“Effect of blockade of the IL-6 and IL-21 pathways in the cynomolgus islet transplantation model.”

National Institute of Health U19 Opportunity Pool

PI: Maria Koulmanda, PhD

“Danger in the creation of tolerance.”

American Diabetes Association

PI: Maria Koulmanda, PhD

**Maria Koulmanda, MSc, PhD**

## Accomplishments in the Past Year

### Research Progress

Recently we have been unraveling the roles of graft infiltrating HSCs and ILCs should provide a new understanding of the biology of the allograft response given the knowledge concerning the crucial role of ILCs in governing inflammation in other systems.

### Individual Accomplishments

- Elected as the “President Elect” for the Cell Transplant Society Chair for the CTS Meeting, International Cell Transplant and International Xenotransplantation Meeting, 2011
- Best Oral Presentation Award, 9th International Conference on New Trends in Immunosuppression and Immunotherapy, Geneva, Switzerland. 2011
- Presented, “Alpha 1 anti-trypsin reverses T1DM by blocking inflammation.” Alpha-1 Foundation’s Twelfth Gordon L. Snider Workshop entitled, “New Formulations and Applications of Alpha-1 Antitrypsin”, Miami, FL 2011

### Reviewer for Grants

American Diabetes Association

Juvenile Diabetes Research Foundation (Australia)

Juvenile Diabetes Research Foundation (USA)

National Institutes of Health, Opportunity Pool for Review of Non-Human Primates

NIAID/NIDDK Non-Human Primate Transplantation Tolerance Cooperative Study Group

National Health and Medical Research Council of Australia

### Reviewer for Journals

*American Journal of Transplantation*  
*Cell Transplantation*  
*Clinical and Experimental Immunology*  
*Diabetologia*  
*Nature Biotechnology*  
*PLoS One*  
*Transplantation*  
*Xenotransplantation*

### Invited Presentations

- “Role of Tim-4 in Transplant Tolerance.” Tim Program Project Grant, Brigham and Women’s Hospital, Boston, MA. 2011
- “The autoimmunity/inflammation connection in type-1 diabetes.” Juvenile Diabetes Research Foundation – JDRF Center at HMS Meeting, Boston, MA. 2011
- “Role of Tim-4 in T1D.” Tim Program Project Grant.” Brigham and Women’s Hospital, Boston, MA. 2011.
- “The role of TIM-4 in Type 1 Diabetes Mellitus.” Juvenile Diabetes Research Foundation, New York, NY. 2011
- “Danger and its impact on diabetogenes T-cell.” Austin Research Institute; Melbourne, Australia. 2011
- “The role of TIM-4 in Transplantation and Immunity.” Therapeutic Area Focused Innovation Meetings, Sanofi-Aventis, Cambridge, MA. 2011
- “Visualizing Danger & Tolerance.” Beaune 2011, Paris, France. 2011
- “In vivo tracking of “color-coded T-cells in allograft response.” 9th International Conference on New Trends in Immunosuppression & Immunotherapy, Geneva, Switzerland. 2011
- “Alpha 1 anti-trypsin reverses T1DM by blocking inflammation.” Alpha-1 Foundation’s Twelfth Gordon L. Snider Workshop entitled, “New Formulations and Applications of Alpha-1 Antitrypsin”, Miami, FL. 2011
- “IL-6 disruption of tolerance: Changing the balance between Th17 and Treg.” CTS/IXT 2011 Joint Congress, Immunology Immunoisolation session; Invited speaker: Cell Special Symposium, Miami, FL 2011

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### Bibliography (January-December 2011)

#### Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media

Reviews, Chapters, Monographs, and Editorials

Hanidziar D, Koulmanda M. Towards cytoprotection in the peritransplant period. *Semin Immunol* 2011;23(3):209-13.



## Research Focus

Research efforts in my group have undergone a transition from laboratory-based transplant immunology to clinical research. One current focus is the evaluation and follow-up of living kidney donors. We are interested in practices in U.S. transplant centers regarding living donor evaluation criteria and are also interested in living donor follow-up. The latter was recently funded by the NIH to permit more detailed and long-term living donor follow-up at the BIDMC.

Another research area of focus involves studies of immunosuppressive regimens in renal transplantation. We recently completed an analysis of the SRTR transplant database, which determined factors that predict benefit from IL-2 receptor blockade. This work was followed by an invited editorial in the *Journal of the American Society of Nephrology* discussing the use of IL-2 receptor antibodies versus anti-thymocyte globulin. We are also interested in the use of sirolimus, particularly analyzing BIDMC data on converting patients from calcineurin inhibitors to sirolimus. This work generated a state-of-the-art review article on the clinical use of sirolimus and another review article concerning the mechanism of action of sirolimus.

We were also involved in an important analysis of the BIDMC experience using donor-after-cardiac-death kidneys as part of a steroid withdrawal protocol. We are currently investigating the BIDMC experience using low-dose anti-thymocyte globulin for induction and are exploring the role of continued immunosuppression in patients with failed grafts who are back on dialysis.

I also serve as the site principal investigator for international multicenter trials of basiliximab, conversion from cyclosporine to sirolimus, the novel calcineurin inhibitor ISA 247, the novel Jak kinase inhibitor CP-690,550 and the use of ramipril for proteinuria induced by sirolimus.

## Research Support

“Kidney Donor Outcomes Cohort (KDOC) Study”  
National Institutes of Health, R01 DK085185  
03/01/2011–02/28/2015  
MPI: James R. Rodrigue, PhD and Didier A. Mandelbrot, MD

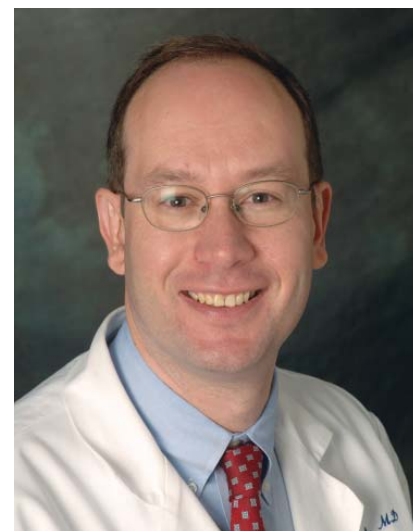
## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Palmer MR, Donohoe KJ, Francis JM, **Mandelbrot DA**. Evaluation of relative renal function for simultaneous liver-kidney transplant patients using Tc-99m-MAG3 scintigraphy with attenuation correction from anatomical images and SPECT/CT. *Nucl Med Commun* 2011;32:738-44.

Rodrigue JR, Ladin K, Pavlakis J, **Mandelbrot DA**. Disclosing recipient information to potential living donors: preferences of donors and recipients before and after surgery. *Am J Transplant* 2011;11:1270-8.



**Dieder A. Mandelbrot, MD**

Associate Professor of Surgery

Group Members  
Ajay Kher, MD

Dieder A. Mandelbrot, MD

Research Investigations (Submitted or in Press)

Francis JM, Palmer MR, Donohoe KJ, Curry M, Johnson S, Karp S, Evenson A, Pavlakis M, Hanto D, **Mandelbrot DA**. Evaluation of native kidney recovery after simultaneous liver-kidney transplant. Transplantation 2011; in press.

## Research Focus

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.

Our work stems from the study of heme oxygenase-1 (HO-1), which has been labeled a protective gene. HO-1 generates CO endogenously as it catabolizes heme. More recently, we have expanded our studies to include 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. To address certain questions, we have generated conditional knockout mice for HO-1 and BVR allowing us to delete either gene in a tissue-specific manner.

More recently we discovered that BVR colocalizes with Toll-like receptor-4 (TLR4) and regulates the response of the cell to bacterial endotoxin. Functionally, this interaction prevents the upregulation of pro-inflammatory cytokines and improves survival in a model of acute hepatitis in mice. We furthered these findings in a paper published in PNAS in 2011 where we demonstrate that BVR becomes nitrosylated and, as such, translocates to the nucleus where it binds to the TLR4 promoter to block expression. We conclude that BVR is an innate regulator of the inflammatory response. Studies are now underway using the BVR conditional knockdown in macrophages in acute liver injury and regeneration. *Figure 1* summarizes our recent findings with BVR. Biliverdin is now under pre-clinical evaluation for treatment of inflammatory disorders with a new biotech company Viridis Biotech for leading the development.

We also maintain a very active bacterial sepsis program, where we have shown that inhaled CO can protect mice from acute severe bacterial sepsis and shock. One mechanism by which CO provides protection is via enhanced activation of the inflammasome. This is evidenced by augmented caspase-1 activation and IL-1 $\beta$  expression as well as bacterial clearance in the peritoneum. Shown in *Figure 2* is our working model of inflammasome activation in macrophages treated with bacteria  $\pm$  CO. Of note is that CO targets the bacterium versus the macrophage, acting to drive ATP release from the bacteria that in turn activates the macrophage. We conclude that CO acts to sense the environment for the presence of bacteria. The binding of endotoxin to TLR receptors activates HO-1 as signal 1. The CO generated then diffuses into the environment and if a bacteria is present, ATP will be generated that acts as signal 2 binding to the P2X7 receptor and fully activating the macrophage to kill. Such a model, much like Tcell activation, permits a elegant system of innate inflammatory regulation, preventing unnecessary cell activation.

We continue our work in models of vascular injury related to arteriosclerosis, which leads to chronic rejection, as well as vascular trauma. We 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. Further that CO enhances recruitment of endothelial progenitor cells to repair the injured vessel in mice.

Inhaled CO is currently in clinical trials to improve kidney function after transplantation. Data generated in a large animal model was the proof-of-concept study that led to the clinical trial.

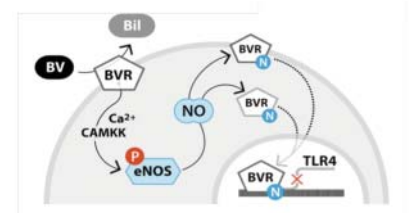


**Leo E. Otterbein, PhD**

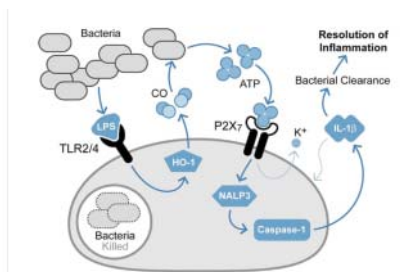
Associate Professor of Surgery

### Staff Members

Beek Yoke Chin, PhD  
Lan Jun Wang, MD  
David Gallo  
Kellie Cunningham  
Andreas Hedblom  
Mailin Li



*Figure 1*



*Figure 2*

## Research Support

“Endogenous gas molecules as transcription factors”

National Institutes of Health, 5R01GM088666

08/01/09-07/31/13

PI: Leo E. Otterbein, PhD

“Heme oxygenase-1 and transplant tolerance”

National Institutes of Health, R56AI092272

08/15/11-07/31/15

PI: Leo E. Otterbein, PhD

“Macrophage gene expression in mucosal inflammation”

National Institutes of Health, RO1 DK054452-05A2

08/01/06-07/31/11

Co-PI: Leo E. Otterbein, PhD

“Inhaled gases as a therapy for septic shock”

CIMIT – Dept of Defense

10/01/09-09/30/11\* on NCE

PI: Leo E. Otterbein, PhD

“Activation of innate immunity in sepsis and trauma”

Affinity Research Collaborative (ARC) - Department of Surgery BIDMC

PI: Carl Hauser, MD

Co-PI: Leo E. Otterbein, PhD

“Training in transplant immunology”

National Institutes of Health, 5T32AI070085-02

PI: John Iacomini, PhD

Preceptor: Leo E. Otterbein, PhD

## Applications Submitted and Pending Review/Funding

“Heme oxygenase-1 and acute lung injury”

National Institutes of Health, R01

PI: Leo E. Otterbein, PhD

“Heme oxygenase-1 and bone marrow progenitor cells in vascular injury”

National Institutes of Health, R01

PI: Leo E. Otterbein, PhD

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## Research Accomplishments in the Past Year

### Research Progress

We published two important papers in 2011, both in *PNAS*, on the two areas of focus in the laboratory, CO and BVR. We were commissioned to submit a review for *Trends in Immunology*, which will be published in 2012. Our work was highlighted at a number of research conferences winning awards and being cited in top impact journals. We were awarded a new NIH R01 (R56) in July to continue our work on heme oxygenase and organ transplantation.

**Administrative Accomplishments**

I continued my role as a member of BIDMC IACUC, was appointed to the Research Vision and Strategy Committee and to the Young Investigators Group as a Faculty Advisor. I was also appointed as a site miner for the BIDMC.

**Patent Disclosures**

I have continuing involvement in the litigation of nine patent applications for the use of carbon monoxide as a therapeutic. Eight of the nine patents have been issued. A new disclosure and patent application was submitted for the use of carbon monoxide in DNA repair and as an anti-aging molecule.

**Individual Accomplishments**

- Selected as the BIDMC representative of CIMIT (Center for Integration of Medicine and Innovative Technology) as the hospital Site Miner. As such, I am tasked with identifying innovative researchers and linking individuals among the member institutions to leverage innovative and entrepreneurial technology to solve difficult medical challenges and bring solutions to clinical application.
- Remained 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. Additionally I was recently appointed to the review committee for the James & Ester King Biomedical Research Program, and an ad hoc member of the UK Medical Research Council as well as the New Zealand research council.

**Invited Presentations**

“Carbon Monoxide and Sepsis.” Beth Israel Deaconess Medical Center, Department of Medicine.  
Boston, MA. September, 2011.

“Therapeutic potential of Carbon Monoxide in Transplantation.” New England Organ Bank Representatives.  
Boston, MA. March, 2011.

“Therapeutic Effects of Carbon monoxide in Sepsis.” 9th Annual Biodefense Vaccines and Therapeutics.  
Washington, D.C. July, 2011.

“Gaotransmitters in Disease: Therapeutic Development of Carbon Monoxide.” British Pharmacological Association, Winter Meeting.  
London, UK. December, 2011.

**Teaching, Training, and Education**

Training of postdoctoral and surgical fellows in the laboratory in the nuances of research design and implementation, scientific writing for grants and manuscripts and preparations for seminars and conference presentations.

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Cerrito MG, Scagliarini A, Froio A, Liloia A, Busnelli M, Giovannoni, **Otterbein LE**, Mainetti L, Villa M, Bach F, Leone BE, Biasi GM, Lavitrano M. Heme Oxygenase-1 inhibition prevents intimal hyperplasia enhancing nitric oxide-dependent apoptosis of vascular smooth muscle cells. *Bio Pharm Bull* 2011;34:1204-14.

Haschemi A, Chin BY, Jeitler M, Esterbauer H, Wagner O, Bilban M, **Otterbein LE**. Carbon monoxide induced PPAR $\gamma$  SUMOylation and UCP2 block inflammatory gene expression in macrophages. *PLoS One* 2011;6(10):e26376.

Kuramitsu K, Gallo D, Yoon M, Chin BY, Csizmadia E, Hanto DW, **Otterbein LE**. Carbon monoxide enhances early liver regeneration in mice after hepatectomy. *Hepatology* 2011;53(6):2016-26.

**Otterbein LE**, Hedblom A, Harris C, Csizmadia E, Gallo D, Wegiel B. Heme oxygenase-1 and carbon monoxide modulate DNA repair through ataxia-telangiectasia mutated (ATM) protein. *Proc Natl Acad Sci U S A* 2011;108(35):14491-6.

Sheikh SZ, Hegazi RA, Kobayashi T, Onyiah JC, Russo SM, Matsuoka K, Sepulveda AR, Li F, **Otterbein LE**, Plevy SE. An anti-inflammatory role for carbon monoxide and heme oxygenase-1 in chronic Th2-mediated murine colitis. *J Immunol* 2011;186(9):5506-13.

Wegiel B, Gallo D, Csizmadia E, Roger T, Kaczmarek E, Harris C, Zuckerman BS, **Otterbein LE**. Biliverdin inhibits toll-like receptor-4 (TLR4) expression through nitric oxide-dependent nuclear translocation of biliverdin reductase. *Proc Natl Acad Sci U S A* 2011;108(46):18849-54.

## Research Focus

My research focus has been in the following areas: industry sponsored multi-center immunosuppression trials, federally funded clinical investigations, unfunded retrospective center and regional analyses, and collaborations with scientists and clinicians at other centers in investigator initiated projects. I am particularly interested in involving our center in research studies of immunosuppressant agents with unusual mechanisms of action.

## Research Accomplishments in the Past Year

### Individual Accomplishments

- Served on and chaired numerous abstract review committees for both the ASN and AST annual meeting.
- Continued as an associate editor of the *American Journal of Kidney Disease* (to serve for the AJT clinical imaging section), and to serve on the UNOS DTAC committee from 2011-2013.

### Administrative Accomplishments

- Revised all clinical pathways with other members of the Transplant Institute and have a paper in publication outlining the development and implementation of our pathways.

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Kasper EM, Bartek J, Johson SR, Kasper BS, **Pavlakis M**, Wong M. Post-transplant aspergillosis and the role of combined neurosurgical and anti-fungal therapies under belatacept immunosuppression. *Surg Neurol Int* 2011;2:75.

**Pavlakis M**. Live kidney donation: a 36 year old woman hoping to donate a kidney to her mother. *JAMA* 2011;305(6):592-9.

Rodrigue JR, Ladin K, **Pavlakis M**, Mandelbrot DA. Disclosing recipient information to potential living donors: preference of donors and recipient, before and after surgery. *Am J Transplant* 2011;11(6):1270-8.

Rodrigue JR, Mandelbrot DA, **Pavlakis M**. A psychological intervention to improve quality of life and reduce psychological distress in adults awaiting kidney transplantation. *Nephrol Dial Transplant* 2011;26(2):709-15.

Rodrigue JR, Mandelbrot DA, Hanto DW, Johnson SR, Karp SJ, **Pavlakis M**. A cross-sectional study of fatigue and sleep quality before and after kidney transplantation. *Clin Transplant* 2011;25(1):E13-21.

Sandhu G, Khattak M, Woodward R, Hanto DW, **Pavlakis M**, Dimitri N, Goldfarb-Rumyantsev A. Impact of substance abuse on access to renal transplantation. *Transplantation* 2011;91(1):86-93



**Martha Pavlakis, MD**

Associate Professor of Surgery



**Martha Pavlakis, MD**

**Research Investigations (Submitted or in Press)**

Francis JM, Palmer MR, Donohoe KJ, Curry M, Johnson S, Karp S, Even-son A, **Pavlakis M**, Hanto D, Mandelbrot DA. Evaluation of native kidney recovery after simultaneous liver-kidney transplant. Transplantation 2011; in press.

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

**Pavlakis M**, Kumar V. Introduction to the well-transplant visit-more than vital signs and a creatinine check. Clin J Am Soc Nephrol 2011;6(7):1773

**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Blumberg B, Barin B, Bloom R, Roland M, Frassetto L, Murphy B, **Pavlakis M**, Roth D, Moore J, Davis C, Saltzberg S, Fine D, Josephson M, Lyon GM, Zhang R, Stosor V, Brayman K, Johnson L, Shapiro R, Weikert B, Fatica R, Mogilishetty G, Hardy, D and Stock P. Oral presentation ATC 2011.

## Research Focus

My research laboratory studies purinergic signaling as it is regulated by ecto-nucleotidases of the CD39/ENTPD family, which are vascular, immune and hepatic sinusoidal cell-expressed ecto enzymes that hydrolyze extracellular nucleotides to adenosine and purine derivatives.

Ongoing studies involve examining platelet activation and coagulation disturbances in transplant rejection; together with innate immune, T-cell responses and immune regulation in solid organ and islet allo and xenotransplantation.

My laboratory has extensive local, national and international collaborations.

## Research Support

“Tolerance approach in xenotransplantation”

NIH NIAID, P01 AI045897-11A1

09/01/00 – 06/30/16

PD/PI: David H. Sachs, MD; Simon C. Robson, MD, PhD

“Thrombus formation in vivo”

Project #3: CD39 and thrombogenesis.

NIH NHLBI, P01 HL087203-04

09/01/08 – 05/31/13

PD/PI: Bruce Furie, MD; Simon C. Robson, MD, PhD

“Which transgenic pig will be used for islet transplantation in humans?”

NHMRC/JDRF, #447718

01/01/08 – 12/31/12

Project Leader: Simon C. Robson, MD, PhD

“Purinergic thromboregulation”

NIH NHLBI, 5 R01 HL094400-02

07/01/09 – 06/30/12

PI: Simon C. Robson, MD, PhD

“Purinergic receptors in inflammation”

NIH/NIAID, 5 R01 AI080582-03

06/15/09 – 05/31/13

PI: Wolfgang Junger, PhD

Co-Investigator: Simon C. Robson, MD, PhD

“Genetically engineered pig organ transplantation into non-human primates”

NIH/NIAID, 5 U19 AI090959-02

08/01/10 – 07/31/15

PI: David K.C. Cooper, MD, PhD (University of Pittsburgh)

Co-Investigator: Simon C. Robson, MD, PhD

“BMP signaling—a therapeutic target in liver disease”

NIH/NIDDK, 5 R01 DK081387-02

04/20/10 – 3/31/15

PI: Seth Karp, MD (Vanderbilt University)

Co-Investigator: Simon C. Robson, MD, PhD



**Simon C. Robson, MD,  
PhD, FRCP**

Professor of Medicine

### Lab Members

Alan Moss, MD

Martina Nowak, MD

Xiaofeng Sun, MD

Yan Wu, PhD

Aiping Bai, MD, PhD

Moritz Schmelzle, MD

Maggie Ham, MD

Eva Csizmadia

## Accomplishments in the Past Year

### Research Accomplishments

- New developments in understanding how CD39 and purinergic signals impact T regulatory cell and T helper Type 17 plasticity (with Terry Strom and Larry Turka).
- Dissection of roles in tumor Immunobiology.
- New mutant mice null for CD39, CD39L1, CD39L3 and with targeted deletions.
- Novel multitransgenic GalT-KO swine overexpressing CD39, thrombomodulin, complement regulatory factors (with Tony d'Apice, Peter Cowan, David Sachs and David Cooper).
- Novel antibodies to CD39 family members and reagents.

### Individual Accomplishments

Simon C. Robson

- NIH AICS Charter Membership in 2011.

Moritz Schmelzle

- Thomas E. Starzl, MD Postdoctoral Research Fellowship  
<[http://www.liverfoundation.org/2012\\_research\\_awards/2011/schmelzle/](http://www.liverfoundation.org/2012_research_awards/2011/schmelzle/)>  
Beth Israel Deaconess Medical Center/Harvard Medical School  
Boston, MA. "Platelet activation triggered by CD39L1/NTPDase2 facilitates stem cell-mediated liver regeneration." Mentor: Simon Robson, MD, PhD, FRCP.
- DGPW Best Oral Presentation, Annual Meeting, 2010  
EASL Young Investigators Bursary 2011  
TRM Excellence Award in Leipzig, Germany.

Maria Serena Loghi

- MRC Clinician Scientist Fellowship (01/10/2010-30/09/2014). 'Autoantigen-specific regulatory T-cells: a new tool for tolerance induction in autoimmune hepatitis' - Medical Research Council, UK

### Invited Presentations

- Visiting professorships/lectures at Kings College Hospital and MRC Transplant Center, Biomedical Forum, London, and NYU; BU BCH (Jan, 11), Denver (May, 11) & Torino, Italy (June, 11).
- Invited talks at NIH (IXCRP), Society Leukocyte Biology (Vancouver, Oct, 10), Areces Foundation (Madrid, March, 11), FEBS Conference (Torino, June, 11), Swine Biomedical Conference (Chicago, July, 11), AASLD in Dec., 2010 and ATC in April, 2011.

## Teaching, Training, and Education

### Graduate School and Graduate Medical Courses

- Preceptor; 7-8 2nd year Harvard Medical School students. Abdominal Examination, Clinical Instructor; 3-4 2nd year Harvard Medical School students.
- Core Medicine I Clerkship. ME600M.5. Gastroenterology Clinic Preceptor. 2nd year Harvard Medical School students,
- Outpatient evaluations of students. Internal Medicine Visiting Attending Physician for student rotations.
- Inpatient evaluations of students on Epstein Trey service.
- Attending Gastroenterologist/Hepatologist for fellow and resident teaching/ pathophysiology lectures.
- DoM resident and intern teaching; Teaching Attending Service in General Medicine. BIDMC.
- Attendee (invited) and Professor's rounds at various Firm Conferences and Grand Rounds, on monthly basis.

### CME Courses/Other Teaching Contributions

- ACP Physician Refresher Course in Gastroenterology, Boston MA.

## Bibliography (January – December 2011)

### Peer-Reviewed Articles in Print or Other Media

#### Research Investigations

am Esch JS, Schmelzle M, Fürst G, **Robson SC**, Krieg A, Duhme C, Tustas RY, Alexander A, Klein HM, Topp SA, Bode JG, Häussinger D, Eisenberger CF, Knoefel WT. Infusion of CD133+ bone marrow-derived stem cells after selective portal vein embolization enhances functional hepatic reserves after extended right hepatectomy. *Ann Surg* 2011;255:79-85.

Feng L, Sun X, Csizmadia E, Han L, Bian S, Murakami T, Wang X, **Robson SC**, Wu Y. Vascular Cd39/Entpd1 directly promotes tumor cell growth by scavenging extracellular adenosine triphosphate. *Neoplasia* 2011;13:206-16.

Fisicaro N, Londrigan SL, Brady JL, Salvaris E, Nottle MB, O'Connell PJ, **Robson SC**, d'Apice AJ, Lew AM, Cowan PJ. Versatile co-expression of graft-protective proteins using 2a-linked cassettes. *Xenotransplantation* 2011;18:121-30.

Ho KJ, Do NL, Otu HH, Dib MJ, Ren X, Enjoji K, **Robson SC**, Terwilliger EF, Karp SJ. Tob1 is a constitutively expressed repressor of liver regeneration. *J Exp Med* 2011;207:1197-1208.

Sun X, Imai M, Nowak-Machen M, Guckelberger O, Enjoji K, Wu Y, Khalpey Z, Berberat P, Munasinghe J, **Robson SC**. Liver damage and systemic inflammatory responses are exacerbated by the genetic deletion of cd39 in total hepatic ischemia. *Purinergic Signal* 2011;7(4):427-34.

Simon C. Robson, MD, PhD, FRCP

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

Cowan PJ, **Robson SC**, d'Apice AJ. Controlling coagulation dysregulation in xenotransplantation. *Curr Opin Organ Transplant* 2011;16:214-21.

Deaglio S, **Robson SC**. Ectonucleotidases as regulators of purinergic signaling in thrombosis, inflammation and immunity. *Adv Pharmacol* 2011;61:301-32.

Friedman DJ, Turka LA, **Robson SC**. There's a goat behind door number 3: from monty hall to medicine. *J Clin Invest* 2011;121:3819-21.

**Robson SC**. Liver endothelial cells. Hemostasis, thrombosis and hepatic vascular diseases. Chapter 1. In: deLeve LD, Garcia-Tsao G, editors. *Vascular Liver Disease*. Springer;2011. p. 3-24.

Schmelzle M, Cowan PJ, **Robson SC**. Which anti-platelet therapies might be beneficial in xenotransplantation? *Xenotransplantation* 2011;18:79-87.

Shalev I, Schmelzle M, **Robson SC**, Levy G. Making sense of regulatory T-cell suppressive function. *Semin Immunol* 2011; 23(4):282-92.

Letter to Editor

Eltzschig HK, **Robson SC**. NT5E mutations and arterial calcifications. *N Engl J Med* 2011;364(16):1577-8.

## Research Focus

My clinical research program has three primary objectives: (1) to enhance patient-centered outcomes in the context of clinical transplantation, (2) to characterize the outcomes of living kidney donors, and (3) to reduce disease burden and mortality by identifying effective strategies for increasing the supply of organs for transplantation.

### Enhance patient-centered outcomes in the context of clinical transplantation

The World Health Organization (WHO) has stressed the importance of a patient's subjective perception of life in the context of his or her value systems, goals, expectations, and standards when evaluating the benefits of medical or surgical intervention. Consistent with the WHO's emphasis on patient-centered research, we are conducting studies designed to help patients prioritize their goals for transplantation and to make informed choices based on these priorities, to enhance provider-patient communication around patients' treatment preferences and goals, and to facilitate transplant providers' clinical decision-making. In other transplant-related studies, we are evaluating the effectiveness of behavioral health interventions to optimize self-management behaviors (e.g., medication adherence), maximize quality of life, enhance cognitive functioning, improve sleep hygiene, and reduce caregiving burden and distress within family systems. All of these studies share the common goal of reducing disease burden and optimizing transplant outcomes that are important to patients and their families.

### Characterize the outcomes of living kidney donors

For adults with end-stage renal disease, kidney transplantation using a healthy living donor has many advantages over deceased donor transplantation, including shorter or no dialysis exposure, immediate graft function, lower perioperative morbidity and mortality, better quality of life, and better long-term graft and patient survival. Indeed, living donors now account for nearly half of all kidney transplant performed in the United States. The transplant community and changes in federal regulations have brought attention to the need for more systematic study of living donor outcomes. The lack of such data is an important problem because, without it, the transplant community will continue to have considerable variability in informed consent processes for living donors and their recipients, as well as limited data to inform clinical practice and policy development.

We have the most ambitious multisite, prospective living donor cohort studies ever funded by the National Institutes of Health. Currently in its first year, this cohort study will assess donor outcomes and their predictors over a 2-year period initially, with the intention of continuing assessments in subsequent years to better characterize long-term outcomes. We are evaluating surgical, medical, functional, and psychological outcomes, as well as important secondary outcomes such as donation costs (direct, indirect), satisfaction, decision stability, and miscellaneous consequences (e.g., problems getting and/or maintaining health or life insurance) associated with donation. Additional aims of the study are to identify the donor, recipient, and center variables that are most strongly associated with living donor outcomes and to identify disparities (race, gender, age, income) in donor outcomes and factors that are associated with such disparities. We are hopeful that once these outcomes and their predictors are known, we can further develop and refine educational strategies and informed consent processes for both living donors and their



**James R. Rodrigue, PhD**

Associate Professor of Psychology and Surgery

#### Group Members

Lauren Finnigan  
Jonathan Berkman  
Aaron Fleischman  
Denny Tsai  
Teresa Williams

intended recipients, as well as provide systematic data to inform policy discussions and clinical care practices.

### **Identifying effective strategies for increasing the supply of organs for transplantation**

The success of transplantation is limited largely by the extreme shortage of transplantable organs. A key part of my research program, therefore, is the empirical evaluation of methods to reduce the escalating gap between the demand for transplantation and the insufficient supply of organs. We are tackling this problem on several parallel tracks of scientific inquiry, with funding from the National Institutes of Health and the Health Resources and Services Administration.

First, we have developed a community-based research partnership with the New England Organ Bank and the Massachusetts Registry of Motor Vehicles to evaluate strategies for increase organ donor registrations in the Commonwealth. Nearly all registered organ donors signed up in the RMV office or on their website, so this is an important portal for public education programs. However, fewer than half of all licensed drivers have registered as organ donors, so we are investigating the effectiveness of RMV clerk training, community outreach programming, and media-based interventions on organ donor registration rates.

Second, donation after circulatory death (DCD) has been endorsed by the Institute of Medicine and the Health Resources and Services Administration as an important strategy for increasing the availability of transplantable organs. In the last decade, while rates of donation after neurological death have remained stable, there has been a nearly 10-fold increase in the number of DCD donors. Although DCD now accounts for 12% of all deceased donor cases in the United States, its growth potential has not been fully realized because of process deficiencies, less favorable attitudes among healthcare providers, and lower rates of consent among family members. Consequently, we are initiating a multisite study to evaluate performance processes in potential DCD donors at several medical institutions in New England, to characterize DCD knowledge and attitudes of critical care providers, and to identify determinants of family consent for DCD. We believe that identifying areas for improvement in the DCD process and the education of critical care staff, as well as a better understanding of the salient explanatory factors in the donation decision will enable targeted interventions to be developed to increase DCD consent rates.

Third, we know that minorities and low-income patients with end-stage renal disease receive live donor kidney transplantation at substantially lower rates, relative to Whites and those with adequate financial resources. We have identified factors contributing to such disparities in living donation and are now evaluating a novel intervention to increase rates of live donor kidney transplantation in these disadvantaged populations. In a randomized clinical trial funded by the National Institutes of Health, we are evaluating the relative effectiveness of educational interventions delivered in an individual, group, or family home setting, with or without the presence of family members and friends. To date, the House Calls intervention has shown to be particularly effective at reducing many of the modifiable barriers faced by minorities and low-income patients who want to pursue the live donor kidney transplant option.



## Research Support

“A randomized trial to reduce the disparity in live donor kidney transplantation”  
National Institutes of Health, R01 DK079665  
10/01/2007–09/30/2012  
PI: James R. Rodrigue, PhD

“Cognitive function in dialysis patients: Ancillary study to the FHN trial”  
National Institutes of Health, R01 DK074715  
10/01/2009–09/30/2012  
PI: John Stokes, MD (University of Iowa)  
Collaborator: James R. Rodrigue, PhD

“Kidney Donor Outcomes Cohort (KDOC) Study”  
National Institutes of Health, R01 DK085185  
03/01/2011–02/28/2015  
MPI: James R. Rodrigue, PhD and Didier A. Mandelbrot, MD

“Massachusetts Registry of Motor Vehicles: Increasing donor registry enrollment: Using targeted community outreach and online media campaigns”  
Health Resources and Services Administration, D71HS22061  
09/01/2011–08/31/2013  
PI: James R. Rodrigue, PhD

“Pegylated interferon +/- ribavirin for children with HCV: PEDS-C long-term follow-up study  
Roche, NV 17424”  
11/01/2011–10/31/2012  
PI: Kathleen B. Schwarz, MD (Johns Hopkins University)  
Collaborator: James R. Rodrigue, PhD

## Applications Submitted and Pending Review/Funding

“Understanding organ donation after circulatory death”  
National Institutes of Health, R01 DK096427  
07/01/2012–06/30/2017  
PI: James R. Rodrigue, PhD

“A DMV-based intervention to increase donor registrations: The New England Dissemination Project”  
Health Resources and Services Administration, HRSA 95285  
08/01/2012–07/31/2014  
PI: James R. Rodrigue, PhD

“Measuring patients’ expectations and success criteria for surgery”  
Patient-Centered Outcomes Research Institute  
07/01/2012–06/30/2014  
PI: James R. Rodrigue, PhD

“Understanding donor motivation and transplant center facilitation for altruistic kidney donation”  
Health Resources and Services Administration  
08/01/2012–07/31/2015  
PI: Prabhakar Baliga, MD (Medical University of South Carolina)

James R. Rodrigue, PhD

## Accomplishments in the Past Year

### Research Progress

In the past year, we have moved into the final phase of our House Calls study and I am now preparing an NIH competitive renewal. Our preliminary analyses suggest that a psycho-educational program delivered in the patient's home (i.e., old-fashioned house calls) increases patients' willingness to consider live donor kidney transplantation, yields more living donor inquiries, and contributes to a higher number of actual live donor kidney transplants, relative to standard care (i.e., education provided by physicians and nurses during a routine clinic visit). These findings essentially replicate what we found in a similar study we conducted in Florida several years ago. We will now evaluate the medical cost offsets associated with the House Calls intervention and evaluate its effectiveness using a peer-based educational approach. I am also developing a manual for the House Calls intervention, as it is now being implemented in two other federally funded studies and in The Netherlands.

We are in the first year of our multisite Kidney Donor Outcomes Cohort (KDOC) study. The start-up phase was lengthy and complex, since we are coordinating research activities across six transplant centers, 11 investigators, three separate cohorts (donors, recipients, healthy controls), five assessment time points, and a new online data collection system. Despite the many practical challenges, we enrolled our first living donor participant in October and now have over 30 total subjects in various phases of assessment – with a recruitment goal of 720 participants.

We completed one large-scale study in which we randomized DMV offices in Florida to receive either an enhanced organ donation intervention on-site (staff training, donor family volunteers, etc.) or simple placement of organ donation materials in the waiting room (i.e., usual care). DMV offices that received the enhanced organ donation awareness campaign showed a significantly higher aggregate monthly donor registration rate than those offices receiving usual care, controlling for baseline donor registration rates and region. We also found that donor registration rates dropped when we withdrew the enhanced intervention. Lower donor registration rates were significantly associated with DMV service regions with more minorities, less education, and lower income. We have since formed a strong research collaborative with the New England Organ Bank and the Massachusetts Registry of Motor Vehicles and have begun implementing a similar study here in the Commonwealth, with the explicit goal of increasing donor registrations by 25% across the state.

We are making excellent progress on our unfunded studies as well. These include studies examining medication adherence post-transplantation, risk factors for alcohol relapse following liver transplantation, and long-term psychological outcomes after living kidney donation.

### Administrative Accomplishments

#### Department of Surgery

- Director, Center for Transplant Outcomes & Quality Improvement
- Director, Behavioral Health Services and Research, Division of Transplantation
- Co-Director, Clinical Scholarship Program

- Co-Director, Surgical Outcomes Group
- Faculty Search Committee (Transplant Surgeon)
- Reviewer, Resident Research Competition

#### Department of Psychiatry

- Member, Department Research Committee
- Chair, Harvard Medical School Mysell Committee

#### Individual Accomplishments

- Funding for new NIH R01 grant for a multisite living kidney donor outcomes study
- Funding for a new HRSA grant for a study to increase organ donation registrations
- Funding for a new subcontract with Roche to investigate the long-term psychological outcomes of interferon and ribavirin treatment in children with Hepatitis C Virus
- Member, Behavioral Medicine Interventions and Outcomes Study Section, National Institutes of Health
- Ad Hoc Grant Reviewer, Healthcare Delivery and Methodologies Integrated Review Group, National Institutes of Health
- Ad Hoc Grant Reviewer, Health Services Organization and Delivery Study Section, National Institutes of Health
- Executive Committee Member, National Kidney Foundation's End the Wait Task Force
- Member, Joint Societies Working Group on Living Kidney Donation, Organ and Transplantation Procurement Network, Living Donor Committee
- Councilor-at-Large, Executive Committee, Community of Allied Health Professionals, American Society of Transplantation
- Member, Psychosocial and Treatment Adherence Program Abstract Selection Committee, American Transplant Congress
- Member, Ethics Committee, American Society of Transplant Surgeons
- Member, Deceased Donor Management Research Task Force, American Society of Transplant Surgeons
- Member, Editorial Board, Progress in Transplantation
- Ad Hoc Reviewer for several transplantation and behavioral medicine journal

#### Invited Presentations

"Ethical considerations in transplantation." Blood, Marrow and Solid Organ Transplantation at BIDMC, a collaborative conference of the New England Organ Bank and Beth Israel Deaconess Medical Center. Boston, MA. April 12, 2011.

**James R. Rodrigue, PhD**

**James R. Rodrigue, PhD**

“Organ donation and transplantation: psychological issues and challenges.” Oklahoma State University, College of Osteopathic Medicine, Keynote address for the Annual Colby Foundation Cassani Lecture Series. Oklahoma City, OK. April 15, 2011.

“Ethical considerations in transplantation.” Oklahoma State University, College of Osteopathic Medicine, Invited presentation to the family medicine and internal medicine residents. Oklahoma City, OK. April 15, 2011.

“Psychological aspects of living donation: what have we learned and where do we go from here?” University of Iowa Hospital and Clinics, Transplant Grand Rounds. Iowa City, IA. October 18, 2011.

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## **Teaching, Training, and Education**

My teaching responsibilities include teaching the psychosocial aspects of transplantation to medical students, interns, residents, and fellows rotating through transplantation. This involves informal teaching of the role that psychological, psychiatric, and behavioral health factors play in transplant selection processes as well as transplant outcomes. In addition, I participate in the teaching of psychiatry residents by participating in the residency’s research mentorship program and lecturing on transplantation annually in the Longwood Psychiatry Consultation-Liaison residency training program. In the Department of Surgery, I serve as Co-Director of the Clinical Scholarship Program and provide ongoing clinical research mentorship to surgical residents and junior faculty. I meet monthly with Surgery junior faculty to provide guidance and mentorship in the conduct of clinical research, grantsmanship, and academic career development.

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## **Bibliography (January–December 2011)**

### **Peer-Reviewed Publications in Print or Other Media**

#### **Research Investigations**

Goldfarb-Rumyantzev A, Barenbaum A, **Rodrigue JR**, Rout P, Isaacs R, Mukamal K. New social adaptability index predicts overall mortality. Arch Med Sci 2011; 7:720-7.

**Rodrigue JR**, Balistreri W, Haber B, et al. Peginterferon with or without ribavirin has minimal effect on quality of life, behavioral/emotional, and cognitive outcomes in children. Hepatology 2011; 53:1468-75.

**Rodrigue JR**, Dimitri N, Reed A, Antonellis T, Hanto DW, Curry M.. Quality of life and psychosocial functioning of spouse/partner caregivers before and after liver transplantation. Clin Transplant 2011; 25:239-47.

**Rodrigue JR**, Hanto DW, Curry M. Patients’ expectations and success criteria for liver transplantation. Liver Transpl 2011; 17: 1309-17.

**Rodrigue JR**, Hanto DW, Curry MP. Patients’ willingness to accept expanded criteria donor liver transplantation. Am J Transplant 2011; 11:1705-11.

**Rodrigue JR**, Ladin K, Pavlakis M, Mandelbrot DA. Disclosing recipient information to potential living donors: Preferences of donors and recipients, before and after surgery Am J Transplant. 2011; 11:1270-8.

**Rodrigue JR**, Mandelbrot DA, Pavlakis M. A psychological intervention to improve quality of life and reduce psychological distress in adults awaiting kidney transplantation. *Nephrol Dial Transplant* 2011; 26:709-15.

**Rodrigue JR**, Mandelbrot DA, Hanto DW, Johnson SR, Karp SJ, Pavlakis M. A cross-sectional study of fatigue and sleep quality before and after kidney transplantation. *Clin Transplant* 2011; 25:E13-21.

**Rodrigue JR**, Nelson DR, Reed AI, Hanto DW, Curry M. Is MELD associated with quality of life after liver transplantation? *Prog Transplant* 2011; 21: 207-14.

**Rodrigue JR**, Schutzer ME, Paek M, Morrissey P. Altruistic kidney donation to a stranger: Psychosocial and functional outcomes at two U.S. centers. *Transplantation* 2011; 91:772-8.

Research Investigations (Submitted or in Press)

Garg J, Karim M, Tang H, Sandhu GS, DeSilva R, **Rodrigue JR**, Pavlakis M, Hanto DW, Goldfarb-Rumyantzev AS. New Social Adaptability Index predicts kidney transplant outcome. *Nephrol Dial Transplant* 2011; in press.

**Rodrigue JR**, Krouse J, Carroll C, McMillen L, Giery K, Fraga Y, Frost T, Edwards E. A Department of Motor Vehicles intervention yields moderate increases in donor designation rates. *Prog Transplant*; 2011: in press.

**James R. Rodrigue, PhD**



## Research Focus

Our goal is to safely render transplant recipients tolerant to their transplants and restore self tolerance in Type 1 diabetes, thereby enabling transplant survival or restoration of normoglycemia in the absence of maintenance in immunosuppressive medications. Through use of basic and translational science, we are pursuing this goal.

At a basic level, we are analyzing the molecular pathways that foster commitment to T-cell tissue destructive- and tissue protective-subsets as well as those that decommitment such commitments. We have learned that T-cells adopt tissue-destructive or tissue-protective modes of action on the basis of cues present within the micro-environment in which they recognize foreign antigen. These cues largely relate to molecular texture of inflammation and inflammatory cells present within the antigen bearing micro-environment. We use this knowledge to design molecules and regimens that foster immune tolerance.

In the absence of biomarkers to identify patients with impending rejection, decreasing or discontinuing immuno-suppressive therapy is fraught with difficulty. To aid in the management of patients on standard therapy or deployment of potentially tolerizing therapies we have also identified molecular signatures that are present in peripheral blood mononuclear cells well in advance of clinically evident kidney transplant rejection. The validity of this signature is now being tested in doubled blind trials.

### Area being developed for funding

We have discovered a molecular pathway that directs a variety of immune and inflammatory cells into either a healing or destructive mode. Initial studies reveal that we can use antibodies to guarantee many immuno-inflammation cells adopt a healing phenotype.

## Research Support

“JDRF Center on immunological tolerance in Type 1 diabetes”

Juvenile Diabetes Research Foundation - 4-2004-368

2008-2012

PI: Terry B. Strom, MD

“The autoimmunity/inflammation connection in Type 1 diabetes”

Juvenile Diabetes Research Foundation Center on Immunological Tolerance in Type 1 Diabetes at Harvard Medical School (response to RFA)

Juvenile Diabetes Research Foundation - 4-2007-1057: Project 8

2008-2013

Co-Investigators: Terry B. Strom, MD; Maria Koulmanda, MSc, PhD

“On the role of regulatory T-cells in transplantation”

National Institute of Health, P01 AI041521

2007-2012

PI: Terry B. Strom, MD

“Inflammation and T-cell memory: inter-related barriers to allograft tolerance.”

National Institute of Public Health, PPG U19 DK080652

2007-2012

Program Director/PI: Terry B. Strom, MD



**Terry B. Strom, MD**

Professor of Medicine and Surgery



**Terry B. Strom, MD**

- “TIM Family of Genes: Regulation of the allograft response by TIM proteins.”  
National Institute of Health, P01 AI 073748  
2008-2013  
Co-Investigator: Terry B. Strom, MD
- “Novel therapies of Chronic Allograft Dysfunction (CTOT)”  
National Institute of Health, U01-063623  
2004-2014  
PI: Terry B. Strom, MD
- “Novel therapies for chronic renal allograft dysfunction in children”  
National Institute of Health, U01 AI77816  
2008-2013  
PI: Terry B. Strom, MD
- “Individualizing therapy for kidney and heart transplant recipients”  
National Institute of Health, U01AI063594-07S1  
2010-2011  
PI: Terry B. Strom, MD
- “Identification of novel biomarkers using a systems approach for accurately predicting onset of Type 1 Diabetes (T1D)”  
Helmsley/Harvard Medical School Catalyst Grant for T1D  
2011-2012  
Co-Investigator: Terry B. Strom, MD
- “To determine whether recombinant C1 esterase inhibitor restores euglycemia and self-tolerance in new onset overtly diabetic NOD mice”  
Viropharma, Inc.  
2011-2012  
Co-Investigators: Terry B. Strom, MD; Maria Koulmanda, M.Sc, PhD
- “Identifying novel inflammatory molecules in the periosteum and bone marrow of chronic headache/migraine”  
GlaxoSmithKline  
2011-2012  
Co-Investigator: Terry B. Strom, MD
- “IL-21 +/- IL-6 pathway blockade”  
Pfizer, Inc.  
2011-2012  
PI: Terry B. Strom, MD
- “Mechanisms of B Cell-Dependent Transplantation Tolerance”  
National Institute of Health, R56 AI 057851-07  
Co-Investigator: Terry B. Strom, MD

**Applications Submitted and Pending Review/Funding**

- “Distinguishing induced & natural regulatory T-cell roles in transplant tolerance”  
National Institute of Health, 1R01DK091285-01A1  
2012-2017  
PI: Terry B. Strom, MD
- “Project 3: Taming inflammation to create tolerance”  
National Institute of Health, 5 P01 AI041521-17  
2012-2017  
Co-PI: Terry B. Strom, MD

Terry B. Strom, MD

“Approaches to tolerance of renal and islet allografts”  
National Institute of Health, U19  
2012-2017  
Co-PI: Terry B. Strom, MD

“Taming inflammation to create tolerance”  
National Institute of Health, 1R01DK096039-01  
2012-2017  
PI: Terry B. Strom, MD

“Taming inflammation to create transplant tolerance”  
National Institute of Health, 1U01AI102427-01  
2012-2017  
PI: Terry B. Strom, MD

“Effect of blockade of the IL-6 & IL-21 pathways in the cynomolgus islet transplantation model”  
National Institute of Health U19 Opportunity Pool  
2012-2014  
Co-PIs: Terry B. Strom, MD; Maria Koulmanda, MSc, PhD

“Visualizing and analyzing the restoration of tolerance to beta cells”  
American Diabetes Association  
2012-2015  
Co-PIs: Terry B. Strom, MD; Maria Koulmanda, MSc, PhD

“Danger in the creation of tolerance”  
American Diabetes Association  
2012-2015  
Co-PIs: Terry B. Strom, MD; Maria Koulmanda, MSc, PhD

“Are infiltrating hematopoietic stem cells the root of intragraft inflammation?”  
National Institute of Health, AN:3466197  
2012-2014  
Co-PIs: Terry B. Strom, MD, and Maria Koulmanda, MSc, PhD

## Accomplishments in the Past Year

### Research Progress

We discovered several new therapeutic targets and crafted agents that are effective in pre-clinical models of transplantation and autoimmunity. Both therapies and diagnostic strategies developed in our lab are now in clinical trials.

### Individual Accomplishments

- Member, Ad Hoc Search Committee for Medical Director of Renal Transplant, Massachusetts General Hospital/Harvard Medical School, Boston, MA. 2011
- Member, Resident Professor Board, Pfizer, Cambridge, MA. 2010-2011
- Biology F1000 Head of Section for Immunomodulation USA. 2011

### Invited Presentations

“Visualizing danger.” Stanford University School of Medicine, Graduate Program in Immunology. Stanford, CA.

“The autoimmunity/inflammation connection in type-1 diabetes.” Harvard Medical School, JDRF Center on Immunological Tolerance in Type-1 Diabetes. Boston, MA.

“Danger: AAT is an antidote.” Pfizer, Inc. Cambridge, MA.

“Taming adverse inflammation to create tolerance.” Vanderbilt University Medical Center, Vanderbilt Transplant Center, Billingham Lectureship in Transplant Immunology. Nashville, TN.

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### Bibliography (January – December 2011)

#### Peer-Reviewed Articles in Print or Other Media

##### Research Investigations

Fujisaki J, Wu J, Carlson AL, Silberstein L, Putheti P, Larocca R, Gao W, Saito TI, Celso CL, Tsuyuzaki H, Sato T, Cote D, Sykes M, **Strom TB**, Scadden DT, Lin CP. In vivo imaging of T(reg) cells providing immune privilege to the haematopoietic stem-cell niche. *Nature* 2011;474(7350):216-9.

Gupta S, Balasubramanian S, Thornley TB, **Strom TB**, Kenny JJ. Direct pathway T-cell alloactivation is more rapid than indirect pathway alloactivation. *Transplantation* 2011;91(9):e65-7.

Park J, Gao W, Whiston R, **Strom TB**, Metcalfe S, Fahmy TM. Modulation of CD4+ T lymphocyte lineage outcomes with targeted, nanoparticle-mediated cytokine delivery. *Mol Pharm* 2011;8(1):143-52.

##### Research Investigations (Submitted or in Press)

El Essawy B, Putheti B, Gao W, **Strom TB**. Rapamycin generates graft-horning murine suppressor CD8(+) T-cells that confer donor-specific graft protection. *Cell Transplant* 2011; in press.

Yamada Y, Boskovic S, Aoyama A, Murakami T, Putheti P, Smith RN, Ochiai T, Nadazdin O, Koyama I, Boenisch O, Najafian N, Bhasin MK, Colvin RB, Madsen JC, **Strom TB**, Sachs DH, Benichou G, Cosimi AB, Kawai T. Overcoming memory T-cell responses for induction of delayed tolerance in nonhuman primates. *Am J Transplant* 2011; in press.

#### Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media

##### Reviews, Chapters, Monographs, and Editorials

Sánchez-Fueyo A, **Strom TB**. Immunologic basis of graft rejection and tolerance following transplantation of liver or other solid organs. *Gastroenterology* 2011;140(1):51-64.

## Research Focus

My laboratory is focused on T-cell immunobiology, with an emphasis on transplantation and translational immunology. I was the first to demonstrate that T-cell costimulatory blockade could prevent allograft rejection and induce tolerance. These findings helped lead to the development of Orencia (Abatacept - FDA approved for rheumatoid arthritis) and belatacept (filed for FDA approval in renal transplantation).

My work also established a paradigm shift in the design of tolerance-inducing strategies, by demonstrating that T-cell tolerance to transplants requires the death of alloreactive T-cells, and moreover that commonly used immunosuppressive drugs inhibited this event. More recent work in my laboratory has focused on pathways that control PI3K metabolism, a key checkpoint in T-cell growth and differentiation. We recently discovered that Toll-like receptors expressed on T-cells function as direct sensors of inflammation, and that this T-cell intrinsic function is required for optimal immune responses and protection against pathogens.

## Research Support

“T-cell activation death and memory in alloimmune responses”

National Institutes of Health, RO1-AI037691

09/01/2010-08/31/2014

PI: Laurence Turka, MD

“Expression and function of the TLRs on T-cells”

National Institutes of Health, RO1-AI062789

01/01/06 – 12/31/10 (NCE 12/31/11)

PI: Laurence Turka, MD

“Costimulation and cytokines in tolerance”

National Institutes of Health, PO1-AI-041521

07/01/07-06/30/12

PI and Project Leader: Laurence Turka, MD

“Molecular and cellular regulation of tolerance”

National Institutes of Health, PO1-AI43620 Project #2

07/01/09-06/30/11

Program Director: Yongwon Choi, PhD

Project Leader: Laurence Turka, MD

“Regulation of T-cell fates by cytokine receptors”

National Institutes of Health, PO1-AI43620 Project #3 (combined with Project #2)

Program Director: Yongwon Choi, PhD

Project Co-Leader: Laurence Turka, MD

“The collaborative network for clinical research in immune tolerance”

National Institutes of Health, NO1-AI-015416

05/01/10-04/30/14

PI: Jeffrey Bluestone, PhD

Subcontract Principal Investigator: Laurence Turka, MD



**Laurence A. Turka, MD**

Professor of Medicine

### Lab Members

Jennifer Mason

Sachin Malhotra, PhD

Jihoon Chang, PhD

Yu Lu, PhD

Ruan Zhang, PhD

Natavudh Townamchai, MD

Bhavana Priyadharshini, PhD

Ryan Newton, PhD

Weihua Gong, MD, PhD

Greg Whitcher

Christopher Borges

Alex Huynh

**Laurence A. Turka, MD**

“Novel therapies of chronic allograft dysfunction”

National Institutes of Health, UO1 AI-063623

09/01/04-08/31/14

Project Director: Mohamed Sayegh, MD

Co-Investigator: Laurence Turka, MD

“Pilot projects in Type 1 diabetes and Crohn’s disease”

Helmsley Foundation

02/01/10-01/31/11

Co-PI: Laurence Turka, MD

“Role of the CD226 pathway in Type 1 diabetes”

Juvenile Diabetes Research Foundation

01/01/10-12/31/13

PI: Diane Mathis, PhD

Subcontract PI: Laurence Turka, MD

**Applications Submitted and Pending Review/Funding**

“T-cell activation death and memory in alloimmune responses”

National Institutes of Health, R01-AI037691-14

09/01/2010-08/31/2014

PI: Laurence Turka, MD

“Expression and function of the TLRs on T-cells”

National Institutes of Health, R01-AI062789-03

09/01/2010-08/31/2014

PI: Laurence Turka, MD

“Distinguishing induced & natural regulatory T-cell roles in transplant tolerance”

National Institutes of Health, AN:3304501

04/01/11-03/31/16

MPI: Terry Strom, MD, Laurence Turka, MD, Maria Koulmanda, PhD

“Molecular and cellular regulation of tolerance”

National Institutes of Health, P01-AI43620

07/01/11-06/30/16

Program Director: Yongwon Choi, PhD

Project Leader: Laurence Turka, MD

“The control of T-cell development in responses by PTEN”

National Institutes of Health, R01-AI083304

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**Administrative Accomplishments**

- Editor-in-Chief, *The Journal of Clinical Investigation* (JCI). In 2005, I assembled a team at the University of Pennsylvania and won a competitive application process to be JCI Editor-in-Chief. The JCI (impact factor ~17) receives 3800 new manuscripts per year, and I have overall responsibility for the review process and the administrative and financial management of the journal.
- Deputy Director, Immune Tolerance Network (ITN). Since 2004 I have been one of two Deputy Directors for the ITN, an NIH-funded (>\$30M/year) consortium conducting early phase trials in allergy, autoimmunity and transplantation. I am also in charge of the ITN’s Tolerance Assay and Data Analysis and Bioinformatics groups (located in Bethesda), in which capacity I have final responsibility assay selection and analysis for all ITN trials.

- Co-Director, Harvard Institute for Translational Immunology (HITI). Dr. Arlene Sharpe and I are the first Directors of HITI, a newly-formed Harvard wide entity created to foster interdisciplinary, innovative approaches for investigation of immune mediated illnesses.

### Invited Presentations

“The Use of Biomarkers in Disease: A Case Study in Transplantation.” Harvard Catalyst course on Biomarkers and Imaging in Drug Development. Cambridge, MA. March, 2011.

“Regulation of T-cell responses by the tumor suppressor gene Pten.” Dana Farber Cancer Institute, Cancer Immunology Program, Dana Farber Cancer Institute. Boston, MA.

“What are the Prospects for Transplant Tolerance: Perspectives from the Immune Tolerance Network.” Massachusetts General Hospital, Combined Transplant Grand Rounds. Boston, MA.

“The Immune Tolerance Network: Where We Stand With Tolerance Trials.” American Transplant Congress. Philadelphia, PA. April 29- May 4, 2011.

“Homeostatic Checkpoints Necessary for the Induction and Maintenance of Tolerance.” American Transplant Congress. Philadelphia, PA. April 29- May 4, 2011.

“Transplantation Tolerance: Progress and Obstacles.” Federation of Clinical Immunology Societies. Washington, DC. June 23-26, 2011.

“Transplant Tolerance: Memory, Regulation, and Other Things.” Sixth World Immune Regulation Meeting. Davos, Switzerland. March 24-27, 2011.

### Teaching, Training, and Education

Throughout my career, I have made significant contributions to teaching and education. At the University of Pennsylvania, I served on the Curriculum, Awards, Student Affairs (as Chair) and Executive Committees of the Immunology Graduate Group, and was the director of two different courses for a total of nine years. In addition, I have trained 20 Postdoctoral fellows and seven PhD students, and served on 20 thesis committees.

### Bibliography (January – December 2011)

#### Peer-Reviewed Publications in Print or Other Media

##### Research Investigations

Rahman AH, Zhang R, Blosser CD, Hou B, DeFranco AL, Maltzman JS, Wherry EJ, **Turka LA**. Anti-viral memory CD8 T-cell differentiation, maintenance and secondary expansion occur independently of MyD88. *Blood* 2011;117(11):3123-30.

Tait WE, Hosken N, Stumhofer JS, O'Hara AC, Mauldin E, Fang Q, **Turka LA**, Levin SD, Hunter CA. A role for IL-27 in limiting T regulatory cell populations. *J Immunol* 2011;187(1):266-73.

**Laurence A. Turka, MD**

Research Investigations (Submitted or in Press)

Feng S, Edong UD, Lobritto SJ, Demetris AJ, Roberts JP, Rosenthal P, Alonso EM, Philogene MC, Idle D, Poole KM, Bridges ND, **Turka LA**, and Tchao NK. Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of parental living donor liver transplants. JAMA 2011; in press.

Haynes LD, Jankowska-Gan E, Sheka A, Keller MR, Hernandez-Fuentes MP, Lechler RI, Seyfert-Margolis V, **Turka LA**, Newell KA, Burlingham WJ. Donor-Specific indirect pathway analysis reveals a B-cell-independent signature which reflects outcomes in kidney transplant recipients. Am J Transpl 2011; in press.

Harris JE, Harris TH, Weninger W, Wherry EJ, Hunter CA, and **Turka LA**. A new adoptive transfer mouse model of vitiligo closely parallels human disease and requires IFNG for depigmentation and autoreactive CD8+ T-cell accumulation in the skin. J Invest Derm 2011; in press.

Xiao X, Gong W, Demirci G, Liu W, Spoerl S, Chu X, Bishop DK, **Turka LA**, Li XC. New insights on OX40 in the control of T-cell immunity and immune tolerance in vivo. J Immunol 2011; in press.

Zhao X, Boenisch O, Yeung M, Mfarrej B, Yang S, **Turka LA**, Sayegh MH, Iacomini J, and Yuan X. Critical role of proinflammatory cytokine IL-6 in allograft rejection and tolerance. Am J Transpl 2011; in press.



## Research Focus

Research in the laboratory focuses on the molecular events of kidney development and repair using the mouse model system. We believe a deeper understanding of the biology driving these processes will help us design new approaches to treat human diseases of the kidney.

Our work centers around two important questions: 1) what are the molecular components that guide the formation of new nephrons from kidney progenitor cells, and 2) what molecular pathways are active during the repair process after acute kidney injury? Answers to the first question will aid in designing a regenerative medicine approach, which is to use nephron progenitors to treat failing kidneys by inducing new nephron formation. To accomplish this we need to understand how nephron development occurs during organogenesis so that we may encourage the same events in adult diseased kidneys and molecularly monitor the results. The second question is designed to identify potential therapeutic targets, such as signaling pathways, to promote kidney repair after organ transplantation. We view both these questions in the context of regenerative medicine. That is, to learn how to coax progenitor cells into new functional nephrons to treat failing kidneys, or enhance the recovery of surviving cells after an injury.

We have been addressing the questions above using transgenic mice to perform lineage tracing and microarray profiling of distinct cell populations during kidney development and repair. This helps us understand the cell activities occurring in these processes and the molecular events controlling them. Further, such mice permit us to examine the role of various genes during development and repair through functional analysis (e.g. using loss-of-function and gain-of-function alleles). Our work makes extensive use of transgenic mouse strains expressing fluorescent proteins and cre-recombinase in specific kidney cell populations. Using a Six2-GFP-Cre mouse strain I created in my postdoctoral work with Andy McMahon, PhD, we can culture embryonic kidneys with labeled nephron progenitors to observe and/or perturb nephron morphogenesis to learn details about this process (*Figure 1*).

We have also altered our traditional kidney explant cultures to adopt a low-volume explant culture technique (see *Figure 2*) recently published by the laboratory of Jamie Davies. We are using this culture system to observe how nephron patterning is altered when the Wnt and Notch signaling pathways are modified at later time points in nephron development. Taking advantage of existing strains, we are tracing the lineage of the Sim1-expressing cell population in the kidney. A Sim1-cre mouse strain was developed by Bradley Lowell's lab here at BIDMC for studies in the brain. Through our previous work, we had examined Sim1 and noted a restricted domain of expression during nephron development. We are now using this mouse strain to map out what mature nephron segments the Sim1-expressing population contribute to as the kidney matures (*Figure 3*).

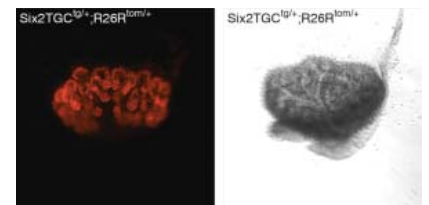
Building on my previous work on nephron progenitors and characterizing the molecular anatomy of the kidney in the GUDMAP.org project, we have been performing expression analysis and building new transgenic tools to study cell activities in development and repair. In 2011, we designed and created three new transgenic lines to label specific kidney cell populations previously inaccessible to molecular analysis. These transgenic mice are designed to label the mature proximal tubule with RFP, and express an inducible form of cre-recombinase. These new tools will enable us to perform detailed analysis of the cellular events that occur during acute kidney injury. Further, they will also permit us to functionally test the role of signaling pathways in the repair



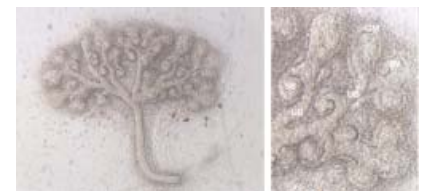
**M. Todd Valerius, PhD**

Instructor in Surgery

Lab Member  
Daniel Blackler



*Figure 1*



*Figure 2*



*Figure 3*

**M. Todd Valerius, PhD**

process and therefore identify clinically relevant targets for promoting tubule repair.

In addition, I have ongoing studies with Seth J. Karp, MD, to identify transcription factors and signaling pathways active during liver development in the mouse using the same high-throughput approaches I developed for GUDMAP. The goal here is to define a similar gene atlas focused on transcription factors and signaling pathways to define molecularly distinct domains in the liver.

For more information, please visit our web site at [www.valeriuslab.org](http://www.valeriuslab.org).

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## Research Support

“Transgenic tools for studies of the proximal nephron tubule”

Harvard Stem Cell Institute Kidney Pilot Grant

10/1/2010-4/30/2012

PI: M. Todd Valerius, PhD

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## Accomplishments in the Past Year

### Individual Accomplishments

I was asked to be an ad hoc reviewer for:

- *Journal of the American Society of Nephrology*
- *American Society of Nephrology Renal Week 2011* - Abstracts

### Teaching, Training, and Education

#### Undergraduate Courses

I mentored two undergraduate students in the summer of 2011, including one student from the Harvard Stem Cell Institute’s Internship Program (HIP).

- Trained and supervised the lab work of Roman Stolyarov of Southern Methodist University.

I was paired with Roman Stolyarov for the Harvard Internship Program hosted by the Harvard Stem Cell Institute, which sponsors about 40 talented undergraduate students each summer. Roman had no prior lab experience but completed a project and both poster and oral presentations of his work. Roman also participated in our lab journal clubs throughout the summer.

- Trained and supervised the lab work of Ceren Gunes of Bilkent University, Turkey.

Ceren is an undergraduate who studied with me for three months over the summer. She completed an expression analysis project using both in situ hybridizations techniques and immunohistochemistry that she learned here in the lab.

## Graduate School and Graduate Medical Courses

- CB 226 Concepts in Development, Self-Renewal, and Repair

I was a part time lecturer and journal club mentor to graduate students from Harvard Medical School, Harvard School of Dental Medicine, and Harvard University under the leadership of course director Iain Drummond, PhD.

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Boyle SC, Kim M, Valerius MT, McMahon AP, Kopan R. Notch pathway activation can replace the requirement for Wnt4 and Wnt9b in mesenchymal-to-epithelial transition of nephron stem cells. *Development* 2011;138(19):4245-54.

Nagalakshmi VK, Ren Q, Pugh MM, Valerius MT, McMahon AP, Yu J. Dicer regulates the development of nephrogenic and ureteric compartments in the mammalian kidney. *Kidney Int* 2011;79:317-30.

### Non-Peer Reviewed Publications in Print or Other Media

#### Reviews, Chapters, Monographs, and Editorials

Balasubramanian S, Kota SK, Valerius MT. The rejection barrier to induced pluripotent stem cells. *J Am Soc Nephrol* 2011;22(9):1583-6.

#### Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Valerius MT. Bowman's  $\beta$ -Catenin. *J Am Soc Nephrol*. 2011; in press.

**M. Todd Valerius, PhD**



## Research Focus

A major focus of my laboratory is the heme degradation pathway and the cytoprotective protein, heme oxygenase-1, which during heme catalysis generates carbon monoxide (CO), iron, and biliverdin (BV). HO-1 acts in concert with biliverdin reductase (BVR) to form one of the strongest cellular antioxidants, bilirubin (BR). We are focused on the role of HO-1 and BVR in the pathogenesis of DNA damage, cancer, and inflammation-associated disorders.

Together with Leo Otterbein, PhD, we demonstrated that HO-1 is a critical regulator of DNA repair pathways and hypothesized its contribution in cancer, premature aging and other diseases. These projects are currently ongoing in the laboratory. Further, we have uncovered novel properties of BVR functioning as a signaling molecule and mediating anti-inflammatory effects of BV. We continue to explore a role of BVR using our newly generated BVR-fl/fl conditional knockout mice.

### Heme oxygenase-1 and carbon monoxide in DNA repair, cancer and aging

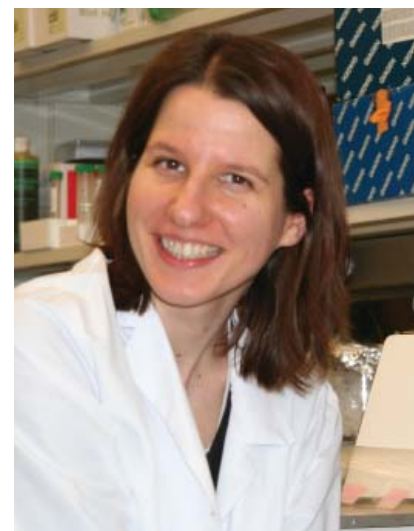
Using biochemical and molecular biological approaches, we are working towards understanding how CO and HO-1 are implicated in the regulation of normal and cancer cells biology. Our preliminary data suggest that cancer cells maintain low levels of enzymatically active nuclear HO-1 which contributes to malignancy, while application of heme degradation products or introduction of enzymatic activity of HO-1 drives cancer cell death (*Figure 1*).

Our data suggests that CO, at low, safe concentrations inhibits prostate cancer growth in a tumor xenograft model in nude mice by accelerating apoptosis and inducing growth arrest, in part, through restoration of mitochondrial respiration. Further, CO sensitizes cancer cells to doxorubicin treatment while preserving normal tissues, making it an ideal candidate for regulating toxicity to mitochondria. We propose that HO-1 and CO act on upstream mitochondrial pathways to modulate responses to chemotherapy based on the metabolic and genomic phenotype of the cells; activating repair/survival in normal cells and blocking repair/accelerating apoptosis in cancer cells.

A focus of our study is the role of HO-1-derived CO regulating mitochondrial biogenesis, influencing oxidative respiration and blockade of glycolysis-driven proliferation and survival of cancer cells in the presence of chemotherapeutics. We are currently working with HO-1 conditional knockout mice to specifically delete HO-1 expression in prostate epithelial cells as well as stroma cells (inflammatory cells) in TRAMP and PTEN/p53-fl/fl-Cre-probasin transgenic mice to test the role of HO-1 in cancer development and progression.

### Biliverdin reductase signaling during the inflammatory responses

We are studying the role of the bile pigments, which act specifically via BVR during inflammatory responses. We showed that BVR, acting as a receptor for BV, mediates its effects through Akt-IL-10 signaling to inhibit TLR4 expression (*Figure 2*). Our hypothesis is that BVR is a major signaling molecule that is activated upon conversion of BV to BR and has potent anti-inflammatory effects in the innate immune system. We have generated BVR-fl/fl conditional knockout mice and we are currently testing evaluating cell specific deletion of BVR in mice models of inflammatory disorders.



## Barbara Wegiel, PhD

Assistant Professor of Surgery

### Lab Members

Kellie Cunningham  
David Gallo

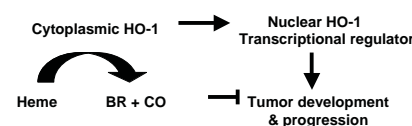


Figure 1

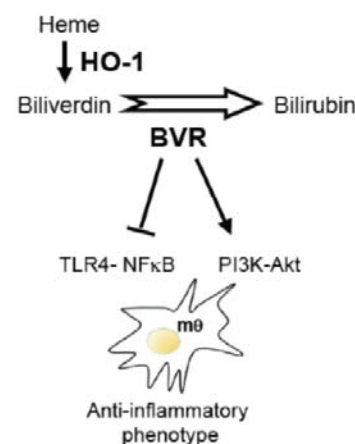


Figure 2

**Barbara Wegiel, PhD**

**Research Support**

“The role of heme oxygenase-1 derived- carbon monoxide in vascular injury and repair”

NCRP Scientist Development Grant, American Heart Association  
2009-2013

PI: Barbara Wegiel, PhD

“Department of Surgery start-up package”

Beth Israel Deaconess Medical Center  
2011-2014

PI: Barbara Wegiel, PhD

“Endogenous gas molecules as transcription factors”

EUREKA National Institutes of Health, R01 GM088666-01  
2009-2013

PI: Leo E. Otterbein, PhD

Co-Investigator: Barbara Wegiel, PhD

**Applications Submitted and Pending Review/Funding**

“The role of heme oxygenase-1 and heme degradation products in prostate cancer”

National Institutes of Health, 1R01CA160550-01A1  
2012-2017

PI: Barbara Wegiel, PhD

“Heme oxygenase-1 and the anti-tumor effects of Sildenafil”

National Institutes of Health, 1R01CA170330-01  
2012-2017

PI: Barbara Wegiel, PhD

“Heme degradation pathway and immunomodulation in prostate cancer”

National Institutes of Health, 1R21CA169904-01  
2012-2014

PI: Barbara Wegiel, PhD

“Carbon monoxide and Kras-driven lung cancer”

Department of Defense, LC110618  
2012

PI: Barbara Wegiel, PhD

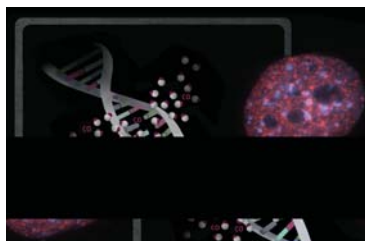
“Protective role of heme oxygenase-1 and biliverdin against vascular stenosis after heart transplantation”

AST Basic Research Grant  
2012-2014

**Accomplishments in the Past Year**

**Research Progress**

We showed that irradiation- or chemotherapeutics- induced HO-1, a homeostatic enzyme, generates carbon monoxide (CO) to accelerate DNA repair (*Figure 3*, image courtesy of Rita Csizmadia shows  $\gamma$ -H2AX staining indicating a DNA damage in red and nucleus in blue).



*Figure 3*



Briefly, naïve HO-1 knockout Hmox1<sup>-/-</sup> mice exhibit excessive tissue levels of  $\gamma$ -H2AX while administration of genotoxic stressors or irradiation in HO-1-deficient cells resulted in loss of ATM/ATR and Brca1 induction with dysfunctional  $\gamma$ -H2AX foci and marked elevations in DNA damage. HO-1 induction or exposure to CO induced homologous recombination (HR)-mediated DNA repair through ATM/ATR. In vivo, mice exposed to CO, followed by a genotoxin (adriamycin) or radiation-induced injury led to diminished tissue DNA damage and improved survival. In this study, we characterized a role for HO-1 and the gasotransmitter CO in orchestrating appropriate DNA repair, and provide a mechanism for their potent cytoprotective effects in various pathologies.

In continuation of our recent work with BV and BVR and stemming from our publication in JBC; 284(32):21369-78), we show that BV activates eNOS and NO production through a calcium/CAMKK-dependent mechanism in macrophages (PNAS 108(46):18849-54). S-nitrosylation of BVR in response to BV-driven NO production directs nuclear translocation of BVR and inhibition of TLR4 via direct effect on TLR4 promoter. This mechanism is a novel addition to the anti-inflammatory effects of the bile pigments and BVR.

To further dissect the role of BV/BVR, we have characterized our recently generated BVR-fl/fl conditional knockout. Our preliminary data suggest that myeloid-specific deletion of BVR (crossing of BVR-fl/fl to Cre-Lyz transgenic mice) results in a proinflammatory phenotype in alveolar and peritoneal macrophages. We are now exploring the role of the bile pigments and BVR specifically in immune cells as well as endothelial cells. Further, we continue to dissect the role of CO and HO-1 in bone marrow-derived endothelial progenitors and platelets following vascular injury proposed in my AHA funded project.

### Individual Accomplishments

- Promotion to the level of Assistant Professor in September 2011.
- Poster of Distinction: Wegiel B, Gallo D, Otterbein LE, 'Carbon monoxide accelerates vessel healing through enhanced reendothelialization acting through eNOS and P-selectin pathways.' American Transplant Society Annual Congress, 2011, April 30–May 4, Philadelphia.
- Ad hoc reviewer for the following journals: *European Urology*, *Molecular and Cellular Biochemistry*, *Respiratory Care*, *Current Chemical Biology*, *Molecular Oncology*, *Radiation Oncology*, *Neurological Research*.
- Accepted as a member of the American Heart Association.

### Invited Presentations

"Carbon monoxide is a host innate immune sensor against bacteria." Beth Israel Deaconess Medical Center, BIDMC GI Research Seminars. Boston, MA. October, 2011.



## Teaching, Training, and Education

### Graduate School and Graduate Medical Courses

I have been training research fellows, summer students and research assistants in the laboratory for the past 3 years. I am involved in teaching of experimental design, molecular and biochemical techniques, data acquisition and analyses as well as manuscript preparation.

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## Bibliography (January- December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Otterbein LE, Hedblom A, Harris C, Csizmadia E, Gallo D, **Wegiel B**. Heme oxygenase-1 and carbon monoxide modulate DNA repair through ataxia-telangiectasia mutated (ATM) protein. *Proc Natl Acad Sci U S A* 2011;108(35):14491-6.

**Wegiel B**, Gallo D, Csizmadia E, Roger T, Kaczmarek E, Harris C, Zuckerbraun BS, Otterbein LE. Biliverdin inhibits toll-like receptor-4 (TLR4) expression through nitric oxide-dependent nuclear translocation of biliverdin reductase. *Proc Natl Acad Sci U S A* 2011;108(46):18849-54.

### Non-Peer Reviewed Publications in Print or Other Media (Submitted or in Press)

#### Reviews, Chapters, Monographs, and Editorials

**Wegiel B**, Hanto DW, Otterbein L. The social networking of carbon monoxide in innate immunity. *Trends Immunol* 2011; in press.

### Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

**Wegiel B**, Bjartell A, Gallo D, Seth P, Sukhatme V, Persson JL, Otterbein LE. Heme oxygenase-1 derived carbon monoxide modulates mitochondria function to inhibit prostate cancer growth and progression. *Cold Spring Harbor Metabolism and Disease*, 2011, June 1-6th, NYC (poster)

**Wegiel B**, Gallo D, Otterbein LE, 'Carbon monoxide accelerates vessel healing through enhanced reendothelialization acting through eNOS and P-selectin pathways.' American Transplant Society Annual Congress, 2011, April 30-May 4th, Philadelphia (poster) and European Vascular Biology Congress, Krakow, Poland, September 21-24th 2011 (oral presentation)

## Division of Urology members

William DeWolf, MD

Jung Min Lee, BS  
Ignacio San Francisco, MD  
W. Mike Schopperle, PhD

Chief, Division of Urology  
Professor of Surgery, Harvard  
Medical School  
Research Assistant  
Research Fellow  
Instructor in Surgery

Simo Arredouani, PhD

Laura Dunn  
Haydn Kissick, PhD

Assistant Professor of Surgery  
Research Assistant  
Research Fellow

Solomon Berg, MD

Assistant Clinical Professor of  
Surgery (Emeritus)

Paul A. Church, MD

Assistant Clinical Professor of  
Surgery

William Connors, MD

Clinical Professor of Surgery

Anurag (Andy) Das, MD

Assistant Professor of Surgery

Nadeem Dhanani, MD

Instructor in Surgery

Gary Kearney, MD

Assistant Clinical Professor of  
Surgery

Michael Kearney, MD

Instructor in Surgery

Stephen Lazarou, MD

Clinical Instructor in Surgery

Abraham Morgentaler, MD

Associate Clinical Professor of  
Surgery

Wilmer Roberts, MD

Instructor in Surgery

Brian Saltzman, MD

Associate Clinical professor of  
Surgery

Ned Saltzman, MD

Clinical Instructor in Surgery

## Division of Urology

**Martin Sanda, MD**  
Donna Cote, LPN  
Catrina Crociani, MPH  
Laura Dunn, BA  
Brianna Kalmykow, MSN  
Dillon Le  
Jonathan Noel, MPH  
Greg Sanda  
Srikanth Vedachalam, BA

**Professor of Surgery**  
Administrative Assistant  
Clinical Trial Specialist  
Research Assistant  
Nurse Practitioner  
Research Student  
Clinical Coordinator  
Research Student  
Research Assistant

**Andrew Wagner, MD**  
  
Jodi Mechaber, NP  
Andrew Percy

**Assistant Professor of Surgery**  
Nurse Practitioner  
Research Assistant

## Research Focus

The research in my laboratory aims at improving the outcome of prostate cancer immunotherapy. My interests span a broad range of disciplines that share the ultimate goal of identifying novel tumor antigens and mechanisms of immune tolerance to prostate tumor antigens, and harnessing such antigens and mechanisms to break immune tolerance for immunotherapy of prostate cancer (PCa). A major strength of the research strategy we use is the availability of humanized mouse models that allow speedy testing of novel vaccine formulations in a way that emulates the human system.

We recently discovered a number of prostate tumor-associated antigens that represent promising targets for immunotherapy of PCa. To this end, we are currently optimizing strategies for inducing human HLA-restricted T-cell responses to the prostate tumor antigens (e.g. ERG, SIM2 and other antigens) identified by unbiased, genome-wide array and proteomic studies of clinical prostate tumor samples and derived, well characterized representative cell lines.

By a stepwise approach of screening epitope targets in 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 HHD/TRAMP/Pb-ERG triple hybrid transgenic mouse) 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-1 or androgen pathways, to overcome T-cell tolerance, is a rational avenue toward inducing effective, prostate cancer-specific immune responses. These studies are expected to lead to clinical trials of new strategies for prostate cancer immunotherapy.

A new line of research in the laboratory is devoted to the molecular profiling of dendritic cell (DC) and T lymphocyte subsets in the context of prostate cancer, with the goal of unraveling key molecules that drive immune tolerance to tumors.

Our data show that a major shift in T-cell differentiation is taking place in the lymphoid organs following malignant transformation of the prostate. This shift is accompanied by major dysregulations in both transcriptome and metabolome of T-cells, and suggests the possibility of exogenous manipulation for an optimal modulation of anti-tumor immunity. A better understanding of this shift at the molecular level might lead to the discovery of novel therapeutic agents to be included in vaccine formulations. Likewise, dendritic cell manipulation through their scavenger or toll-like receptors, using antagonist or agonist agents, seems to ameliorate the outcome of anti-tumor vaccines. Efforts at molecular dissection of DC biology in the context of prostate cancer are ongoing using the class A of scavenger receptors (MARCO and SRA-I/II) as a model system.

Finally, we are working in collaboration with PIs from the BIDMC/Surgery, Johns Hopkins, and the University of North Carolina to target the highly prostate cancer-specific antigens ERG and SIM2 using peptide-loaded nanoparticles that are specifically directed to dendritic cells to induce cytotoxic immune responses, and to evaluate synergy of concurrently enhancing the T-cell response component by overcoming PD1 and LAG3. This will be the first study to construct and use nanoparticle-targeted prostate cancer peptide vaccines in the preclinical setting and we anticipate this work will lead to a first-in-man trial of this strategy.



**Mohammed Simo Arredouani, PhD**

Assistant Professor of Surgery

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Lab Members  
Haydn Kissick, PhD  
Laura Dunn

## Research Support

“Targeting tim-1 to circumvent immune tolerance in prostate cancer”

Department of Defense, PC080363

06/01/2009-05/31/2012

PI: Mohammed Simo Arredouani, PhD

“Invariant NKT-cell ligands for prostate cancer vaccines”

Department of Defense, PC081107

06/01/2009-05/31/2012

PI: Steven P. Balk, MD, PhD

Co-I: Mohammed Simo Arredouani, PhD

“Nanoparticle-targeted peptide vaccines for prostate cancer: Harvard-Hopkins-Carolina Consortium”

Prostate Cancer Foundation

Project Period: 2011-2013

Principal Investigator: Martin Sanda, MD

BIDMC Site PI: Mohammed Simo Arredouani, PhD

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## Accomplishments in the Past Year

### Research Progress

In our efforts to identify novel targets for PCa immunotherapy, we have used human prostatectomy specimens and the branched DNA platform to validate differential gene expression and have identified several promising antigens that are being processed for immunogenicity. This is supplemented with the use of specific human cell lines and mass spectrometry to identify HLA-A2.1- and HLA-DR-restricted, immunogenic peptides.

Using various mouse models, we have performed gene expression profiling of T-cell and dendritic cell subsets in the context of prostate cancer. We have revealed important dysregulations in key pathways that drive cell activation and differentiation. T-cell differentiation is also investigated using in vitro systems to address gene expression and metabolic changes that drive T-cells to commit to specific lineages such as regulatory T-cells and Th17 cells. A better understanding of these changes will help identify drugs that could be used to manipulate immunity and improve vaccine outcome.

After we have demonstrated that castration enhances cytotoxic lymphocyte (CTL) responses to prostate tumor-associated antigens, we sought to determine the mechanisms driving this enhancement. Gene expression profiling of CD4 T-cells from prostate-draining lymph nodes of castrated mice showed a significant upregulation in IL-17 and IL-17R, among others. Increase of IL-17A and IL-17F was validated by RT-PCR. Treatment of immunized mice with IL-17 resulted in diminished CTL responses in WT mice and enhanced responses in a transgenic mouse of prostate cancer (TRAMP mouse). The enhancement seen in the TRAMP mice was accompanied by a drop in the number of regulatory T-cells. The mechanism leading to this interesting discrepancy is being addressed using a IL-17 KO mouse.

### Individual Accomplishments

- Invited to review grants for the Department of Defense, CDMRP PCRP.
- Invited to review research articles for several scientific journals.

- Invited to participate in the Qatar Foundation Arab Expatriate Scientists Forum, November 2011, Doha, Qatar.

### Invited Presentations

“Insights into the Mechanisms of Immune Tolerance to Prostate Tumor Antigens.” Dana Farber Cancer Institute, DF/HCC Cancer Immunology Seminar Series. Boston, MA. May 2011.

“Title: Novel Interventions for Prostate Cancer Immunotherapy.” PCF Young Investigator Forum. Lake Tahoe, NV. September 2011.

“Nanoparticle-Targeted Peptide Vaccines for Prostate Cancer: The Harvard – Hopkins – Carolina Consortium.” PCF Young Investigator Forum. Lake Tahoe, NV. September 2011.

### Teaching, Training, and Education

- In March-April of 2011, I was a tutor in the IMP course at Harvard Medical School. For this, I managed a tutorial for Immunology-Microbiology-Pathology for 1st year students.
- I also participated in the Explorations Program (4 middle school students) and Red Sox Scholar Program (10 middle school students).

### Bibliography (January – December 2011)

#### Peer-Reviewed Publications in Print or Other Media

##### Research Investigations

Lu B, Asara JM, Sanda MG, Arredouani MS. The role of the transcription factor SIM2 in prostate cancer. PLoS One 2011;6(12):e28837.

#### Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

Arredouani MS, Yue W, Dunn L, Putheti P, Strom TB, Sanda MG. Targeting Tim-1 to circumvent immune tolerance in prostate cancer. Department of Defense IMPACT Conference, 2011, Orlando, FL.

Arredouani MS, Yue W, Lu B, Dunn L, Finke J, Asara J, Sanda MG. Molecular profiling of T lymphocytes in prostate cancer. Multi-institutional Prostate Cancer Program Retreat, 2011, Ft-Lauderdale, FL.

**Mohammed Simo Arredouani, PhD**





## Research Focus

Our basic science research focuses on studying and characterizing unique and specific human cancer stem cell molecules with goals to further understand and define the molecular make-up of a 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, embryonal 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 a 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 podocalyxin in human cancer stem cells was the first report of podocalyxin in either human cancer or human stem cells. Since this discovery, numerous laboratories have discovered podocalyxin 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 podocalyxin 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 serum 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.

Our current studies on podocalyxin are now focused in two directions; the first direction is to determine the function of podocalyxin in human cancer stem cells by identifying other molecules in cancer stem cells that interact with podocalyxin. We have identified six true podocalyxin-interacting proteins including a glucose transporter – the molecules responsible for supplying 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 podocalyxin is more clinically oriented; we are exploring the expression of podocalyxin in human blood



**William C. DeWolf, MD**

Chief, Division of Urology

Professor of Surgery

### Lab Members

Ignacio San Francisco, MD

Jung Min Lee

**W. Mike Schopperle, PhD**

Instructor in Surgery

**William C. DeWolf, MD**

**W. Mike Schopperle, PhD**

samples from patients with prostate and other cancers to determine the potential of using podocalyxin as a serum cancer marker.

### **Clinical Research**

Clinical research is quite active and deals with diagnostic urologic oncology, sexual rehabilitation and qualitative analysis of urologic teaching. Our most active clinical research project is directed at the characterization of active surveillance as a management option for treatment of prostate cancer. Currently we have over 150 patients collected over 10 years and followed a strict active surveillance protocol refereed by a 20 core saturation biopsy technique performed every 12 - 18 months. We are currently gathering statistical data as to predictive indices characterizing these patients that progress vs those that do not progress. For example, those patients with a PSA density less than 0.085 seem to do well with a progression rate of only 20% over 8 years.

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### **Research Support**

#### **Intramural Funding**

Urology Division, Beth Israel Deaconess Medical Center

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### **Accomplishments in the Past Year**

#### **Research Progress**

##### **Basic Science**

In our research studies we have confirmed that the stem cell/cancer cell adhesion protein podocalyxin forms a specific complex with the glucose 3-transporter in human cancer stem cells and have published a research paper entitled: "The Human Cancer/Stem Cell Marker Podocalyxin Interacts with the Glut-3 transporter in malignant pluripotent stem cells." Also, we have discovered a novel temperature dependent mechanism which regulates the differentiation of human cancer stem cells and are further studying this new regulation system. Finally we are investigating the use of podocalyxin as a specific marker for metastatic cancer cells.

##### **Clinical**

Our results regarding active surveillance were presented at the New England AUA Meeting. For this work the study population consisted of 111 consecutive patients who were prospectively enrolled with low risk prostate cancer with intent to cure from January 2003 to January 2009 by one urologist (WCD). All patients were followed with 20-core saturation biopsy technique. The inclusion criteria were clinically localized cancer (T1c-T2), less than 3 positive cores, Gleason score 6 or less, and no more than 50% of core involved. The criteria for progression, and therefore treatment were: > 3 positive cores, increase in grade (Gleason score >7) and > than 50% of any core involved with cancer. Patients were monitored with an office visit every 6 months and restaging 20-core saturation biopsy every 12-18 months. Definitive treatments as RRP or Radiotherapy were performed in patients who progressed.

From the 111 patients who fit the entering criteria, 3 withdrew the protocol before an endpoint was reached. Therefore 108 patients were analyzed in the final cohort. The mean age of the study group at the time of the first biopsy was 62 years. The median time of follow-up was 25 months. The median number of total biopsies was 2 (range, 1-5). Ninety five patients had at least one saturation re-biopsy. The progression rate was 26% (28/108). Fifty one patients (54%) had a negative first re-biopsy. Of the patients who progressed 54% did so due to an increased number of positive cores. Univariate analyses revealed PSA density, using cut point the median value 0.08 ng/ml/cc ( $p=0.0048$ ), PSA velocity ( $p=0.01$ ) and family history of prostate cancer ( $p=0.01$ ) were predictors of progression. PIN and atypia were non predictors of progression. Most of the patients who progressed did so at second biopsy (17 patients). The median time to progression was 24 months. Of the patients who progressed 11 underwent RRP. Of those 10 patients (91%) had organ confined, low volume disease with negative margins, 4 had Gleason 3+4 and one patient had a T3b disease. Interestingly, 2 of 4 (50%) patients, who had Gleason 7 as criteria of progression on needle biopsies, had Gleason 6 on the final RP specimens.

In our study PSA density, PSA velocity and family history of prostate cancer are predictors of progression in univariate analysis. Most of the first re-biopsies (54%) had no cancer. In the group of patients with negative first re-biopsy there was still subsequent progression revealing a 30 months lead time bias as noted by Kaplan Meier curves. Of the patients who progressed and underwent RP, 91% had a final pathology with organ-confined and low volume disease. In our setting AS with delayed intervention appears to be a safe and viable option in selected men with low risk prostate cancer.

### Individual Accomplishments

William DeWolf, MD

- AUA Program Co-Chair for Basic Research: Prostate Cancer
- Member of Medical Advisory Board, Boston Prostate Cancer Walk
- Co-investigator, NIH CA 011391
- Editorial Board: *Harvard Men's Health Watch*
- Editorial Board: *Harvard Perspectives in Prostatic Disease*
- Member ad hoc Search Committee for Chief of Urology, Boston Children's Hospital
- Member ad hoc Search Committee for Chief of Urology Massachusetts General Hospital
- Member ad hoc Professors Committee for promotion of Dr. Gary Curhan to Professor of Medicine

### Teaching, Training, and Education

#### Undergraduate and Medical School Courses

William DeWolf, MD

Undergraduate Research Opportunities Program: This is an MIT-based

William C. DeWolf, MD

W. Mike Schopperle, PhD

**William C. DeWolf, MD**

**W. Mike Schopperle, PhD**

teaching program in which 3-5 undergraduates rotate through our laboratory on 6-12 month basis working on 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.

### **CME Courses**

CME Course - Men's Health: Opening A New Frontier; course directors William DeWolf and Abraham Morgentaler, Saturday/Sunday, April 9-10, 2011

### **Other Teaching Contributions**

Urologic Oncology Fellowship: Dr. Ignacio San Francisco (Santiago, Chile) finished a 15 month fellowship with us completing work on our prostate cancer active surveillance program and other clinical projects.

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## **Bibliography (January – December 2011)**

### **Peer-Reviewed Publications in Print or Other Media**

#### **Research Investigations**

Bhatt RS, Werner L, Regan MM, Yannucci J, Wang HY, Rosen S, Genega E, Morrissey ME, Duggan S, Vazquez C, Sanda MG, **DeWolf W**, Balk S, Yuan X, Bubley GJ. Possible risk factors associated with relapse in patients treated with neoadjuvant chemohormonal therapy for high risk prostate cancer. *Open Prostate CA J* 2011; 4:1-8.

Chang P, Szymanski K, Dunn R, Chipman J, Litwin M, Nguyen P, Sweeney C, Cook R, Wagner A, **Dewolf WC**, Bubley G, Funches R, Aranowitz J, Wei J, Sanda M. Expanded prostate cancer index composite for clinical practice (EPIC-CP): development and validation of a practical health related quality of life instrument for use in routine clinical care of prostate cancer patients. *J Urol* 2011;186:865-72.

San Francisco I, Werner I, Regan M, Garnick M, Bubley G, **DeWolf WC**. Risk stratification and validation of PSA density as an independent predictor of progression in men with low risk prostate cancer treated with active surveillance. *J Urol* 2011; 185:471-6.

## Research Focus

The principal areas of research in the Sanda laboratory include 1) discovering and validating prostate cancer antigens or other biomarkers to improve prostate cancer detection and 2) evaluating prostate cancer antigens as targets for immunotherapy and biomarkers for cancer screening and severity assessment.

Efforts to develop new biomarker targets for prostate cancer detection have been centered in the ongoing leadership by the Sanda Lab of the Harvard-Michigan-Cornell Prostate Biomarker Clinical Center, and NIH U01 that Dr. Sanda has led as PI since 2005. Among various accomplishments of the Biomarker Clinical Center over the past year was co-leadership and completion of a national trial of PCA3 as a urine test to identify men at risk of prostate cancer.

The Sanda Lab's research toward developing new prostate cancer vaccines was expanded in 2011 by establishment of a program to develop peptide vaccine for prostate cancer delivered by nanoparticles, funded through a prestigious, \$1 million Challenge Grant from the Prostate Cancer Foundation (Sanda, PI). The BIDMC vaccine project includes collaborators at University of North Carolina (J. Desimone) and Johns Hopkins (C. Drake) and was the top-ranked proposal from among scores of projects submitted to the PCF Challenge Grant peer-review process.

A notable milestone in the Sanda Lab in 2011 was establishment of an independent research effort by Dr. M. Simo Arredouani, who was promoted to Assistant Professor and continued to build his independent research program in prostate cancer immunotherapy after transitioning from his earlier role as Instructor in the Sanda Lab.

## 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. Initially findings from the cohort had been described in a publication in the *New England Journal of Medicine* in 2008, and new findings to enable individualized prediction of sexual outcome after prostate cancer treatment were published in *JAMA* in 2011.

Dr. Sanda also leads a national study funded by NIH to compare effectiveness of robot-assisted laparoscopic and open prostatectomy. The study is on track to complete accrual of 600 patients in mid 2012, and is the largest prospective study evaluating outcomes of robot-assisted surgery nationwide.



**Martin Sanda, MD**

Professor of Surgery (Urology)

### Lab Members

Laura Dunn  
Srikanth Vedachalam  
Jonathan Noel, MPH  
Catrina Crociani, MPH  
Brianna Kalmykow, MSN  
Donna Cote, LPN  
Greg Sanda  
Dillon Le

## Research Support

“Harvard/Michigan prostate cancer biomarker clinical center”

National Institutes of Health, U01 CA011391-01

Project Period: 2010-2012

Principle Investigator: Martin Sanda, MD

“Nanoparticle Prostate Cancer Vaccines: Harvard-Hopkins-Carolina Consortium”

Prostate Cancer Foundation

Project Period: 2011-2013

Principal Investigator: Martin Sanda, MD

BIDMC Site PI: M. Simo Arredouani, PhD

“Effectiveness of Robotic Compared to Standard Prostatectomy for Prostate Ca”

National Institutes of Health, 1RC1EB011001-01

Project Period: 2009-2012 (No cost extension in 2012)

Principle Investigator: Martin Sanda, MD

“Effectiveness of Early Stage Prostate Cancer Treatment”

National Institutes of Health, 1RC1CA146596-01

Project Period: 2009-2012 (No cost extension in 2012)

MPI: Martin Sanda, MD, P. Carroll, UCSF

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## Accomplishments in the Past Year

### Research Accomplishments

In the past year the Prostate Cancer Program at BIDMC has made major advances to improve prostate cancer care and develop new treatments, including:

- We reported in *JAMA*, a revolutionary approach to individualized prediction of prostate cancer treatment outcomes that was featured nationwide on WABC-TV, and the *New York Times*. The findings expanded on a large study the group had previously reported in the *New England Journal of Medicine*.
- The Prostate Cancer Foundation awarded the Sanda and Arredouani Labs a Challenge Award to BIDMC for studies to develop new vaccine therapy for prostate cancer.
- We are leading the largest study nationwide to compare effectiveness of robotic and traditional open prostate cancer surgery, that was initiated in 2011, and that has already enrolled over 500 patients across 9 leading cancer centers, including the vast majority of patients undergoing prostatectomy at BIDMC.
- In collaboration with the NCI-EDRN network, we are developing new urine tests to detect prostate cancer, and co-led an NCI trial that showed the PCA3 urine test outperformed the PSA blood test in detecting prostate cancer.
- Together with William Dewolf, MD, Chief of Urology, we are assembling the largest group of patients in the Northeast whose prostate cancer is being managed without surgery or radiation, and are developing genomic analysis techniques to discern which prostate cancers can be safely left untreated from those cancers requiring immediate treatment, providing hundreds of men the opportunity to avoid treatment side effects.



## Honors and Awards

- I was promoted to Professor of Surgery in Urology at Harvard Medical School, effective October 1, 2011.
- I was named to the registry of Best Doctors in Massachusetts, 2011-2012, representing 8 consecutive years in the Best Doctors registry.

## Invited Presentations – National

“Comparison of open, robotic, and laparoscopic prostatectomy.” International Prostate Cancer Symposium, New York, NY.

“Measuring side effects with validated QOL instruments: meaningful use at the point of care.” Prostate Cancer: Predictive Models. European School of Oncology & Memorial Sloan-Kettering Cancer Center, New York, New York.

“QOL: implications after diagnosis - the unmeasurable variable.” Oncology Congress, San Francisco, CA.

“Comparative effectiveness research in prostate cancer: role of observational studies.” Plenary Session, Society of Urological Oncology Annual Meeting, Bethesda, MD.

## Invited Presentations – International

“Predicting individualized outcomes of early stage prostate cancer.” Chilean Society of Urology, Santiago, Chile.

“Quality of life and satisfaction with therapy amongst prostate cancer survivors.” Societe International d’Urologie Annual Meeting Plenary Session, Berlin, Germany.

“Predicting quality of life effects of prostate cancer treatment.” Plenary Session, Annual Norwegian Oncology Conference, Oslo, Norway

“New molecular targets for prostate cancer early detection.” Genitourinary Section Meeting,

Annual Norwegian Oncology Conference, Oslo, Norway

## Teaching, Training, and Education

- Mentored Peter Chang, Urology Chief Resident, in a research project that led to his receiving the New England AUA Annual Resident Research Prize (EPIC for measuring patient-reported HRQOL at the point of care in clinical practice). The work led to a subsequent AUA Scholar Award to Dr. Chang (to support a scholarly fellowship in Urology Research from 2012-2014)
- Participated as examiner of HMS III Surgery Clerkship.
- Participated as a preceptor in the Physical Exam courses – Male GU Exam for HMS I and HMS II medical students.
- Participated as educator in the BIDMC Urology clerkship at HMS.

**Martin Sanda, MD**



## Bibliography (January–December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Alemozaffar M, Regan MM, Cooperberg MR, Wei JT, Michalski JM, Sandler HM, Hembroff L, Sadetsky N, Saigal CS, Litwin MS, Klein E, Kibel AS, Hamstra DA, Pisters LL, Kuban DA, Kaplan ID, Wood DP, Ciezki J, Dunn RL, Carroll PR, **Sanda MG**. Prediction of erectile function following treatment for prostate cancer. *JAMA* 2011; 306(11):1205-14.

Bhatt RS, Werner L, Regan MM, Yannucci J, Wang HY, Rosen S, Genega E, Morrissey ME, Duggan S, Vazquez C, **Sanda MG**, DeWolf W, Balk S, Yuan X, Bubley GJ. Possible risk factors associated with relapse in patients treated with neoadjuvant chemohormonal therapy for high risk prostate cancer. *Open Prostate CA J* 2011; 4:1-8.

Catalona WJ, Partin AW, **Sanda MG**, Wei JT, Klee GG, Bangma CH, Slawin KM, Marks LS, Loeb S, Broyles DL, Shin SS, Cruz AB, Chan DW, Sokoll LJ, Roberts WL, van Schaik RHN, Mizrahi IA. A multi-center study of [-2] pro-prostate-specific antigen (PSA) in combination with PSA and free PSA for prostate cancer detection in the 2.0 to 10.0 ng/mL PSA range. *J Urology* 2011;185(5):1650-5.

Chang P, Szymanski KM, Dunn RL, Chipman JJ, Litwin MS, Nguyen PL, Sweeney CJ, Cook R, Wagner AA, DeWolf WS, Bubley GJ, Funches R, Aronovitz JA, Wei JT,\* **Sanda MG**.\* Expanded prostate cancer index composite for clinical practice (EPIC-CP): development and validation of a practical health-related quality of life instrument for use in the routine clinical care of prostate cancer patients. *J Urology* 2011;186(3):865-72.

Kamo N, Dandapani SV, Miksad RA, Houlihan MJ, Kaplan I, Regan M, Greenfield TK, **Sanda MG**. Evaluation of the SCA instrument for measuring patient satisfaction with cancer care administered via paper or via the Internet. *Ann Oncol* 2011; 22(3):723-9.

Kasperzyk JL, Shapple WV 3rd, Kenfield SA, Mucci LA, Kurth T, Ma J, Stampfer MJ, **Sanda MG**. Watchful waiting and quality of life among prostate cancer survivors in the Physicians' Health Study. *J Urol* 2011;186(5):1862-7.

Kazer MW, Harden J, Burke M, **Sanda MG**, Hardy J, Bailey DE; PROSTQA Study Group. The experiences of unpartnered men with prostate cancer: a qualitative analysis. *J Cancer Surviv* 2011;5(2):132-41.

Lu B, Asara JM, **Sanda MG**, Arredouani MS. The role of the transcription factor SIM2 in prostate cancer. *PLoS One* 2011;6(12):e28837.

Tomlins SA, Aubin SM, Siddiqui J, Lonigro RJ, Sefton-Miller L, Miick S, Williamsen S, Hodge P, Meinke J, Blase A, Penabella Y, Day JR, Varambally R, Han B, Wood D, Wang L, **Sanda MG**, Rubin MA, Rhodes DR, Hollenbeck B, Sakamoto K, Silberstein JL, Fradet Y, Amberson JB, Meyers S, Palanisamy N, Rittenhouse H, Wei JT, Groskopf J, Chinnaiyan AM. Urine TMPRSS2:ERG fusion transcript stratifies prostate cancer risk in men with elevated serum PSA. *Science Transl Med* 2011; 3(94):94ra72.

## Research Investigations (Submitted or in Press)

Ankerst DP, Koniarski T, Liang Y, Leach RJ, Feng Z, **Sanda MG**, Partin AW, Chan DW, Kagan J, Sokoll L, Wei JT, Thompson IM. Updating risk prediction tools: a case study in prostate cancer. *Biom J* 2011; in press.

Hayn MH, Orom H, Shavers VL, **Sanda MG**, Glasgow M, Mohler JL, Underwood W. Racial/ethnic differences in receipt of pelvic lymph node dissection among men with localized/regional prostate cancer. *Cancer* 2011; in press.

Salami SS, Schmidt F, Laxman B, Regan MM, Rickman DS, Scherr D, Bueti G, Siddiqui J, Tomlins SA, Wei JT, Chinnaiyan AM,\* Rubin MA,\* **Sanda MG.\*** Combining urinary detection of TMPRSS2:ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer. *Urol Oncol* 2011; in press.

Williams SB, Salami S, Regan MM, Ankerst DP, Wei JT, Rubin MA, Thompson IM, **Sanda MG**. Selective detection of histologically-aggressive prostate cancer: an Early Detection Research Network (EDRN) prediction model to reduce unnecessary prostate biopsies with validation in the Prostate Cancer Prevention Trial (PCPT). *Cancer* 2011; in press

## Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media

## Reviews, Chapters, Monographs, and Editorials

Alemozaffar M, **Sanda MG**. Quality of life after treatment for early stage prostate cancer. In: Vogelzang NJ, Scardino PT, Zelefsky MJ, Linehan WM, editors. *Comprehensive textbook of genitourinary oncology*. Lippincott Williams & Wilkins. 2011.

## Reviews, Chapters, Monographs, and Editorials (Submitted or in Press)

Chang P, Alemozaffar A, and **Sanda MG**. Clinical implications of measuring quality-of-life in early stage prostate cancer. In: Klein E, editor. *Management of prostate cancer*, 3rd edition. 2011; in press.

Wagner AA, **Sanda MG**. Retropubic and robotic-assisted radical prostatectomy. In: Fischer JE, Jones DB, Pomposelli FB, editors. *Fischer's mastery of surgery*, 6th ed. Lippincott Williams & Wilkins 2011; in press.

## Professional Educational Materials or Reports, in Print or Other Media

## Educational Video

Eleni Efstathiou E, Smith MR, Sartor AO, Drake CG, Rathkopf D, DePinho R, Efstathiou JA, **Sanda MG**, Feldman AS, Chabner BA. Prostate Cancer – Progress and Promise, Part I. *The Oncologist*, 2011.

Martin Sanda, MD



## Research Focus

Our research interests focus on robotic surgical simulation and on clinical outcomes of patients with kidney and prostate cancer.

With regard to kidney cancer outcomes projects, we recently received seed funding to develop a multi-center project to prospectively evaluate patients following kidney surgery. In particular we are interested in short-term recovery issues after both open and robotic kidney surgery. We have over 400 patients in our clinical database and the last 150 have been evaluated prospectively using validated quality of life instruments. Pilot data from this work was recently presented at the American Urologic Association (AUA) annual meeting in Washington D.C. and has been submitted for publication.

Our team has a high volume of advanced kidney cancer surgical cases and we are interested in recovery trends, particularly in the group needing cytoreductive nephrectomy. By prospectively evaluating their health related quality of life we found most patients after cytoreductive nephrectomy recovered to near baseline HRQOL by 4 weeks postoperative. The HRQOL was measured using 2 validated questionnaires which were found to be sensitive to changes after surgery as displayed in *Figure 1*. This work will be presented by our team at the European Urologic Association annual meeting in Paris, February 2012.

We are also interested in investigating cost-effectiveness of various approaches to kidney surgery (*Figure 2*). We recently evaluated the costs of open, laparoscopic and robotic partial nephrectomy at BIDMC. Our results demonstrated similar variable costs for all 3 approaches but increased fixed costs related to robotic equipment. The overall costs could be mitigated by improvements in surgical volume, time, and disposables. This work was also recently presented at the New England section of the AUA in Orlando, October 2011 and has been submitted for publication.

With regard to robotic simulation, our team has developed a completely new method of simulating a robotic prostatectomy using inanimate porcine tissue (*Figure 3*). Our high-fidelity tissue based simulator is reproducible and allows urology residents, fellows, and attending surgeons alike to practice robotic surgery in a safe environment prior to operating on patients. A video of our simulator recently won first prize at the World Congress of Endo-Urology held in Chicago in October, 2010. We are currently validating this simulator in a prospective fashion by comparing performance among novice, intermediate and expert robotic surgeons.

## Research Support

“Evaluating comparative effectiveness of open and minimally invasive kidney surgery: patient-reported quality of life outcomes and cost effectiveness”

Kidney Cancer Association Developmental award

2011

PI: Andrew A. Wagner, MD



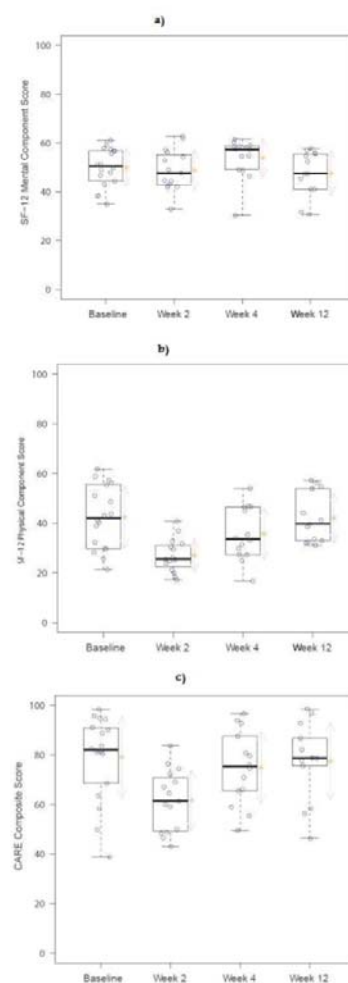
**Andrew A. Wagner, MD**

Assistant Professor of Surgery

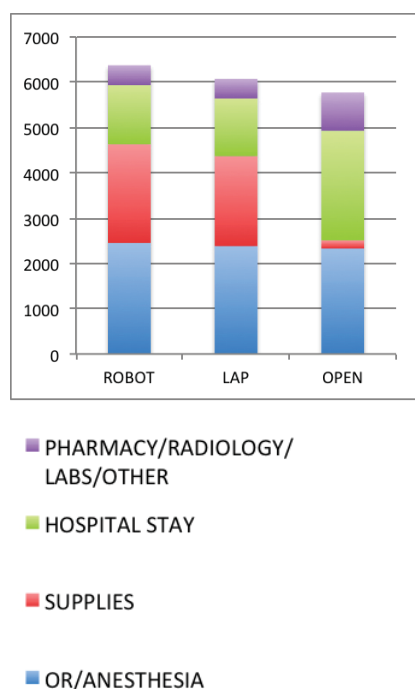
### Group Members

Andrew Percy

Jodi Mechaber, NP



*Figure 1*



*Figure 2: Comparing Costs of Robotic, Laparoscopic, and Open Partial Nephrectomy. Overall variable costs were similar for RPN, LPN, and OPN. OR supplies contributed greater cost for RPN and LPN than OPN ( $p < 0.0001$ ), while inpatient stay costs were higher for OPN compared to LPN and RPN ( $p < 0.0001$ ). Sensitivity analysis of variable costs demonstrates that RPN and LPN can represent less costly alternatives to OPN if hospital stay for RPN and LPN is  $< 2$  days and OR time  $< 204$  and  $196$  minutes, respectively. Inclusion of fixed costs always made OPN less costly than LPN or RPN.*

## Accomplishments in the Past Year

### Research Progress

Our group succeeded on a number of fronts in the last year. We were able to analyze our pilot data of prospective evaluation of patient-reported quality of life after kidney surgery on the first 71 patients and submit this for publication. Additionally we have now evaluated HRQOL and clinical outcomes in 42 patients after cytoreductive nephrectomy which will be presented at the EUA in Paris in 2012. We have also set up and transferred our data to a RedCap-based system which is web-based and allows for improvements in collaboration between institutions. Using this system we are able to follow clinical outcomes and prospectively assess HRQOL through web-based surveys

We have completed a comparison of hospital costs associated with partial nephrectomy, the first such analysis, which has been submitted for publication. We continued our validation of the robotic prostatectomy simulator and have neared completion of that study, recruiting 18 subjects to take part in a vigorous evaluation and validation testing.

### Administrative Accomplishments

- **2006-present:** Director of Minimally Invasive Urologic Surgery, BIDMC Div. of Urology

Design/manage GU robotic credentialing, train/educate staff, advise hospital robotic purchasing

- **2006-present:** Co-Director: Multidisciplinary Renal Tumor Clinic, BIDMC Dept of Oncology

Design clinic workflow, oversee website.

- **2009-present:** Director, Endourology Fellowship, BIDMC Div of Urology.

Design clinical and research activities for fellow in urology

- **2009:** Prostate Cancer Executive Committee, BIDMC.

Develop clinical program, advertising, equipments needs, research priorities

- **2011:** Leader, Robotic Faculty Hour, BIDMC.

Develop and implement efficiency models for robotic surgery at BIDMC

### Individual Accomplishments

Moderator: Scientific Session: Kidney Laparoscopy, New England Section of American Urologic Session Annual Meeting, Orlando, FL.

### Invited Presentations

“Minimally Invasive Kidney Surgery.” Beth Israel Deaconess Medical Center, Harvard combined Urology Resident Grand Rounds. Boston, MA. February 2011.

“GU Oncology.” Beth Israel Deaconess Medical Center, HMS Urology Interest Day. Boston, MA. March 2011.

“Robotic Surgery in Urology.” Beth Israel Deaconess Medical Center, IDEAS conference. Boston, MA. April 2011.

“Kidney Cancer Surgery: The Next Step.” Roswell Park Cancer Institute, Surgical Grand Rounds. Buffalo, NY. July, 2011.

“Workup Of Localized Kidney Cancer.” Kidney Cancer Association Annual Meeting. Chicago, IL. October 2011.

## Teaching, Training, and Education

### Other Teaching Contributions

“Focused Therapies For Renal Cell Carcinoma.” DFHCC Kidney cancer survivor conference. Boston, MA. June, 2011.

“Robotic Prostatectomy.” Innovation in Prostate Cancer Care Patient Conference. Boston, MA. November 2011.

“Is Radical Prostatectomy Still the Gold Standard?” MA Prostate Cancer Association Annual Symposium. June 2011.

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Chang P, Szymanski KM, Dunn RL, Chipman JJ, Litwin MS, Nguyen PL, Sweeney CJ, Cook R, **Wagner AA**, Dewolf WC, Bubley GJ, Funches R, Aronovitz JA, Wei JT, Sanda MG. Expanded prostate cancer index composite for clinical practice: development and validation of a practical health related quality of life instrument for use in the routine clinical care of patients with prostate cancer. *J Urol* 2011;186: 865-72.

Hyams ES, Pierorazio P, Proteek O, Sukumar S, **Wagner AA**, Mechaber JL, Rogers C, Kavoussi L, Allaf M. Iatrogenic vascular lesions after minimally invasive partial nephrectomy: a multi-institutional study of clinical and renal functional outcomes. *Urology* 2011;78: 820-6.

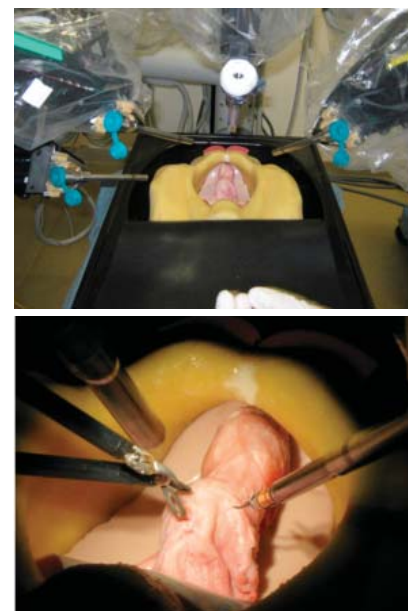
San Francisco IF, Sweeney MC, **Wagner AA**. Robot-assisted partial nephrectomy: early unclamping technique. *J Endourol* 2011;25:305-8.

#### Research Investigations (Submitted or in Press)

Pedrosa I, Rafatzand K, Robson P, **Wagner AA**, Atkins MB, Rofsky NM, Alsop DC. Arterial spin labeling MR imaging for characterization of renal masses in patients with impaired renal function: initial experience. *Eur Radiol* 2011; in press.

Williams SB, Kacker R, Alemozaffar M, Fancisco IS, Mechaber J, **Wagner AA**. Robotic partial nephrectomy versus laparoscopic partial nephrectomy: a single laparoscopic trained surgeon's experience in the development of a robotic partial nephrectomy program. *World J Urol* 2011; in press.

### Andrew A. Wagner, MD



*Figure 3. Robotic prostatectomy simulator using porcine tissue.*

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

Reviews, Chapters, Monographs, and Editorials

Chang P, **Wagner AA**. Commentando citacoes classicas, in Einstein: Educ Contin Saude 2011;9:64-70.

**Wagner AA**, Sanda MG. Retropubic and robotic-assisted radical prostatectomy. In: Fischer JE, Jones DB, Pomposelli FB, editors. Fischer's mastery of surgery, 6th ed. Lippincott Williams & Wilkins 2011; in press.

**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Alemozaffar M, Chang SL, Sun M, Kacker R, **Wagner AA**. Cost comparison of open, laparoscopic, and robot-assisted partial nephrectomy. NEAUA meeting, Orlando 2011.

Kim SB, Cheng SC, Mongiu AK, Sanda MG, **Wagner AA**. Internet based evaluation of quality of life outcomes after robotic, laparoscopic, and open radical or partial nephrectomy. AUA meeting, Washington DC, 2011



## Division of Vascular and Endovascular Surgery members

Marc Schermerhorn, MD	Chief, Division of Vascular and Endovascular Surgery; Associate Professor of Surgery
Rodney Bensley, MD	Research Fellow
Jeremy Darling	Clinical Research Assistant
Carla Joseph	Administrative Associate
Ruby C. Lo, MD	Research Fellow
David Campbell, MD	Vascular Surgeon
Elliot L. Chaikof, MD, PhD	Johnson and Johnson Professor of Surgery; Chairman, Department of Surgery; Surgeon-in-Chief
Julianty Angsana	Student, PhD candidate, Georgia Tech
Perla Ayala, PhD	Research Fellow
Jeffrey M. Caves, PhD	Instructor in Surgery
Erbin Dai, MD	Instructor in Surgery
John Dingus	Undergraduate Student, Harvard
Carolyn A. Haller, PhD	Instructor in Surgery
Wookhyun Kim, PhD	Instructor in Surgery
Venkata R. Krishnamurthy, PhD	Instructor in Surgery
Vivek Kumar, PhD	Research Fellow
Liyang Liu, MD	Research Associate
Nisarga Naik, PhD	Research Fellow
Zheng Qu	Student, PhD candidate, Georgia Tech
Mohammed Sardar, PhD	Research Fellow
Christiane Ferran, MD, PhD	Professor of Surgery
Jean Choi	Research Assistant
Eva Czismadia	Senior Research Associate
A. Katie Daniels	Part time Research Assistant
Cleide Da Silva, PhD	Instructor of Surgery
Andy Lee, MD	Surgical Resident, T32 Research Fellow
Herwig Moll, PhD	Research Fellow
Alon Neidich	Medical Student
Ashley Rogers, MD	Research Assistant
Allen D. Hamdan, MD	Associate Professor of Surgery; Vice-Chairman for Communications
Elzbieta Kaczmarek, PhD	Assistant Professor of Surgery
Douglas Clarke, PhD	Research Fellow

## Division of Vascular and Endovascular Surgery

<b>Frank W. LoGerfo, MD</b>	<b>William McDermott Professor of Surgery; Gener Augustin Visiting Research Fellow</b>
Maggie Chun	Research Assistant
Mauricio A. Contreras, MD	Instructor in Surgery
Julia Glaser	Research Fellow
Allisandra Mowles	Undergraduate Student
Priya Patel	Premedical Student
Leena Pradhan-Nabzdyk, PhD	Instructor in Surgery
Wande Pratt, MD, MPH	Research Fellow
Natasha Resendes	Research Assistant
Ravi Vissapragada, MD	Research Fellow

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<b>Mark C. Wyers, MD</b>	<b>Assistant Professor of Surgery</b>
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## Research Focus

Our laboratory is focused on the development of biologically-inspired materials, devices, and pharmacotherapeutics based upon the principles of molecular engineering and nanofabrication technologies. Ongoing research is directed at the following:

### 1. Tissue Engineering and Regenerative Medicine

*Engineering blood vessels:* After decades of research, small to medium (4–7 mm) diameter prosthetic vascular grafts continue to occlude due to peri-anastomotic intimal hyperplasia, surface thrombogenicity, and a failure to develop an endothelialized lumen. A bio-inspired design, motivated by the molecular structure, supramolecular organization, and micro-structural architecture of natural collagen and elastin fiber networks establishes an important paradigm for the artery replacements of the future. Our research addresses this challenge on multiple levels: (1) We are working to determine the molecular features of collagen and elastin fiber analogues that influence the mechanical behavior and physiochemical properties of protein-based fiber networks. Elastin and collagen analogues are produced by biosynthetic and chemical schemes and processed into fiber networks by a range of micro-fabrication techniques. We employ both solution and solid-state methodologies to define essential material structure-property relationships of these materials. (2) We seek to identify the micro-scale characteristics of protein fiber reinforced biopolymer composites that dictate mechanical responses relevant to the design of an arterial substitute. This encompasses the study of the mechanical behavior of both single and multicomponent fiber network composites by static and dynamic mechanical testing under physiologically relevant conditions. (3) We are defining the morphological and structural remodeling of collagen and elastin fiber reinforced vascular constructs in vivo.

Acellular constructs, as well as conduits seeded with living cells, are subject to investigation in relevant animal models. Specifically, we are interested in the effect of the local biological and mechanical environment on short- and long-term conduit properties, including patency and biostability.

*Materials for soft tissue repair:* Although abdominal wall repairs are the most common class of operations performed by general surgeons in the US, results remain far from ideal due to chronic inflammation, poor integration of implanted biomaterials, and infection. In preliminary studies, we have developed biomaterials to serve as artificial fascia for the repair of abdominal wall hernias. These materials are generated from purified proteins and do not contain residual antigenic and inflammatory factors found in donor animal and cadaver tissue products.

Currently, we are investigating the addition of various bioactive constituents, as well as the application of fabrication techniques to enhance our control over the patch microstructure. Our objectives are optimal integration with host tissue, rapid development of neovasculature, cellularity within and around the patch, and durability in the presence of bacterial infection.

*Cell transplantation:* A major obstacle in islet transplantation is the high rate of primary nonfunction and early islet destruction, which has been observed after intraportal islet infusion, both in animal models and in clinical trials. Substantial evidence now suggests that an acute blood mediated inflammatory injury is largely responsible for the observed functional stunning or destruction of islets and may well amplify subsequent immune reactions.



### Elliot L. Chaikof, MD, PhD

Johnson and Johnson  
Professor of Surgery

Chair, Department of Surgery  
Surgeon-in-Chief

#### Lab Members

Jeffrey M. Caves, PhD  
Erbin Dai, MD  
Carolyn A. Haller, PhD  
Wookhyun Kim, PhD  
Venkata R. Krishnamurthy, PhD  
Liyang Liu, MD  
Perla Ayala, PhD  
Vivek Kumar, PhD  
Nisarga Naik, PhD  
Mohammed Sardar, PhD  
Julianty Angsana  
Zheng Qu  
John Dingus

We postulate that molecularly engineered systems, including conformal barriers, anti-thrombotic fusion proteins, and heparan sulfate glycomimetics that limit inflammatory and pro-coagulant responses at the graft-host interface will reduce early islet destruction and, thereby, enhance islet engraftment. In dampening the early innate inflammatory response, a concomitant improvement in long-term islet survival may be attained by modulating the evolution of an adaptive immune response.

## 2. Vascular Biology

*Targeted therapies to promote vascular wall healing:* The treatment of lower extremity vascular disease through the use of balloon or laser angioplasty, stenting, or atherectomy remains limited by a significant incidence of restenosis. Thus, new approaches that target thrombotic and inflammatory events, which contribute to restenosis and delayed vessel wall healing are required. We postulate that thrombin and purinergic dependant pathways can be inhibited by antibody mediated targeting of thrombomodulin, CD39, and CD73 to the site of vessel wall injury.

Moreover, we hypothesize that nanoparticles produced from recombinant protein polymers will provide an effective mechanism for site-specific delivery of resolvins and their metabolic precursors that will further accelerate both the resolution of the inflammatory response and the reconstitution a functionally intact endothelium. As such, we anticipate that by abrogating early inflammatory and thrombotic responses, intimal hyperplasia will be limited after catheter-based interventions.

*Preventing and treating aortic aneurysms:* The cause of an aortic aneurysm remains poorly understood and successful pharmacotherapy is lacking despite the role of aneurysms as a major source of morbidity and death. Unregulated inflammatory and tissue repair processes underlie the maladaptive response of the vascular wall that leads to aneurysm formation. Thus, there is great motivation for understanding the interplay between the complex biochemical, cellular, and biomechanical phenomena, which control inflammation and tissue repair in the vascular wall.

We postulate that expression and shedding of the heparan sulfate proteoglycan syndecan-1 may provide an important mechanism that inhibits abdominal aortic aneurysm (AAA) formation by limiting proteolytic or inflammatory activity and by promoting local reparative responses. The experimental approach within this project area is designed to yield fundamental knowledge regarding the regulated expression and shedding of syndecan-1, which we believe is an important molecular determinant modulating inflammatory and tissue repair processes in the vascular wall.

## 3. Chemical Biology and Materials Science

*Design of anti-thrombogenic surfaces:* This project is directed at identifying and harnessing biologically inspired designs to limit blood clotting on artificial surfaces. Thrombomodulin (TM), a transmembrane protein expressed by endothelial cells, is an established negative regulator of thrombin generation in the circulatory system. We are utilizing molecular engineering and bioorthogonal chemistry to site-specifically immobilize a biologically active recombinant human TM fragment onto the luminal surface of small diameter prosthetic vascular grafts. In addition, we are developing computational models that describe surface induced coagulation events under flow as a design tool for this effort.

*Chemoenzymatic synthesis of P-selectin glycoprotein-1 (PSGL-1):* Selectins (L, E- and P) are class of vascular endothelial molecules that play an important role in the recruitment of leukocytes to inflamed tissue. In this regard, PSGL-1 has been identified as the best characterized ligand for P-Selectin. PSGL-1 binds to P-Selectin through the interaction of core-2 O-glycan expressing Sialyl Lewis x oligosaccharide and three tyrosine sulfate residues. Some of the challenges associated with the synthesis of PSGL-1 are i) obtaining the hexasaccharide component with the Sialyl Lewis x portion in the peptide ii) synthesis of tyrosine sulfates in the peptide backbone. The Chaikof lab is currently investigating chemical ligation approaches to synthesize these glycosulfo peptides and mimics that can pave way for studying their biological activity within PSGL-1.

## Research Support

“Antithrombogenic membrane-mimetic assemblies”

National Institutes of Health, R01 HL56819

5/1/2006-4/30/2012

PI: Elliot L. Chaikof, MD, PhD

“A bioinspired small diameter vascular conduit”

National Institutes of Health, R01 HL083867

6/1/2006-5/31/2012

PI: Elliot L. Chaikof, MD, PhD

“Syndecan-1 in aortic aneurysm formation”

National Institutes of Health, R01 HL060903

6/1/2008-5/31/2013

PI: Elliot L. Chaikof, MD, PhD

Co-I: Carolyn A. Haller, PhD

“Site-specific therapies to prevent intimal hyperplasia”

National Institutes of Health, R01 HL106018

12/1/2011-11/30/2016

PI: Elliot L. Chaikof, MD, PhD

Co-I: Carolyn A. Haller, PhD

“Molecularly engineered blockade of islet induced inflammatory responses”

National Institutes of Health, R01 DK069275

07/01/2010-6/30/2015

PI: Elliot L. Chaikof, MD, PhD

“Engineered fascia for stem cell therapy in hernia repair”

Harvard Stem Cell Institute, SG-0065-11-00

07/01/2011-06/30/2013

PI: Elliot L. Chaikof, MD, PhD

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Caves JM, Cui W, Wen J, Kumar VA, Haller CA, Chaikof EL. Elastin-like protein matrix reinforced with collagen microfibers for soft tissue repair. *Biomaterials* 2011; 32:5371-79.



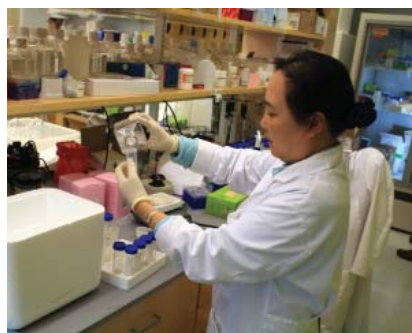
**Elliot L. Chaikof, MD, PhD**



*Jeff Caves*



*Juli Angsana*



*Liying Liu*



*Mohammed Sardar*

Chung J, Kasirajan KK, Veeraswamy RK, Dodson TF, Salam AA, **Chaikof EL**, Matthew A. Corriere MA. Left subclavian artery coverage during thoracic endovascular aortic repair and risk of perioperative stroke or death. *J Vasc Surg* 2011;54:979-84.

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Feng X, Pinaud J, **Chaikof EL**, Taton Y, Gnanou Y. Sequential functionalization of janus-type dendrimer-like poly(ethylene oxide)s with camptothecin and folic acid. *J Polymer Sci Part A-Polym Chem* 2011;49:2839-49.

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Wilson JT, Cui W, Kozlovskaya V, Kharlampieva E, Pan D, Qu Z, Krishnamurthy VR, Mets J, Kumar V, Wen J, Song Y, Tsukruk VV, **Chaikof EL**. Cell surface engineering with polyelectrolyte multilayer thin films. *J Am Chem Soc* 2011;133:7054-64.

**Non-Peer Reviewed Scientific or Medical Publications/Materials in Print or Other Media**

**Proceedings of Meetings or Other Non-Peer Reviewed Research Publications**

Naik N, Kumar V, **Chaikof EL**, Allen MG. MEMS-assisted spatially homogeneous endothelialization of a high length-to-depth aspect ratio microvascular network. *Conf Proc IEEE Eng Med Biol Soc* 2011:290-3

**Reviews, Chapters, Monographs, and Editorials**

Martinez AW, **Chaikof EL**. Microfabrication and nanotechnology in stent design. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2011;3:256-68

**Clinical Guidelines and Reports**

Murad MH, Montori VM, Sidawy AN, Ascher E, Meissner MH, Chaikof EL, Gloviczki P. Guideline methodology of the Society for Vascular Surgery including the experience with the grade framework. *J Vasc Surg* 2011;53:1375-80

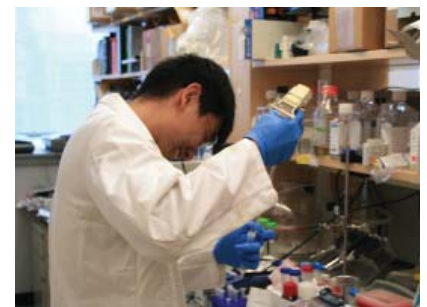
**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Angsana J, Haller CA, Chaikof EL. Expression of syndecan-1 enhances macrophage motility. *Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions*, Chicago, IL; April 28-30, 2011.

Kumar V, Caves J, Norred S, Collins M, Chaikof EL. Fabrication and characterization of large scale structurally and mechanically anisotropic nanofibrous collagen matrices for soft tissue engineering. *Gordon Research Conference: Biomaterials/Tissue Engineering*, Holderness, NH; July 31-August 5, 2011.

Kumar V, Martinez A, Caves J, Dingus J, Jain S, Chaikof E. Generation of mechanically robust collagen-based biomaterials with defined laser ablated patterns for soft tissue engineering. *Tissue Engineering and Regenerative Medicine*, Houston, TX; December 11-14, 2011.

Qu Z, Muthukrishnan S, Urlam M, Haller C, Kumar V, Marzec U, Hansen S, Lahann J, Chaikof E. A biologically active surface enzyme assembly that attenuates thrombus formation. *Gordon Research Conference: Biomaterials/Tissue Engineering*, Holderness, NH; July 31-August 5, 2011.

**Elliot L. Chaikof, MD, PhD***Vivek Kumar**Zheng Qu**Wookhyun Kim*





## Research Focus

The work in my laboratory is focused on understanding the function(s) of the homeostatic genes A20 (an ubiquitin-editing enzyme), Bcl-2, Bcl-xL and A1 in different T-cell types, and their relationship to the pathophysiology of disease processes centered on inflammation. Since inflammation is critical to many disease processes, we are exploring therapeutic use of these genes or their bioproducts in vascular diseases including atherosclerosis, micro and macrovascular complications of diabetes, islet transplantation, liver injury and transplantation, cancer, neurodegenerative disorders, among other diseases. This interest is based on our original finding that these genes serve a broad cytoprotective function in endothelial cells (EC). Expression of A20 (and other homeostatic genes including A1, Bcl-2 and Bcl-xL) in EC protects the cells from apoptosis and is potently anti-inflammatory through blocking activation of the transcription factor NF- $\kappa$ B, a key definer of their homeostatic potential (Figure 1).

While we usually study EC cells, we have expanded the work to pancreatic  $\beta$ -cells, in which A20 retains its anti-apoptotic and anti-inflammatory potential and thus is an ideal candidate to genetically engineer islet grafts for the treatment of type I diabetes.

The specific projects currently in the lab are as follows:

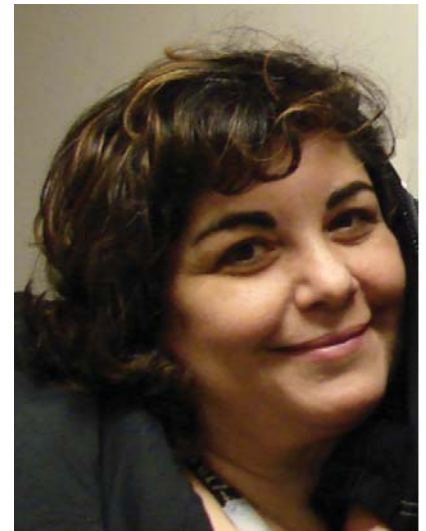
### A20 and Vascular Remodeling

A20 serves an anti-atherogenic function in smooth muscle cells (SMC) via inhibition of cell proliferation and induction of apoptosis of neointimal SMC. This translates into prevention but also regression of lesions of neointimal hyperplasia following balloon angioplasty of rat carotid arteries and protection from transplant arteriosclerosis (TA), thanks to an additional modulation of the immune response, skewing it towards an immunomodulatory and away from a pathogenic phenotype, in a paper that was accepted for publication (Transplantation 2011, in press). This work received the Young Investigator Award at the American Transplant Congress.

Extensive analysis of these in vivo results and of gene expression microarrays from A20-over-expressing and A20-silenced human SMC has identified novel targets of A20 in EC/SMC that help explain this positive outcome. Over-expression of A20 in EC and SMC transforms the molecular signature of the vessel wall to change its response to injury, in part through modulation of IFN $\gamma$  signaling in SMC. This later finding was presented by Dr. Herwig Moll and won the Annual Surgery Research Award in the basic science category for Residents and Postdoctoral Fellows at BIDMC.

Interestingly, we have also unraveled that high glucose/hyperglycemia decreases A20 levels in the vasculature of diabetic patients and animals. In response to high glucose, A20 undergoes unique post-translational modifications (PTM), i.e. O-glycosylation, ubiquitination and degradation in the proteasome. Loss of A20's atheroprotective effect is part of the molecular basis for increased risk of atherosclerosis in diabetes. This work was recently published in PLoS One (see *Bibliography*).

In addition, A20 demonstrates anti-angiogenic function in retinal endothelial cells. Diabetes-related degradation of A20 would significantly contribute to proliferative diabetic retinopathy. We are mapping/mutating A20 glycosylation sites to generate a glycosylation resistant protein.



**Christiane Ferran, MD, PhD**

Professor of Surgery

### Lab Members

Elzbieta Kaczmarek, PhD  
Cleide Gonçalves Da Silva PhD  
Andy Lee, MD  
Herwig Moll, PhD  
Eva Czismadia  
Jean Choi  
A. Katie Daniels  
Ashley Rogers, MD  
Alon Neidich



Figure 1

Christiane Ferran, MD, PhD

Intriguingly, A20 deficiency as seen in heterozygote mice seems to protect from the development of aortic abdominal aneurysms (AAA) by modulating differentiation status of SMC, through modulation of microRNA patterns. This work received the Excellence in Research Award at the American College of Surgeons Clinical Conference (presented by Dr. Scott Damrauer), and is being finalized for publication.

### The Hepatoprotective Functions of A20

We recently showed that A20 protects mice from lethality in models of acute toxic hepatitis, lethal radical hepatectomy, and prolonged warm ischemic time by promoting hepatocyte survival, protecting them from necrosis through a PPAR-dependent mechanism, containing inflammation and unexpectedly promoting their proliferation by shutting down the cell cycle inhibitor: p21<sup>waf1</sup> and also promoting IL-6 proliferative signals by shutting down SOCS-3. This work is accepted for publication in *Hepatology*.

Systems Biology approach to further uncover the molecular basis for the pro-regenerative function of A20 in the liver demonstrated that its benefits largely rely on optimizing energy production through improved lipid/fatty acid metabolism, and down-regulated inflammation. This finding suggests therapeutic potential for A20 in non-alcoholic steatotic hepatitis (NASH), a hypothesis we will pursue.

Interestingly, we have also unraveled in loss-of-function experiments, using A20 heterozygote mice (A20 +/-), that partial loss of A20 significantly delays liver regeneration, and drastically increases lethality (50% lethality) following 2/3 partial hepatectomy, an otherwise safe procedure. These results are extremely important in light of the newly described A20 (tnfaip3) gene polymorphisms, recognized as susceptible loci for several inflammatory and autoimmune diseases. Although A20 heterozygote mice are phenotypically normal, by interrogating the transcriptome we found subtle baseline differences affecting lipid metabolism and circadian rhythm that could account for the drastic difference in outcome following liver resection. This work received an award at the ATC and is being finalized for publication.

Additionally, we recently discovered that Hepatocyte Growth Factor upregulates A20 in renal epithelial cells and endothelial cells without promoting against inflammation. These results could be particularly important for the design of preventive or pre-conditioning regimen that would limit inflammation in many disease processes including prior to major vascular interventions and organ transplantation. This work will be published in 2012 in the *Journal of Cellular Physiology*.

We are also working on defining at the molecular level the intracellular targets that account for the function(s) of these proteins, and on establishing a structure/function analysis to map the domains associated with their different functions. In collaboration with Dr. Roya Khosravi-Far, we discovered that A20 is involved in the resistance of cancers to TRAIL and Chemotherapy. We have defined mechanisms of A20-mediated resistance of tumor cells to death, which uncovered leads for novel anti-cancer therapeutics. The versatility of A20 functions in cancer is intriguing: its upregulation in solid tumors (glioblastomas) is a marker of malignancy, while its loss is associated with >70% of B cell lymphomas.

Our overall goal is to translate our findings to the clinic. We have engaged in some proof of principle large animal models of vascular remodeling and liver resection, with the hope that defining specific domains and targets responsible

for the function(s) of A20 and other homeostatic genes may allow the development of peptide-based therapies and drug-design strategies.

**Christiane Ferran, MD, PhD**

### Clinical Research on A20

Given our results unraveling a striking phenotype in A20 heterozygous mice upon challenge with liver resection and other models of vascular injury, we were interested to see whether A20/tnfaip3 gene polymorphisms could also affect the rate of liver regeneration in recipients of living donor liver transplants.

Recently, a certain number of GWAS have identified multiple polymorphisms in the tnfaip3 region that associated with increased susceptibility to inflammatory and auto-immune diseases. At least three of these single nucleotide polymorphisms (SNPs) affected A20 mRNA levels or function. Accordingly, we collaborated with Dr. Elizabeth Pomfret at the Lahey Clinic to study in a pilot group the impact of A20 gene polymorphisms on liver regeneration in recipients and donors of living donor liver transplantation. Funding for this proposal was recently secured through the NIH. Genotyping living liver donors for A20 gene polymorphisms could be one of the first reliable parameters for donor selection, and for influencing the type of resection that could be safely performed (left lateral, extended right, full right or full left). It could also predict donor and recipient prognoses, and inspire A20-based therapies in liver transplantation.

### Research Support

“Improved liver function and regeneration with A20”  
National Institutes of Health, R01 DK063275-08  
01/01/2003-05/31/2014  
PI: Christiane Ferran, MD, PhD

“Vascular remodeling in transplant arteriosclerosis”  
National Institutes of Health, R01 HL080130A1-05  
06/15/2006-05/31/2012  
PI: Christiane Ferran, MD, PhD

“A20 gene polymorphisms in LDLT”  
National Institutes of Health, R21 DK091822-01  
9/1/2011-8/31/2013  
PI: Christiane Ferran, MD, PhD

“Mechanisms of vein graft failure”  
National Institutes of Health, R01 HL021796-26  
04/15/2010-03/31/2015  
PI: Frank W. LoGerfo, MD  
Co-PI: Christiane Ferran, MD, PhD

“Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery”  
National Institutes of Health, R01 HL086741-05  
02/01/2007-01/31/2012  
PI: Frank W. LoGerfo, MD  
Co-PI: Christiane Ferran, MD, PhD

**Christiane Ferran, MD, PhD**

“Role of neuropeptides in diabetic foot problems”  
National Institutes of Health, R01 NS066205-02A2  
6/1/2010-05/31/2015  
MPI: Aristidis Veves, MD, and Frank W. LoGerfo, MD  
Co-I: Christiane Ferran, MD, PhD

“Harvard-Longwood Research Training in Vascular Surgery”  
National Institutes of Health, 5T32-HL00734-17  
07/01/1997-06/30/2014  
Program Director: Frank W. LoGerfo, MD  
Co-director: Christiane Ferran, MD, PhD

**Applications Submitted and Pending Review/Funding**

“Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery”  
National Institutes of Health, R01 HL086741-05  
02/01/2007-01/31/2012  
PI: Frank W. LoGerfo, MD  
Co-PI: Christiane Ferran, MD, PhD

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**Accomplishments in the Past Year**

**Research Progress**

The past year, we have extended our program to studying the impact of A20 upon diabetic retinopathy. Additionally, we have been successful in expanding our work demonstrating the beneficial effect of A20 in preventing intimal hyperplasia in model of transplant arteriosclerosis. Extensive analysis of these in vivo results and of gene expression microarrays from A20-over-expressing and A20-silenced human SMC has identified novel targets of A20 in EC/SMC that help explain this positive outcome. Over-expression of A20 in EC and SMC transforms the molecular signature of the vessel wall to change its response to injury, in part through modulation of IFN signaling in SMC. This result set the basis for a fellowship grant proposal that was submitted by Dr. Moll to the Austrian Government, and has laid ground for a novel R01 proposal that we plan on submitting in the next few months.

We discovered that partial knockdown of A20 predisposes to aortic abdominal aneurysms. This result is partially based on a novel effect of A20 on SMC differentiation. We are exploring the molecular basis for that and in particular the impact of A20 on TGF/BMP signaling in the vasculature.

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 but also through decreasing SOCS3 to improve IL-6 proliferative signals. This data is being revised for publication in Hepatology.

As part of the liver work, we have also demonstrated that partial loss of A20 is a critical determinant of life and death following liver resection in mice. In other words, we unraveled a significant phenotype in A20 heterozygous mice facing injury such as liver resection. This was also true in models of proliferative retinopathies, and of transplant arteriosclerosis. These results are extremely important given the newly discovered SNPs in the A20 region that have been associated with decreased expression or function of A20 and increased susceptibility to auto-immune and inflammatory diseases. Accord-

ingly, not all of us are created equal for A20, i.e. in the face of diseases. To test this hypothesis in a clinical setting resembling our animal models, we have strated a collaboration with Dr. Elizabeth Pomfret at the Lahey Clinic to study, in a pilot group of recipients and donors of living donor liver transplantation, the impact of A20 gene polymorphisms on liver regeneration. Funding for this proposal was recently secured through an R21 NIH grant allocated to our laboratory.

Based on the intriguing properties of A20 and its multifaceted mechanisms of action that hold hope for novel therapies, I have been asked to edit a book on the multiple therapeutic facets of A20, to be published by Landes Biosciences and Elsevier. This book is now well in progress with the help and assistance of Ashley Rogers, MD, who recently joined my group.

### Administrative Accomplishments

- Chair of the Subcommittee for Junior Faculty at the Center for Vascular Biology Research, Beth Israel Deaconess Medical Center. This Subcommittee is aimed at mentoring the Junior Faculty of the Center in their career development with particular emphasis on their pursuit of independent funding
- Member of the Search Committee for Division Chief of Cardiac Surgery at the Massachusetts General Hospital, Harvard Medical School, Boston, MA
- Member of the Search Committee for Division Chief of Pediatric Nephrology at Children's Hospital, and Harvard Medical School, Boston, MA
- Member of the Search Committee for Chief of Thoracic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
- Member of the Search Committee for Chief of Plastic Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
- Member of the Search Committee for Chief of Integrated Cancer Biology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
- Member of Search Committee for Junior Faculty to be appointed in the Division of Vascular Surgery and The Department of Pathology, Beth Israel Deaconess Medical School, Boston, MA
- Chair of the Affinity Research Collaborative (ARC), Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School
- Director of Research Faculty Career Development, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School

### Individual Accomplishments

Christiane Ferran, MD, PhD

- Invited speaker at the NIH sponsored workshop: Defining Molecular Pathways and Mechanisms that predict CVD Risk Associated with Sleep Disordered Breathing. NIH, Bethesda, MD.. Topic: Intermittent Hypoxia and the Disruption of Endothelial Cell Homeostasis: The NF- $\kappa$ B inhibitory protein A20 as a novel molecular target.
- Member of the scientific advisory committee, Roche Organ Transplant Research Foundation (ROTRF), The International Society of Transplantation.

**Christiane Ferran, MD, PhD**

- Member of the A2ALL (Adult to adult liver transplantation) Consortium and Steering Committee, NIDDK, NIH. Co-chair of the subcommittee on Liver Regeneration.
- Reviewer for the NIH-NHLBI/NIAID Scientific Review Group ZRG1 2009/05 Immunology IMM-G(02) Special Emphasis Panel. Immunology: Member Conflicts and Special Grant Applications.
- Ad hoc reviewer for Circulation, Circulation Research, Journal of Clinical Investigation, Oncogene, Journal of Immunology, American Journal of Transplantation, Transplantation, Hepatology, Blood, Biochimica Biophysica Acta, Kidney International, Journal of the American Society of Nephrology.
- R21 DK091822-01, submitted in February 2010, awarded September 2011.

**Cleide da Silva, PhD**

- Recipient of the Eleonor Shore Award from Harvard Medical School.
- Recipient of the young Investigator Award, International Society for Applied Cardiovascular Biology Meeting.

**Scott Damrauer, MD**

- Recipient of the Excellence for Research Award. American College of Surgeons Annual Clinical Congress.

**Herwig Moll, PhD**

- Winner of the Annual Abstract Competition for Surgical Residents and Research Fellows, basic science category, Beth Israel Deaconess Medical Center.

**Clayton Peterson, MD**

- Recipient of the young Investigator Award, American Transplant Congress.
- Recipient of the young Investigator Award, International Society for Applied Cardiovascular Biology Meeting.

**Peter Studer, MD**

- Recipient of the Best Poster Award, American Transplant Congress.

**Invited Presentations**

“A20: An Integral Regulator of Vascular Homeodynamics.” Brigham and Women’s Hospital Pulmonary Grand Rounds. Boston, MA. January 10, 2011.

“The Pathophysiology of Abdominal Aortic Aneurysms.” Beth Israel Deaconess Medical Center, Center for Vascular Biology, Translational Seminars Series. Boston, MA. January 14, 2011.

“A20: A Homeodynamic Regulator Of Allograft Fate.” Massachusetts General Hospital, Transplantation Grand Rounds. Boston, MA. January 27, 2011.



“A20: An Integral Regulator of Vascular Homeodynamics.” Beth Israel Deaconess Medical Center, Surgical Grand Rounds. Boston, MA. Feb. 16, 2011.

“Sweet A20 and the Vascular Complications of Diabetes.” Joslin Diabetes Clinic Grand Medical Rounds. Boston, MA. April 4, 2011.

“A20: A Tale Of The Homeodynamic Response To Vascular Injury.” Beth Israel Deaconess Medical Center, Annual Retreat of the Center for Vascular Biology Research. Falmouth, MA. June 14, 2011.

**Christiane Ferran, MD, PhD**

## Teaching, Training, and Education

### Undergraduate Courses

“The Vascular Response to Injury in Health and disease” Vascular Biology Course for undergraduate summer students at the Center for Vascular Biology Research, Beth Israel Deaconess Medical Center

Dana Kapeller-Liberman: Tutoring of a high school student who was in the laboratory as a summer student, and has since then enrolled for undergraduate college studies at Columbia University.

### Graduate School and Graduate Medical Courses

#### Graduate Students

I had 4 medical students rotating through the laboratory, mainly as summer students two of whom were part of the Von Liebig summer fellowship program in vascular surgery research, one is part of an International Exchange Program with the University Balamand, Lebanon, in addition to a medical student from Tufts Medical School, enrolled in a 6 months research activity. Also, Ms Jean Choi a BS. From MIT has joined the laboratory as a Research Assistant in preparation to entering medical school. These students benefit from bench top teaching as well as didactic teaching sessions, including the vascular Biology Summer Course held at the CVBR.

- Timothy Ayodele Adesanya, Medical Student, Ohio State University, recipient of the Von Liebig Fellowship
- Sabrina Khan, Medical Student, University of Rochester School of Medicine and Dentistry, recipient of the Von Liebig Fellowship
- Charbel Awwad, Medical Student, University Balamand, Balamand, Lebanon
- Alon Neidich, Medical Student, Tufts University Medical School
- Jean Chi, BS, Research Assistant

#### Postgraduate Fellows

I organize weekly teaching sessions for the 3 surgical residents, and three PhDs who are currently or were working in the laboratory for a significant time during 2011. In addition I provide informal bench based teaching, guidance in writing manuscripts and preparing for talks, as well as help in grant writing.

**Christiane Ferran, MD, PhD**

- Clayton Peterson, MD, Surgical Resident, BIDMC
- Scott Damrauer, MD, Surgical Resident, Massachusetts General Hospital
- Andy Lee, MD, Surgical Resident, BIDMC
- Cleide Gonçalves Da Silva, PhD, Instructor, BIDMC
- Sanah Essayagh, PhD, Postdoctoral Fellow, BIDMC
- Herwig Moll, PhD, Postdoctoral Fellow, BIDMC

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**Bibliography (January – December 2011)**

**Peer-Reviewed Publications in Print or Other Media**

Research Investigations

Damrauer SM, Studer P, da Silva CG, Longo CR, Ramsey HE, Csizmadia E, Shrikhande GV, Scali ST, Liebermann TA, Patel VI, Bhasin MK, **Ferran C**. A20 modulates lipid metabolism and energy production to promote liver regeneration. *PLoS One* 2011;6:e17715.

Research Investigations (Submitted or in Press)

Wang H, **Ferran C**, Attanasio C, Calise F, Otterbein LE. Induction of protective genes leads to islet survival and function. *J Transplant* 2011; in press.

**Professional Educational Materials or Reports, in Print or Other Media**

“The New NIH Grant Format from the Reviewer’s Perspective” Distributed to Faculty of the Center for Vascular Biology Research, and the Department of Surgery

**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Damrauer SM, Peterson CR, Studer P, Marusyk VL, Csizmadia E, da Silva CG, **Ferran C**. Partial loss of A20 (Tnfrsf3) promotes resistance to abdominal aortic aneurysms through altering smooth muscle cell differentiation. Oral Presentation at the Surgical Forum, American College of Surgeons 96th Annual Clinical Congress, Washington DC, October 3-7, 2010. Recipient of the Excellence for Research Award.

da Silva CG, Shrikhande G, Shrikhande GV, Scali ST, Damrauer SM, Csizmadia E, Matthey M, Kaczmarek E, **Ferran C**. Glucose-mediated loss of vascular A20 contributes to accelerated atherosclerosis in diabetes. Oral presentation at the International Society for Applied Cardiovascular Biology (ISACB) 12th Biannual Meeting, Boston MA. September 22-25, 2010. Recipient of the Young Investigator Award.

da Silva CG, Studer P, Skroch M, Ma A, Csizmadia E, **Ferran C**. A20 modulates SOCS-3 expression by modulating miR 203 levels, enhancing IL-6 pro-proliferative signals and promoting hepatocyte proliferation. Oral Presentation at the Liver meeting of the American Association for the Study of Liver Diseases (AASLD), Nov. 3-November 8 2011, San Francisco, CA.

Kaczmarek E, Daniel S, Essayagh S, Choi L, da Silva CG, **Ferran C**. A20 regulates eNOS expression and activity in human coronary artery endothelial cells. Oral presentation at the International Society for Applied Cardiovascular Biology (ISACB) 12th Biannual Meeting, Boston MA. September 22-25, 2010. Recipient of the Young Investigator Award.

Moll H, Lee A, Peterson CR, Siracuse JJ, Csizmadia E, **Ferran C**. A20 inhibits interferon-g signaling in human smooth muscle cells to contain pathological vascular remodeling of transplant arteriosclerosis. Winner of the Annual Beth Israel Deaconess Medical Center Department of Surgery Research Competition Award for Surgical residents and Postdoctoral fellows, November 2011.

Peterson C, Siracuse JJ, Fisher MD, da Silva CG, PhD1, Csizmadia E, Damrauer SM, , Studer P, Essayagh S, Kaczmarek E, **Ferran C**. A20 Protects Vascular Allografts from Transplant Arteriosclerosis by Modulating Inflammatory and Apoptotic Responses to Skew the Immune Response. Oral Presentation at the American Transplant Congress (ATC) 2010. May 2010, San Diego California. Recipient of the Young Investigator Award.

Peterson CR, Siracuse JJ, Fisher MD, da Silva CG, Csizmadia E, Damrauer SM, Studer P, Essayagh S, Kaczmarek E, **Ferran C**. Vascular remodeling in Transplant Arteriosclerosis: the role of A20. Oral presentation at the International Society for Applied Cardiovascular Biology (ISACB) 12th Biannual Meeting, Boston MA. September 22-25, 2010. Recipient of the Young Investigator Award.

Studer P, da Silva C, Longo C, Bhasin M, Lieberman T, **Ferran C**. Gene Chip Analysis of A20 expressing Livers following Extended Liver resection uncovers its Multiple Targets that promote Liver Repair and regeneration. Poster Presentation at the American Transplant Congress (ATC) 2010. May 2010, San Diego California. Recipient of Best Poster Award.

**Christiane Ferran, MD, PhD**



## Research Focus

My major research interest is in the field of vascular biology. Specifically, I am focused on the role of purinergic signaling in the endothelium exposed to various insults, including pro-inflammatory factors, high glucose, or hypoxia, such as observed in diabetes or sleep apnea.

Extracellular nucleotides play a significant biological role in many tissues and cell types as signaling molecules regulating cellular functions 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.

We showed that in endothelial cells (EC) extracellular nucleotides initiate many important signal transduction pathways, including FAK, paxillin, and ERK, that lead to cytoskeletal rearrangements, increased cell migration, and EC proliferation. These data suggested the involvement of P2 receptors in regulation of angiogenesis and were further supported by the additional findings showing a connection between P2Y receptors and  $\alpha v\beta 3(\beta 5)$  integrins.

Moreover, we identified a new nucleotide-induced signaling pathway of eNOS activation in EC that is calcium and PKC $\delta$ -dependent but does not require the activities of PI3K/Akt, AMPK or ERK. Importantly, this new pathway is functional in EC cultured under high glucose conditions, suggesting that extracellular nucleotides can override the damaging effects of high concentrations of glucose, by maintaining NO bioavailability. We also elucidated a new pathway of AMP-activated kinase (AMPK) activation by extracellular nucleotides in EC. AMPK is recognized as a key energy regulator and a primary protective kinase in diabetes mellitus. These data, complemented by our new results showing that extracellular nucleotides increase the levels of intracellular ATP, indicate that purinergic signaling might have an impact on metabolic diseases.

Importantly, we examined our in vitro data in the animal model and confirmed activation of eNOS and AMPK in mouse aortas following ATP administration. Further, we demonstrated protective effects of ATP administration in diabetic ApoE-null mice, and showed decreased expression of oxidative stress proteins and pro-inflammatory molecules in aortic arches, and attenuated steatosis and inflammation in the livers.

Given the similarity in molecular targets of high glucose and hypoxia/intermittent hypoxia in the vasculature, we hypothesized that the protective effects of purinergic signaling observed in EC exposed to high glucose could also be pertinent to patients with obstructive sleep apnea. The R21 grant proposal aimed at investigation of the role of extracellular nucleotides in sleep apnea has been just awarded. I intend to use new results obtained in this project in my next R01 application this fall.

I believe that others and our data documenting important functions of extracellular nucleotides in vasculature, strongly suggest that purinergic receptors may be new targets in treatment of diseases associated with endothelial dysfunction. My long-term plan is to investigate purinergic mechanisms in EC in the context of vascular complications associated with diabetes and sleep apnea.



**Elzbieta Kaczmarek, PhD**

Assistant Professor of Surgery

Lab Members

Douglas Clarke, PhD

Elzbieta Kaczmarek, PhD

## Research Support

“Purinergic signaling in sleep apnea”

National Institutes of Health R21 HL106227

Project period: 01/01/2011-12/31/2012

PI: Elzbieta Kaczmarek, PhD

“Extracellular ATP: potential regulator of hypoxia-induced vasa vasorum neovascularization”

National Institutes of Health, R01 HL086783

Project period: 01/07/2008-06/30/2013

PI: Evgenia Gerasimovskaya, PhD

Subcontract PI: Elzbieta Kaczmarek, PhD

Subcontract period: 01/01/2010-12/31/2011

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## Accomplishments in the Past Year

### Research Progress

With Douglas Clarke, PhD, (*photo, left*), who joined the laboratory in March 2011, we established a new system to study the effects of intermittent hypoxia (repetitive changes in oxygen levels from 20% to 1%) in vitro. Our preliminary results indicate that in endothelial cells exposed to 1-4 h of intermittent hypoxia, the expression of several genes, including eNOS, VCAM-1, VEGF, A20, and selected P2 purinergic receptors, is modulated. We validated these data using skin biopsies obtained from sleep apnea patients and aortas isolated from mice exposed to intermittent hypoxia for four weeks, in collaboration with Dr. Malhotra (Brigham and Women’s Hospital, Boston) and Dr. O’Donnell (University of Pittsburgh, Pittsburgh). Moreover, we demonstrated that extracellular nucleotides may modulate intermittent hypoxia responses in EC. The data obtained in this study are the basis for two papers under preparation.

We have recently demonstrated that extracellular nucleotides acting via P2 receptors upregulate expression of two “protective” genes, A20 and A1 in human EC. Furthermore, extracellular nucleotides activate eNOS, even under high glucose levels. The molecular mechanisms of these purinergic regulations of A20 and A1 expression and eNOS activation are currently under investigation.

In collaboration with Drs. Gerasimovskaya (University of Colorado) and Yegutkin (University of Turku, Finland) we showed that extracellular nucleotide catabolism is decreased in vasa vasorum endothelial cells (VVEC) isolated from pulmonary artery adventitia of neonatal calves exposed to two-week chronic hypoxia compared to controls. Our data indicated that chronic hypoxia decreased ANTPDase-1/CD39 and ecto-5’-nucleotidase/CD73 activities, leading to increased basal ATP and ADP levels. We also demonstrated a higher proliferative response to low micromolar concentrations of ATP and ADP in VVEC previously exposed to chronic hypoxia and enhanced permeability due to impaired vascular barrier function in these cells compared to controls.



Douglas Clarke, PhD

## Individual Accomplishments

- Reviewer of grant application for the Polish National Science Center (equivalent of NIH).
- Member of the Editorial Advisory Board: *The Open Circulation and Vascular Journal*.
- Ad hoc reviewer for several peer reviewed journals, including *Journal of Thrombosis and Haemostasis*, *Thrombosis Research*, *Thrombosis and Haemostasis*, *Biochemical Biophysical Acta*, *British Journal of Pharmacology*, *Cellular and Molecular Life Sciences*, *Recent Patents on Regenerative Medicine*, *Pharmacological Research*, *Cancer Research*, *Sleep*, *Journal of Clinical Sleep Medicine*.

## Invited Presentations Local, National, and International

“Endothelial Dysfunction in Sleep Apnea: A Possible Role of Purinergic Signaling.” American Thoracic Society International Conference. Denver, CO. May 2011.

## Teaching, Training, and Education

### Graduate School and Graduate Medical Courses

I trained one Postdoctoral Fellow and a Research Associate. This includes weekly meetings, discussing the projects, and analyzing the data.

## Bibliography (January – December 2011)

### Peer-Reviewed Articles in Print or Other Media

#### Research Investigations

Wegiel B, Gallo D, Csizmadia E, Roger T, **Kaczmarek E**, Harris C, Zuckerbraun BS, Otterbein LE. Biliverdin inhibits TLR4 expression via nitric oxide-dependent nuclear translocation of biliverdin reductase. *PNAS* 2011;108:18849-54.

Yegutkin GG, Helenius M, **Kaczmarek E**, Burns N, Jalkanen S, Stenmark K, Gerasimovskaya EV. Chronic hypoxia impairs extracellular nucleotide metabolism and barrier function in pulmonary artery vasa vasorum endothelial cells. *Angiogenesis* 2011; 14:503-13.

#### Research Investigations Submitted or in Press

da Silva CG, Maccariello ER, Wilson SW, Putheti P, Daniel S, Damrauer SM, Peterson C, Siracuse JJ, **Kaczmarek E**, Ferran C. Hepatocyte growth factor preferentially activates the anti-inflammatory arm of NF- $\kappa$ B signaling to induce A20 and protect renal proximal tubular epithelial cells from inflammation. *J Cell Physiol* 2011; in press.

**Elzbieta Kaczmarek, PhD**



**Elzbieta Kaczmarek, PhD**

Other Peer-Reviewed Publications

*Reviews*

**Kaczmarek E, Koziak K.** Targeting stenosis with nucleotide-hydrolyzing enzymes. *Curr Pharm Biotechnol* 2011;12(11):1799-804.

**Kaczmarek E, Koziak K.** Extracellular nucleotide-induced responses in endothelial cells. *Postepy Polskiej Farmacji i Medycyny* 2011; in press.

**Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings**

Drozdowska J, Zyzynska-Granica B, Paradowska A, Jarzyna R, Maciejko D, **Kaczmarek E, Koziak K.** Extracellular nucleotides enhance procoagulatory effect of proinflammatory cytokines. *Arteriosclerosis, Thrombosis and Vascular Biology Meeting, Chicago IL; April 2011.*

Paradowska A, Drozdowska J, Zyzynska-Granica B, Zegrocka-Stendel O, Nowis D, Ciemerych MA, **Kaczmarek E, Koziak K.** Statins attenuate glucose uptake by disrupting actin cytoskeleton. *Arteriosclerosis, Thrombosis and Vascular Biology Meeting, Chicago IL; April 2011.*

Zyzynska-Granica B, Drozdowska J, Paradowska A, Bocian K, **Kaczmarek E, Koziak K.** Interleukin-15 induces human endothelial cell migration and proliferation. *Arteriosclerosis, Thrombosis and Vascular Biology Meeting, Chicago IL; April 2011.*

## Research Focus

My large research group is extensively involved in four main areas of vascular biology research: 1) evaluating mechanisms responsible for prosthetic graft failure; 2) prevention of intimal hyperplasia (IH) in vein grafts; 3) developing and testing novel biomaterial surfaces for drug delivery, tissue engineering, and vascular prosthetic grafts; and 4) examining the role of neuropeptides in diabetic wound healing and heart failure.

### Prosthetic graft failure

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.

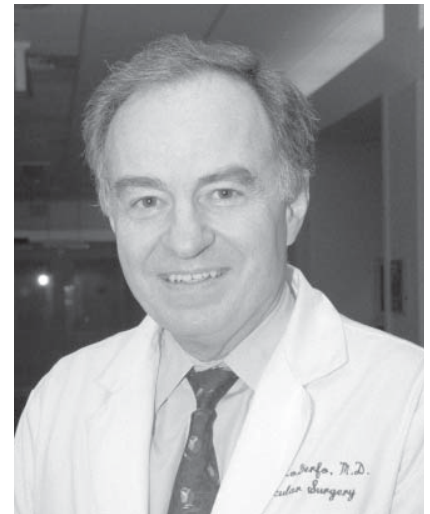
Based on our previous work we identified two gene targets, myristoylated alanine-rich C kinase substrate (MARCKS) and thrombospondin-2 (TSP-2), which are upregulated in AIH. Both of these targets are known to affect vascular cells. Our current work is focused on understanding the biology of these molecules and developing prosthetic grafts that can deliver silencing RNA (siRNA) to the vessel wall to silence these two targets and hence mitigate the development of AIH. Results from these projects have been presented at several national and international meetings and have resulted in manuscripts.

### Intimal hyperplasia

Similar to AIH, IH in vein grafts is responsible for vein graft failure. Using a canine model of vein bypass graft and advanced tissue sampling with laser capture microdissection (LCM) we followed simultaneously the transcriptome response of endothelial cells and smooth muscle cells of the vein wall at several time-points after graft implantation, compared with unimplanted control vein samples. This was followed with a systems biology analysis to define targets for gene silencing that are most likely to have the greatest impact in ameliorating implantation injury. This work has also been presented at several national and international conferences.

### Biomaterials Development and Testing

The Biomaterials research we do in the lab is lead by Mauricio Contreras, MD, in collaboration with our industry partner, Biosurfaces Inc. In this productive collaboration, we have designed and patented new biomaterials that are ideal for drug delivery systems and tissue engineering scaffolds, and for vascular prosthetic grafts. Assembled through electro-spinning, these modified (polyester based) materials provide a unique distribution of highly porous networks of nanofibers that resemble the structural architecture of extracellular matrix, thus fostering cellular adhesion and improve overall healing. In addition, one of the great advantages is that while these materials are being synthesized, different biological/pharmaceutical agents can be incorporated into the biomaterial, such as antibiotics, antithrombotic agents, growth factors (VEGF) to promote endothelial cell healing, or siRNA to knock down gene expression. Upon release, these agents have been shown to maintain their biological activity. Furthermore, our electro-spinning tech-



**Frank W. LoGerfo, MD**

William McDermott  
Professor of Surgery

#### Lab Members

Mauricio A. Contreras, MD  
Leena Pradhan-Nabzdyk, PhD  
Wande Pratt, M.D, MPH  
Christoph Nabzdyk, MD  
Maggie Chun  
Natasha Resendes  
Gener Augustin  
Julia Glaser  
Priya Patel  
Allisandra Mowles



*Mauricio Contreras, MD*

**Frank W. LoGerfo, MD**



*Leena Pradhan-Nabzdyk,  
PhD*

nology is performed at low temperatures, unlike standard polymers which are extruded at high temperatures via melt spinning.

Using this technology we have designed several new products that we have tested in vitro and in our in vivo models. Some of these products include: 1) a nanofibrous bioactive prosthetic sewing cuff for valvular prosthesis with fabric (polyester) in their design; 2) a bioactive prosthetic vascular graft for ventricular assist devices; and 3) a conduit for arterial localized gene delivery.

In addition, we are in the process of designing new applications using this technology for infection resistant catheters and surgical sutures, as well as new prosthetic vascular graft for AV fistula access with self-sealing properties.

### **Neuropeptides in wound healing**

The neuropeptide-diabetic wound healing research we do in the lab is lead by Dr. Leena Pradhan-Nabzdyk in collaboration with Dr. Aristidis Veves (Podiatry). To study this area, we first developed important in vivo and in vitro models. Current findings from our diabetic rabbit neuroischemic model of wound healing suggests that in the skin of diabetic rabbits, the expression of neuropeptides such as Substance P (SP) and Neuropeptide Y (NPY) is down-regulated whereas the expression of inflammatory cytokines is upregulated.

Neuroischemic wounds have the slowest healing rate and post-injury focused upregulation of cytokines is not achieved in wounds from our diabetic rabbit model. We have employed this model to test therapeutic efficacy of temperature-sensitive hydrogels in collaboration with Lynntech Inc. (Texas). Based on the positive results of this Phase I study we applied for funds to carry-out a Phase II study at the NIH. Our in vitro studies using dermal vascular endothelial cells are specifically designed to monitor the role of neuropeptides in angiogenesis in a hyperglycemic environment. The results of this study suggest that hyperglycemia inhibits angiogenesis whereas SP and NPY both restore it. Similarly in dermal fibroblasts, hyperglycemia inhibits proliferation and migration whereas SP and NPY restore it. All of these findings were published and presented at national and international meetings in 2011 (see below).

In addition to investigating the role of neuropeptides in wound healing, we are also investigating their role in diabetic heart failure. Heart failure (HF) is a major cause of mortality in the United States, affecting nearly 5 million Americans and causing 300,000 deaths annually. Approximately 15 to 25% of patients with HF are diabetics and it has been suggested that diabetes may play an important role in the pathogenesis, prognosis, and response to treatment of HF. Advanced HF is related to marked insulin resistance.

Coronary artery disease and cardiomyopathy are major causes of HF in diabetics. In addition, diabetes is known to cause both peripheral and autonomic neuropathy. The goal of this project is to investigate the role of SP, NPY and Calcitonin Gene Related Peptide (CGRP) in diabetic heart failure. Similar to our wound healing studies, we observed that expression of SP and NPY and their receptors are down-regulated in the right atrium of the diabetic patients compared to the non-diabetic patients. More importantly, the low ejection fraction correlates with reduced neuropeptide expression. Parts of these results are also published and presented at national meetings in 2011.

**Research Support****Frank W. LoGerfo, MD**

“Mechanisms of prosthetic arterial graft failure”

NIH/NHLBI, R01HL021796-27

04/15/10-01/31/15

PI: Frank W. LoGerfo, MD

“Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery”

NIH/NHLBI, R01HL086741-05

02/01/07-12/30/11 (No-cost extension)

PI: Frank W. LoGerfo, MD

“Harvard-Longwood research training in vascular surgery”

NIH/NHLBI, T32HL007734-16

07/01/09 – 06/30/14

PI: Frank W. LoGerfo, MD

“Localized gene delivery from implantable arterial devices”

NIH/NHLBI,

NSF STTR Phase II 0923674

08/01/09-02/29/12

PI: Matt Phanuef, PhD (Biosurfaces, Inc.)

Site PI: Mauricio Contreras, MD

Co-I: Frank W. LoGerfo, MD

“A bio-active prosthetic vascular graft”

NIH/NHLBI, 5 R42 HL087466-03

01/15/11-11/30/12

PI: Matt Phanuef, PhD (Biosurfaces, Inc.)

Site PI: Mauricio Contreras, MD

Co-I: Frank W. LoGerfo, MD

“Role of neuropeptides in diabetic foot problems”

NIH/NIDDK, R01NS066205-02

06/01/10-05/31/15

PI: Aristidis Veves, MD

Co-PI: Leena Pradhan-Nabzdyk, PhD

Co-I: Frank LoGerfo, MD

“Contractile hydrogel dressing for primary wound closure”

NIH/NIDDK, R41DK089789-01

06/01/2010-08/31/11

PI: Anjal Sharma, PhD (Lynnntech Inc., TX)

Site PI: Aristidis Veves, MD

Co-I: Leena Pradhan-Nabzdyk, PhD

“Stimuli responsive topical gels for mechanically assisted wound debridement”

NIH/NIDDK, R41DK089350-01

09/30/2010-09/30/11

PI: Anjal Sharma, PhD (Lynnntech Inc., TX)

Site PI: Aristidis Veves, MD

Co-I: Leena Pradhan-Nabzdyk, PhD

“Mechanisms of neuropeptides action in diabetes”

NIH/NIDDK, R01DK091949-01A1

09/01/11-08/31/2016

MPI: Aristidis Veves, MD, Janice Zabolotny, PhD

Co-I: Frank W. LoGerfo, MD

Co-I: Leena Pradhan-Nabzdyk, PhD

**Frank W. LoGerfo, MD**

**Applications Submitted and Pending Review/Funding**

“Harvard-Longwood short-term research training in vascular surgery”  
NIH/NIDDK, T35 HL110843-01  
06/01/2012-05/31/2017  
Program Director: Frank W. LoGerfo, MD  
Program Co-Director: Leena Pradhan-Nabzdyk, PhD

“Novel, effective topical treatment for diabetic ulcer”  
NIH/NIDDK STTR  
06/01/2012-05/31/2013  
PI: Gyula Varadi, PhD (Biochemics Inc, MA)  
Site PI: Leena Pradhan-Nabzdyk, PhD

“Novel therapeutic approaches for the management of diabetic foot ulceration”  
NIH/NIDDK, R24DK091210-01  
04/01/12-03/31/13  
MPI: David Mooney, PhD, William Shih PhD, Frank W. LoGerfo, MD, Aristidis Veves, MD  
Co-I: Leena Pradhan-Nabzdyk, PhD

“Contractile hydrogel for primary wound closure”  
NIH/NIDDK Phase II STTR  
06/01/2010-08/31/11  
PI: Anjal Sharma, PhD (Lynntech Inc., TX)  
Site PI: Aristidis Veves, MD  
Co-I: Leena Pradhan-Nabzdyk, PhD

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**Accomplishments in the Past Year**

**Research Progress**

**Mechanisms of Prosthetic Arterial Graft Failure**

In the past year, we successfully published our results based on in vitro effects of TSP-2 siRNA treatment. In brief, the results indicate that, single transfection with TSP-2 siRNA allows suppression of TSP-2 protein expression for more than 30 days, does not affect human Aortic Smooth Muscle Cell (HAoSMC) migration or proliferation but significantly improves their attachment to fibronectin. We also successfully transfected and silenced TSP-2 in HAoSMC using fluorescently tagged TSP-2 siRNA with the in vivo transfection reagent Polyethylenimine (PEI). The 3' modification of TSP-2 siRNA with cholesterol even in smaller amounts significantly silenced TSP-2 gene. Part of these results will be presented at Academic Surgical Congress, Feb, 2012.

In collaboration with Biosurfaces Inc., we are developing electrospun (e) prosthetic grafts made of Polyethylene terephthalate (PET) polymer to which siRNA could be adsorbed. Our results indicate that HAoSMC attach significantly more and are more viable on ePET and ePET-ePGA combination graft materials compared to commonly used PTFE. PGA or Polyglycolic Acid is a biodegradable polymer and is used for slow delivery of biomaterials. These results were presented at the European Society for Vascular Surgery meeting in Strasbourg, France where Dr. Nabzdyk received 2nd place award as a young investigator.

When grafts were dip-coated with siRNA, adsorption to ePET was also greater when compared to PTFE. Overall, siRNA adsorption to both grafts increased with siRNA complexed to PEI and siRNA adsorption was greater



in ePET compared to PTFE. Repeated dipping of ePET into siRNA also increased adsorption. This work was presented at New England Society for Vascular Surgery, Sept, 2011, Providence RI. We could successfully deliver fluorescently tagged siRNA complexed with PEI from ePET grafts to HAoSMCs either by placing cells on top of siRNA-PEI coated grafts (reverse transfection) or by placing siRNA-PEI coated grafts on a confluent monolayer of HAoSMCs (forward transfection) and using confocal microscopy we could visualize robust growth of cells in both cases (*Figure 1*). Moreover, we could successfully silence TSP-2 gene in HAoSMC by forward transfection method. This work will be presented at Academic Surgical Congress, Feb, 2012, Las Vegas, NV.

### Prevention of intimal hyperplasia (IH) in vein grafts

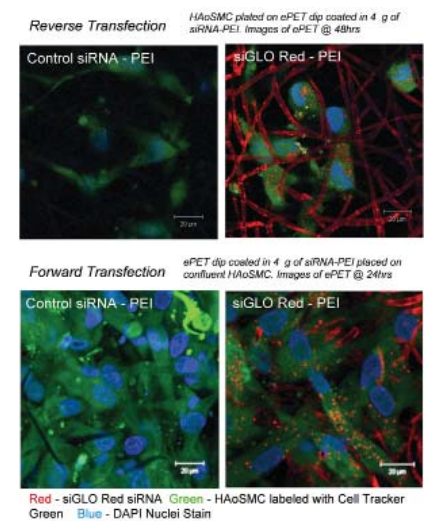
About 250,000 coronary artery bypass grafts (CABG) and 80,000 lower extremity vein graft implantations are performed each year with an average cost of 44 billion dollars. Over 50% of CABG fail within 10 years, and 30-50% of lower extremity vein grafts fail within 5 years. Although some pharmacological therapies such as aspirin and dipyridamole, as well as statins have shown modest benefit in improving CABG outcome, there has been no corresponding benefit for lower extremity vein grafts. The primary objective of this project is to identify high profile targets for gene silencing to ameliorate the injury associated with implantation of vein grafts. Canine femoral artery interposition bypass using reversed autologous cephalic vein grafts were harvested, along with contralateral cephalic vein controls, after 2, 12 and 24 hours and 7 and 30 days (n=3 for each time point). RNA was purified from laser capture microdissection (LCM)-isolated endothelial cells (EC) and medial smooth muscle cells (SMC), converted to cDNA, and prepared for Affymetrix Canine2.0 GeneChip hybridization. Isolate purities were quantified via qRT-PCR (EC marker: CD31; SMC marker: SMC-MHCII). Average isolate purities were 34-90% for ECs and 79-100% for SMCs.

Our results demonstrate a robust genomic response beginning at 2 H, peaking at 12-24 H, declining by 7 D, and resolving by 30 D. Gene ontology and pathway analyses of differentially expressed genes indicate that implantation injury affects inflammatory and immune responses, apoptosis, mitosis, and extracellular matrix reorganization in both cell types. Through back propagation, an integrated network was built, starting with genes differentially expressed at 30 D, followed by adding upstream interactive genes from each prior time point. This identified significant enrichment of IL-6, IL-8, NF- $\kappa$ B, dendritic cell maturation, glucocorticoid receptor, and Triggering Receptor Expressed on Myeloid Cells (TREM-1) signaling, as well as PPAR $\alpha$  activation pathways in graft EC and SMC.

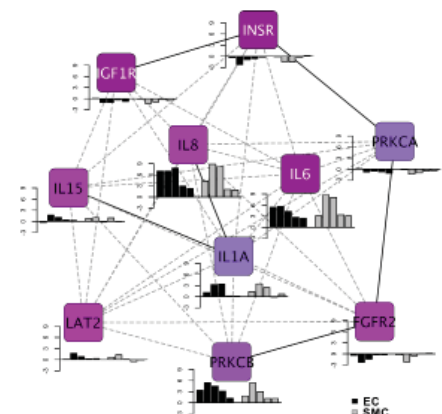
Interactive network-based analyses identified IL-6, IL-8, IL-1 $\alpha$ , and Insulin Receptor (INSR) as focus hub genes within these pathways (*Figure 2*). Real-time PCR was used for the validation of two of these genes: IL-6 and IL-8, in addition to Collagen 11A1 (COL11A1), a cornerstone of the back-propagation (*Figure 2*). In conclusion, these results establish causality relationships clarifying the pathogenesis of vein graft implantation injury, and identifying novel targets for its prevention. This work has also been presented at several national and international meetings and is currently being prepared for manuscript submission.

Based on these data and data from the AIH project, we have started testing siRNA in vivo. The first target to be tested was MARCKS. IH was created in a rat carotid artery balloon angioplasty denudation model and saline, control

### Frank W. LoGerfo, MD



*Figure 1*



*Figure 2*

Frank W. LoGerfo, MD



Figure 3



Figure 4

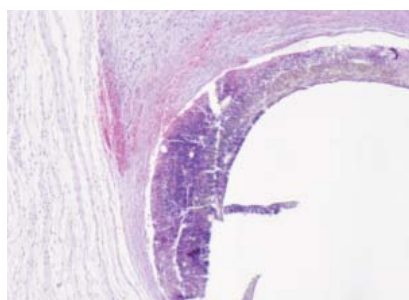


Figure 5

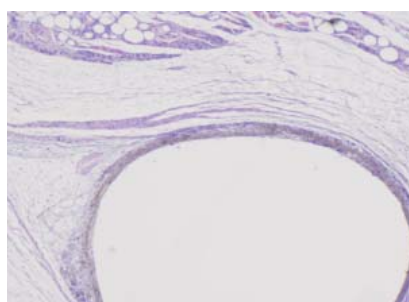


Figure 6

siRNA or MARCKS siRNA were delivered without any transfection reagent or with PEI using distending pressure. At 5 days we get some IH development which is robust at 21 days. Preliminary data suggest that although we can effectively silence MARCKS gene (80% knock-down) using PEI, there is no reduction in IH development. This underscores our point that more than one gene needs to be simultaneously silenced to have a positive outcome. Based on our previous in vitro studies wherein we could simultaneously silence 3 genes, we are currently conducting studies geared towards silencing more than one gene in this in vivo rat model.

#### Nanofibrous Bioactive Prosthetic Sewing Cuff

Valve-replacement surgery has dramatically altered the natural history of valvular heart disease. Unfortunately valvular prosthesis with fabric (polyester) materials in their design, continue to be a serious problem due to infection. Therefore, the design and development of a new bioactive (molecularly engineered materials) polyester sewing cuff, assembled through micro-fabrication (nanofiber) techniques, that would be anti-thrombogenic, promote/foster cell healing and be infection resistant is not only necessary, it is well justified and warranted.

To this end, we developed a novel nanofibrous sewing cuff with antimicrobial (Moxifloxacin or Moxi) and antithrombin (recombinant hirudin or rHir) properties was synthesized (BioCuff). Evaluation of physical (tensile strength and suture retention) and surface (SEM) properties between control and BioCuff sewing rings showed no significant difference between these two properties. Release pharmacokinetics of Moxi and rHir under static and stringent wash conditions for 30 days was then evaluated, with both agents shown to be released at biologically-active levels over this time period.

In vitro biologic activity (antimicrobial and antithrombin) of washed BioCuff materials persisted over the entire wash period, confirming a significant amount of each agent remained with the BioCuff after washing. Antithrombin activity from the washed BioCuff materials was also confirmed with the whole blood assay, which showed extended clotting times for the BioCuffs (greater than 6-fold) as compared to controls. BioCuffs also demonstrated superior antimicrobial, antithrombin and healing properties as compared to controls after implantation into subcutaneous pockets (with and without *S. aureus*) in the rabbit dorsum. Overall physical and biologic properties of the BioCuff did not change after implantation for 14 days as compared to unimplanted BioCuffs.

Using our in vivo rabbit subcutaneous implantation model, all explanted BioCuff sewing rings had retained their shape and form after being subcutaneously implanted in a rabbit for 2 weeks. Upon explantation, there was a visual difference between control and BioCuff sewing rings that had been challenged with *S. aureus*. Control sewing rings (Figure 3) had gross signs of infection, as indicated by purulence directly around the sewing ring. In stark contrast, BioCuff sewing rings (Figure 4) had no evident signs of infection and showed excellent incorporation into the surrounding tissue. These rings were removed from the same rabbit, indicating the sensitivity of testing two different materials within the same animal. No evidence of infection was seen with control or BioCuff sewing rings that were implanted but were not exposed to bacteria. Histologic examination of these cuffs confirmed the gross findings in that control sewing rings (Figure 5) had a significant inflammatory response with limited tissue incorporation compared to BioCuff sewing rings (Figure 6).



### A Novel Bioactive Conduit for Assist Devices

Ventricular assist devices (VAD) are prone to two major complications: thrombosis and infection, resulting in significant morbidity/mortality. The high frequency with which these events occur is the impetus behind this research study, particularly, targeting the prosthetic vascular graft segments that connect to the VAD. Our goal was to create a new Dacron (electrospun) prosthetic vascular graft with antithrombotic and infection-resistant properties by incorporating recombinant-Hirudin (rHir) as well as Ciprofloxacin (Cipro) and assess the release from this new bioengineered vascular graft in vivo (CCA) in a canine model. For this, test conduits (BioSpun-VAD or Hemashield) were used.

Upon initial observation, the Hemashield conduits, were grossly flat, suggesting complete conduit occlusion. In contrast, the BioSpun-VAD conduits were patent, with the wall fully distended. Similar to the 60 day explants, there was increased capsular formation around the Hemashield conduits as compared to the BioSpun-VAD conduits. Histology was performed on patent specimens that were retrieved at 30 and 60 days following conduit implantation. The histology and immunohistochemistry results demonstrate that the healing that takes place on the BioSpun-VAD conduits is unique and different from other biomaterials implanted within the vasculature.

**Future Studies:** Beyond this contract, future development of the BioSpun-VAD conduit would require additional implantations at 60 days in order to increase the power of the study as well as longer implantation periods (6 months/2 years). With these promising results, our next goal outside the contract is to seek out a strategic partner to further develop this new VAD product.

### Localized Gene Delivery from Implantable Arterial Devices

The specific objectives for our STTR Phase II study were to: 1) synthesize control and MARCKS siRNA-loaded nanofibrous polyester materials, 2) characterize physical properties, 3) examine siRNA release and cellular uptake, 4) assess MARCKS siRNA knockdown of targeted cellular mRNA and protein expression in rat and human vascular smooth muscle cells, 5) implant control and MARCKS siRNA-loaded nanofibrous materials in rat carotid artery denudation model and 6) evaluate explanted arterial segments using histological, morphometric and molecular biology techniques. This research study is ongoing. Our study using surgical balloon EC/CCA denudation and siMARKS-loaded nPET-PBT implants (*Figure 7*) will be completed within the next couple of months, followed by histology and immunohistochemistry analysis.

### Neuropeptides in Diabetic Wound Healing

One of the most debilitating complications of both Type I and Type II diabetes is the development of chronic non-healing foot ulcerations leading to severe morbidity and mortality. The cause of impaired wound healing in diabetes is multi-factorial and includes vascular, neurologic and inflammatory alterations. Impaired diabetic wound healing exists exclusively in skin areas that are affected by peripheral neuropathy and there is growing evidence that cutaneous peripheral nerves regulate immune and cytokine response via mediators such as the neuropeptides substance P and neuropeptide Y.

Frank W. LoGerfo, MD

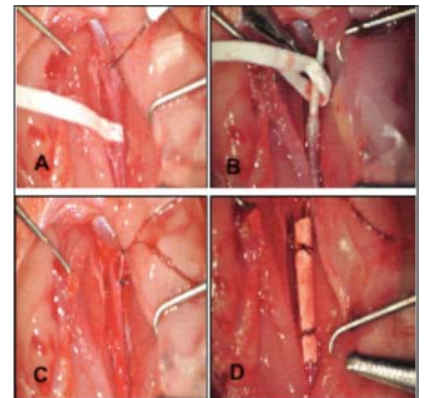


Figure 7

**Frank W. LoGerfo, MD**

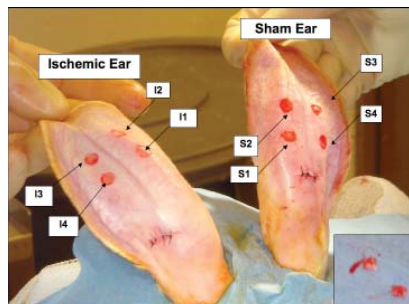


Figure 8

Our lab has shown that these neuropeptides not only control cytokine release from immune cells but also affect endothelial cell function. A previous study from our lab that employed the rabbit ear wound healing model has shown that diabetes affects the focused inflammatory cytokine response to injury and dysregulated neuropeptide gene expression but this study did not directly assess the role of vascular ischemia and neuropathy, two of the major contributing factors of diabetes-associated complications.

Additionally, we have developed a neuroischemic model of wound healing to understand the phenotypic changes and evaluate changes in gene and protein expression of neuropeptides, their receptors and inflammatory cytokines (Figure 8). In New Zealand White rabbits with alloxan-induced diabetes, one ear served as a sham and in the other ear we generated ischemia (ligation of the central and rostral arteries), denervation (resection of central and rostral nerves) or neuroischemia (ischemia along with resection of the corresponding nerves) followed by four 6mm punch biopsy wounds in each ear. Animals were euthanized ten days after wounding.

Our results indicate that non-diabetic sham and ischemic wounds healed better than diabetic sham and ischemic wounds, with no such difference in neuroischemic and denervation wounds. Pre-injury, SP and NPY protein expression was lower and DPPIV, the enzyme that converts NPY into its angiogenic form, IL-8, CXCR1 which is the IL-8 receptor and IL-6 was higher in diabetes. Post-injury, the fold change over baseline in gene expression of SP, NEP, the enzyme that breaks down Substance P, NPY and DPPIV was lower in the neuroischemic wounds in diabetes. SP protein expression was decreased and NPY2R was increased in the neuroischemic diabetic wounds. Moreover we see that the number of infiltrating immune cells are significantly lower in diabetic wounds irrespective of the type of surgical intervention.

These results using a novel and relevant diabetic animal model, suggest that in diabetes, reduced expression of neuropeptides, a chronic-proinflammatory state and failure to mount an acute post-injury inflammatory response contribute to wound healing impairment.

We used this rabbit model to test the therapeutic efficacy of temperature sensitive hydrogel from Lynntech Inc., through a formal STTR award we have with them. The hydrogels have thermoresponsive and biodegradable properties, with the added property of strong adhesion to cell surfaces. These are composed of PNIPAAm and poly Lactic acid-co-glycolic acid (PLGA) functionalized with GGGRGDS polypeptide units. The biodegradable blocks are incorporated into the thermoresponsive blocks to vary the degradability, biocompatibility, hydrophilicity, and mechanical properties.

The incorporation of PNIPAAm provides the hydrogels with thermoresponsive properties. Also, the hydrophobic behavior, which leads to chain collapse and aggregation of the PNIPAAm blocks at physiological temperatures additionally, provides enhanced exudate removal and entrapment to help keep the wound site fairly clean. The results from this study showed a significant improvement in the diabetic neuroischemic wounds treated with the active hydrogel compared to the control hydrogel. Data also suggest that the active hydrogel increases immune cell infiltration in these wounds. Based on these data, we have applied for a Phase II award.

We are also using this wounding model in collaboration with investigators at the Wyss Institute at Harvard to develop new therapeutics for wound treatment. With this group the goal is to design bioengineered treatment modali-

ties for treatment of diabetic wounds. Currently we are awaiting a decision on a R24-NIH-NIDDK award in collaboration the Wyss investigators.

The current in vitro project is directed towards understanding the effect of neuropeptides on fibroblasts exposed to hyperglycemia more specifically on the migration and proliferation of fibroblasts. Our results show that compared to 5 mM, 30 mM glucose significantly decreases migration of Adult Dermal Fibroblasts (ADFB) at 12 and 24 hr ( $p < .01$ , and  $p < .001$ , respectively). Co-treatment with 100 nM SP to 30 mM D-glucose increased the migration of ADFB though not to the level of normoglycemic (5 mM glucose) pattern. Whereas, the addition of 100 nM SP to 5 mM glucose decreased migration of ADFB at 12 hr and 24 hr, suggesting a homeostatic role of SP. Although not significant, addition of 100 nM NPY to 30 mM D-glucose showed an increased trend in migration of ADFB. No statistically significant changes were observed with the addition of 100 nM NPY to 5 mM D-glucose.

Compared to 5 mM glucose, 30 mM glucose significantly decreased proliferation of ADFB by days 4 and 5. The addition of 100 nM SP to 30 mM of D-glucose increased proliferation of ADFB at days 3, 4, and 5 ( $p < .001$ ). Similarly, the addition of 100 nM NPY also increased proliferation of ADFB at days 3, 4 and 5 ( $p < .01$ ,  $p < .001$ , and  $p < .001$ , respectively). We also saw that hyperglycemia increases the protein expression of NEP, the enzyme that breaks down SP without affecting the receptor of SP, NK-1R in ADFB. Additionally, hyperglycemia decreases the activity of MMP2 and MMP9 in ADFB, which cannot be restored by SP.

These results suggest that SP has its effect on fibroblast migration via mechanisms other than affecting the activity of MMP2 or MMP9. Efforts are ongoing to further decipher the mechanisms by which SP and NPY restore the function of ADFBs exposed to hyperglycemia.

### Neuropeptides in Cardiac Complications

We are also looking at the expression of neuropeptides in human right atrial tissue and human saphenous veins of diabetic and non-diabetic patients. Our published results suggest that gene and protein expression of SP its receptor NK1R and, NPY receptors, NPY2R and NPY5R, is significantly reduced whereas that of NPY and NPY1R are unchanged in the right atrium of diabetic patients compared to non-diabetic patients. The results from saphenous vein are summarized in *Table 1* and indicate that the expression profile is the opposite in saphenous veins compared to atrial muscle of diabetic patients.

Table 1 Gene and protein expression of neuropeptides and their receptors in the saphenous veins of diabetic patients as compared to non-diabetic patients								
Target	SP	NK1R	NEP	NPY	NPY1R	NPY2R	NPY5R	CGRP
N=23	Fold Change in Diabetic Patients Compared to Non-Diabetic Patients in Human Saphenous Vein (Mean±SEM)							
Gene Expression	5.46±1.90	1.66±0.55	0.69±0.18	7.70±4.12	2.41±1.13	14.3±8.84	7.60±2.95	3.06±1.33
P-Values	0.01	0.1	0.03	0.04	0.09	0.05	0.01	0.05
Protein Expression	2.70±0.99	0.59±0.15	0	1.31±0.10	1.21±0.41	1.38±0.18	1.13±0.25	0.99±0.27
P-Values	0.06	0.15	0	0.1	0.41	0.18	0.25	0.27

Frank W. LoGerfo, MD

**Frank W. LoGerfo, MD**

**Individual Accomplishments**

Frank W. LoGerfo, MD

- Received University of Rochester School of Medicine: Alumni Service Award in Oct 2011, which honors a graduate who has furthered the interests of the School and the Alumni Council through significant support, commitment and service to the school.
- Reviewed grants for the NIH BTTS Study section (ad hoc)

Christoph Nabzdyk, MD

- Young Investigator award (2nd place) at the European Symposium of Vascular Biomaterials Meeting, May 2011, Strasbourg, France. Christoph's presentation was titled: Composite Electrospun Polyethylene Terephthalate Materials for Arterial Bypass Grafting.

Julia Glaser, BA

- Based on her work during her Sarnoff Fellowship in our lab, Julia received the Lifeline Foundation fellowship.

**Invited Presentations**

Frank W. LoGerfo, MD

"Vein graft genomics." Society for Vascular Surgery Annual Meeting Special Lecture. Chicago, IL, April 2011.

"The biology of vascular injury." New England Society for Vascular Surgery Annual Meeting, Robert R. Linton Distinguished Address. Providence, RI. September, 2011.

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**Teaching, Training, and Education**

**Undergraduate Courses**

Frank W. LoGerfo, MD

- 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.
- Tutorial for HMS 3 students during their surgical clerkship. Four students, 1 hour per week.
- Lectures to Primary Clinical Elective students: Four per year.

William J. von Liebig Research Training in Vascular Surgery  
Program Director: Frank W. LoGerfo, MD

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 athero-

genesis, IH, 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 2011, five students were enrolled in the program.

**Mentor:** Leena Pradhan-Nabzdyk, PhD

**Student:** Hunter S. Olliver-Allen, Indiana University School of Medicine  
*siRNA Transfection from electrospun PET*

**Mentor:** Marc Schermerhorn, MD

**Student:** Patric Liang, Albert Einstein College of Medicine of Yeshiva University  
*Operative treatment trends for renal artery stenosis in the United States: surgical revascularization vs percutaneous transluminal angioplasty and stenting*

**Mentor:** Bruce Furie, MD Department of Medicine, Beth Israel Deaconess Medical Center; Professor of Medicine, Harvard Medical School

**Student:** Nnaemeka M. Ndubisi, Brody School of Medicine at Eastern Carolina University  
*Protein Disulfide Isomerase's Exocytotic Pathway: Are SNARE Proteins involved?*

**Mentor:** Richard N. Mitchell, MD, PhD Department of Pathology, Brigham and Women's Hospital

**Student:** Nyssa F. Fox, Medical University of South Carolina  
*Assays for smooth muscle cell migration as a model for graft vascular disease*

**Mentor:** Jim Lederer, MD, Department of Surgery, Brigham and Women's Hospital; Associate Professor of Surgery, Harvard Medical School

**Student:** David Huie, Case Western Reserve University School of Medicine  
*Comparative Studies in Burn Injury and Sepsis*

#### Research Laboratory Students

**Mentors:** Frank W. LoGerfo, MD and Leena Pradhan- Nabzdyk, PhD

**Gener Augustin** is currently a MSIII at University of Rochester School of Medicine and Dentistry. She worked as a University of Rochester Clinical Translational Research Fellow from June 2010 to May 2011. She worked under the mentorship of Dr. Pradhan- Nabzdyk and her project focused on understanding the effects of hyperglycemia and neuropeptides on fibroblast function. This work will be presented at the Academic Surgical Congress in 2012, Las Vegas NV.

**Julia Glaser** is currently a MSIV at Dartmouth School of Medicine. She worked as a Sarnoff Cardiovascular Research Foundation Fellow from June 2010-May 2011 and as a Lifeline Foundation Fellow from September 2011 to October 2011. Under Dr. LoGerfo's and Dr. Pradhan's mentorship, Julia worked on the project that focused on localized gene silencing in a rat model of intimal hyperplasia. This work was presented at the American College of Surgeons Clinical Congress, October 2011, San Francisco, CA.

**Allisandra Mowles** is currently a senior at Eastern Nazarene College. She worked on her senior thesis under the mentorship of Dr. Pradhan from May 2011 to present. Her work is focused on understanding the effect of hyperglycemia on the neuropeptide pathways in fibroblasts. She is expected to matricu-

**Frank W. LoGerfo, MD**



**Frank W. LoGerfo, MD**

late into a PhD program for fall of 2012.

**Maggie Chun** is a graduate of Mount Holyoke and a Pre-Med student. Although she is a senior Research Assistant, her role in the lab is more of graduate student. Maggie has been working on the Mechanisms of Prosthetic Graft Failure project. She recently presented her work at the New England Society of Vascular Surgeons. She is also assisting in the vein graft and the rabbit wound healing projects. Maggie will matriculate in the New York College of Osteopathic Medicine in May of 2012.

**Natasha Resendes** is a graduate of Smith College and also a Pre-Med student. Natasha is primarily helping with the coordination of the T-32 training program. She is also conducting bench research on the Neuropeptide and Mechanisms of Graft Failure project.

**Priya Patel** completed is a graduate of Rutgers University and will matriculate into Robert Wood Johnson Medical School in August of 2012. She joined the lab in December of 2011 and is working on the vein graft failure project.

**Graduate School and Graduate Medical Courses**

Frank W. LoGerfo, MD

***NIH T-32 Training Program***

*Harvard-Longwood Research Training Program in Vascular Surgery (T32):  
Director: Frank W. LoGerfo, MD*

This training program is designed to provide two years of intense basic research training in vascular surgery for academic clinicians. The training program in its sixteenth year, addresses the absence of adequate research training for vascular surgeons as it applies to specific areas of clinical disease. 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, IH, 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 Postdoctoral 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.

## Current Trainee

## General Surgery Training Program

Frank W. LoGerfo, MD

*Second Year (matriculated in the program: July 2010)*Barry Gibney, DO  
Rodney Bensley, MDPenn State Hershey Medical Center  
BIDMC*First Year (matriculated in the program: July 2011)*Alexander T. Hawkins  
Andy M. Lee, MD, MS  
Ruby C. Lo, MD  
Christine R. Mauro, MD  
Wande B. Pratt, MD, MPHMassachusetts General Hospital  
BIDMC  
BIDMC  
BIDMC  
Washington University School of  
Medicine in St. Louis

Five trainees graduated from the program in 2011:

## Trainee General Surgery

## Training Program

Nathan J. Aranson, MD  
Antonia J. Henry, MD, MPH  
Binh T. Nguyen, MD  
Clayton Peterson, MD  
Shunsuke Yoshida, MDUniversity of Southern California  
Brigham and Women's Hospital  
University of Texas, Galveston, TX  
BIDMC  
East Carolina University, Brody  
School of Medicine, NC*Laboratory Fellows (2011):*

**Asma Ejaz, PhD** ended her fellowship in 2011. Her project was to investigate the role of neuropeptides in diabetic heart failure. Her work is published in two manuscripts in 2011.

**Shunsuke Yoshida, MD** was a T32 fellow in the lab from 2009 until 2011. His project was to investigate the role of thrombospondin-2 in prosthetic graft failure. His work is published in a manuscript in 2011. He returned to surgical residency as a PGY-3 at the Brody School of Medicine in Greenville, NC.

**Christoph Nadzdyk, MD** was a research fellow from 2010 until 2011. His project was the implantation of siRNA delivery into vascular prosthetic grafts. His work is published in a manuscript in 2011. He began surgical residency at Tufts Medical Center in Boston, MA.

**Nathan Aranson, MD** was a T32 research fellow in the lab from Jan 2011-May 2011. His project involved electroporation of cells for acceleration of wound healing. He returned to surgical residency as a PGY-4 at University of Southern California.

**Wande B. Pratt, MD** is in his first year of his T32 fellowship. Prior to his fellowship, he completed his PGY-3 year at Washington University in Saint Louis School of Medicine. His project is to determine the in vivo effectiveness of a delivery system employing siRNA technology to silence genes responsible for intimal hyperplasia in a small animal model.



## Community Outreach Programs

The LoGerfo research laboratory continued its history of participation in Explorations program run by Harvard Medical School Office of Diversity and Community Partnership. Select 6th, 7th and 8th grade students from Boston and Cambridge public middle schools are hosted by Harvard faculty and research associates for a day of presentations, panel discussions about educational paths, and the pairing of individual students with researchers for laboratory activities

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## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Ejaz A, LoGerfo FW, Khabbaz K, Pradhan L. Expression of neuropeptide y, substance p, and their receptors in the right atrium of diabetic patients. Clin Transl Sci 2011;4(5):346-50.

Jain M, LoGerfo FW, Guthrie P, Pradhan L. Effect of hyperglycemia and neuropeptides on interleukin-8 expression and angiogenesis in dermal microvascular endothelial cells. J Vasc Surg 2011;53(6):1654-60.e2.

Nabzdyk CS, Chun M, Pradhan L, LoGerfo FW. High throughput RNAi assay optimization using adherent cell cytometry. J Transl Med 2011;9:48.

Pradhan L, Cai X, Wu S, Andersen ND, Martin M, Malek J, Guthrie P, Veves A, LoGerfo FW. Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing. J Surg Res 2011;167(2):336-42.

Yoshida S, Nabzdyk CS, Pradhan L, LoGerfo FW. Thrombospondin-2 gene silencing in human aortic smooth muscle cells improves cell attachment. J Am Coll Surg 2011;213(5):668-76.

### Other Peer-Reviewed Publications

#### Reviews

Ejaz A, LoGerfo FW, Pradhan L. Diabetic neuropathy and heart failure: role of neuropeptides. Expert Rev Mol Med 2011;13:e26.

### Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

Chun M, Nabzdyk CS, Glaser JD, Pathan S, Phaneuf M, Pradhan L, LoGerfo FW. siRNA dip-coating of prosthetic arterial graft materials. New England Society of Vascular Surgery Meeting, September 2011, Providence, Rhode Island

Ejaz A, Pradhan L, LoGerfo FW. Effect of diabetes on the expression of neuropeptides, their receptors, and associated enzymes in saphenous Vein. Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions, April 29, 2011, Chicago, IL.

Glaser JD, Nabzdyk CS, Contreras MA, Pradhan L, LoGerfo FW. Localized gene silencing in a rat model of intimal hyperplasia. Podium presentation at 97th Annual American College of Surgeon (ACS) Clinical Congress, October 24-27, 2011, San Francisco, CA.

Korepta L, Pradhan L, Landis EA, Essayagh S, Ferran CJ, **LoGerfo FW**, “MARCKS and p27kip1 in smooth muscle cell signaling: implications in intimal hyperplasia”, American Surgical Congress Annual Conference February 1-3, 2011, Huntington Beach, CA

Nabzdyk CS, Chun M, Phaneuf MD, Pathan SG, You J, Pradhan L, **LoGerfo FW**. siRNA-coating and release from electrospun polyethylene terephthalate materials with various surface properties. Podium presentation, Society of Vascular Surgery (SVS) Research Initiatives Conference, and poster at Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions, April 2011, Chicago, Illinois

Nabzdyk CS, Glaser JD, Chun M, Pathan S, Phaneuf M, You JO, Pradhan L, **LoGerfo FW**. Composite electrospun polyethylene terephthalate materials for arterial bypass grafting. Podium presentation, European Symposium of Vascular Biomaterials Meeting, May 2011, Strasbourg, France

Yoshida S, Nabzdyk CS, Chun MC, Pradhan L, **LoGerfo FW**. ‘The Effects of thrombospondin-2 silencing in human aortic smooth muscle cells in-vitro’. American Surgical Congress Annual Conference on February 1, 2011, Huntington Beach, CA

Huang ZS, Malek JY, Bhasin M, Contreras MA, **LoGerfo FW**. Differential Temporal Gene Expression in Selectively Isolated Vein Graft Endothelial and Smooth Muscle Cells Using Laser Capture Microdissection- 5th Annual Academic Surgical Congress February 2010, San Antonio, TX.

Huang ZS, Malek JY, Bhasin M, Contreras MA, **LoGerfo FW**. Selective Isolation of Vein Graft Endothelial and Smooth Muscle Cells Using Laser Capture Microdissection for Microarray Gene Analysis. North American Vascular Biology (NAVBO at Experimental Biology), 2009, New Orleans.

Huang ZS, Malek JY, Bhasin M, Contreras MA, **LoGerfo FW**. Temporal Genetic Profile of Vein Graft Endothelial and Smooth Muscle Cells Isolated by Laser Capture Microdissection. Arteriosclerosis, Thrombosis and Vascular Biology April 2010, San Francisco, CA - Poster presentation.

Jain M, Guthrie P, Pradhan L, **LoGerfo FW**. Diabetic Foot Ulceration: The Role of Interleukin-8 in the Neuropeptide Y Pathway Academic Surgical Congress – Association for Academic Surgery February 2010, San Antonio, TX.

Jain M, Pradhan L, **LoGerfo FW**. Impaired Wound Healing: Increasing the Transfection of Endothelial Cells with cDNA to a Key Inflammatory Neuropeptide Receptor via Electroporation Arteriosclerosis, Thrombosis, and Vascular Biology 2010 Scientific Sessions, April 8-10 2010, San Francisco, CA.

Jain M, Pradhan L, Wu SQ, **LoGerfo FW**. Diabetic Foot Ulceration: Modeling Endothelial Cell Proliferation with Key Immunomodulator Treatments Massachusetts Medical Society – 4th Annual Research Symposium March 2009, Waltham, MA.

Korepta L, Pradhan L, Landis EA, Essayagh S, Ferran CJ, **LoGerfo FW**, “MARCKS and p27kip1 In Smooth Muscle Cell Signaling: Implications In Intimal Hyperplasia”, American Surgical Congress Annual Conference February 1-3, 2011, Huntington Beach, CA.

Korepta L, Martin MC, Guthrie P, Pradhan L, Ferran CJ, **LoGerfo FW**. “A Possible Role for MAP Kinases, MARCKS Interaction in the Development of Intimal Hyperplasia and Graft Failure.” September 23-26, 2010 New England Society for Vascular Surgery Annual Meeting, Rockport, ME.

**Frank W. LoGerfo, MD**

Nabzdyk CS, Chun M, Phaneuf MD, Pathan SG, You J, Pradhan L, **LoGerfo FW**. siRNA-Coating and Release from Electrospun Polyethylene Terephthalate Materials with Various Surface Properties. Podium presentation, Society of Vascular Surgery (SVS) Research Initiatives Conference, and poster at Arteriosclerosis, Thrombosis and Vascular Biology Scientific Sessions, April 2011, Chicago, Illinois.

Nabzdyk CS, Glaser JD, Chun M, Pathan S, Phaneuf M, You JO, Pradhan L, **LoGerfo FW**. Composite Electrospun Polyethylene Terephthalate Materials for Arterial Bypass Grafting. Podium presentation, European Symposium of Vascular Biomaterials Meeting, May 2011, Strasbourg, France.

Pradhan L, Wu S, Guthrie P, Martin MC, Kuchibhotla S, Malek JY, Andersen ND, **LoGerfo FW**, Veves A. Neuropathic and Ischemic In Vivo Models of Diabetic Wound Healing. American Diabetes Association, 68th Annual Scientific Sessions. June 6-11, 2009, New Orleans, LA.

Yoshida S, Nabzdyk CS, Chun MC, Pradhan L, **LoGerfo FW**. 'The Effects of Thrombospondin-2 Silencing in Human Aortic Smooth Muscle Cells In-Vitro'. American Surgical Congress Annual Conference on February 1, 2011, Huntington Beach, CA.

## Research Focus

My clinical research group has an active interest in outcomes research on a local and national level. Our main interest is to compare outcomes after open surgery and endovascular surgery for a variety of vascular diseases, including aortic aneurysm, carotid disease, and lower extremity arterial disease, to help guide patient selection for each type of procedure. 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 have also recently purchased data from statewide databases that also include procedures performed without an admission to the hospital that may be missed by other administrative databases with only inpatient admissions.

Since BIDMC is a participating hospital for data collection, we have access to the American College of Surgeons National Surgical Quality Improvement Program data. These data consist of detailed and surgery-specific preoperative, intraoperative, and 30-day postoperative information with a specific risk adjustment variable for mortality and morbidity. Open surgical vascular operations as well as major endovascular operations such as AAA repair, TAA/A repair, and ruptured aneurysm repair are collected in this database and thus we can perform detailed evaluations of surgical outcomes as well as comparative analysis between open and endovascular procedures.

BIDMC has recently joined the Vascular Study Group of New England (VSGNE), and in doing so we now have access to their regional, multi-institutional database. This registry consists of prospectively collected clinical data concerning open and endovascular treatment of carotid, aortic aneurysmal, and lower extremity peripheral arterial disease. Follow-up data is available to one year. Data elements include not only baseline patient demographics but also detailed intraoperative and perioperative information, making this a veritable wealth of information from which we can derive risk factors and outcome predictors. I sit on the executive committee and research advisory committee for the VSGNE. The VSGNE has now been adopted nationally by the Society for Vascular Surgery (SVS) as the Vascular Quality Initiative (VQI) and will combine data from regional registries such as VSGNE. I serve on the executive committee for the SVS VQI, as well.

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 from Part A files, but with access to Part B files we can adjust for pre-existing conditions based on diagnoses made prior to the index admission. The use of part B files also allows the extra specificity and accuracy from CPT codes submitted by the treating physician, rather than ICD-9 codes submitted by the hospital coders. We also have unique identifiers allowing us to track long term readmission, re-intervention, and survival of patients after open or endovascular treatment. Collaboration with James O'Malley, PhD, from the Department of Health Policy at Harvard Medical School allows us to perform detailed statistical analyses, including propensity score matching of patients undergoing open or endovascular surgery.



**Marc L. Schermerhorn, MD**

Associate Professor of Surgery  
Chief, Division of Vascular and Endovascular Surgery

### Group Members

Rodney Bensley, MD  
Ruby C. Lo, MD  
Rob Hurks, MD  
Jeremy Darling, BA

**Marc L. Schermerhorn, MD**

We also have our own database within our institution's vascular division with all vascular procedures captured prospectively. This allows tailored evaluation of comorbidities and various outcomes with physician chart review and angiographic review. This allows appropriate risk adjustment for various factors associated with choice of a given treatment strategy.

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**Research Support**

“Long-term outcomes of open versus endovascular AAA repair”

NIH/NHLBI, R01HL105453-01

12/15/10-11/20/2013

Contact PI and Project Leader: Bruce Landon, MD (HSPH)

PI: Marc L. Schermerhorn, MD

“Carotid revascularization endarterectomy vs. stent (CREST) trial”

NIH/NINDS

9/15/2003-12/31/2011

PI: Marc L. Schermerhorn, MD

“Evaluation of the GORE conformable TAG thoracic endoprosthesis for treatment of acute complicated type B aortic dissection” - Clinical Trial

TAG 08-01

10/22/09-10/21/2011

PI: Marc L. Schermerhorn, MD

Clinical Trial

Akaza Research, Akaza Data Management Project

12/1/2005-11/30/2011

I: Marc L. Schermerhorn, MD

“A Boston Scientific study of the ERIC nitinol stent system in the treatment of atherosclerotic lesion in iliac arteries”

Boston Scientific Corporation, ORION Clinical Trial

4/26/2010-4/25/2012

I: Marc L. Schermerhorn, MD

“Evaluation of the clinical performance of the valiant thoracic stent graft system for the endovascular treatment of blunt thoracic aortic injuries”

Metronic Vascular, Incorporated, IP#117

6/10/2010-6/9/2012

I: Marc L. Schermerhorn, MD

“Clinical evaluation of the GORE TAG endoprosthesis in the primary treatment of descending thoracic aortic aneurysms”

W.L. Gore & Associates, Inc., TAG 05-02

9/18/2007-9/17/2012

I: Marc L. Schermerhorn, MD

“U.S. study for evaluating endovascular treatments of lesions in the superficial femoral artery and proximal popliteal by using the protégé everflex nitinol stent system II”

Ev3 Endovascular, Inc., DURABILITY II

3/14/2008-3/13/2013

I: Marc L. Schermerhorn, MD

**Marc L. Schermerhorn, MD**

“Clinical evaluation plan for advanced 3D tools for vascular surgery” –  
Clinical Trial  
Phillips Healthcare, Clinical Trial  
5/4/2011-5/3/2013  
PI: Marc L. Schermerhorn, MD

“Evaluation of the GORE TAG thoracic endoprosthesis – 45 mm for the  
primary treatment of aneurysms of the descending thoracic aorta”  
W.L. Gore & Associates, Inc., TAG 06-02  
1/13/2009-1/12/2014  
I: Marc L. Schermerhorn, MD

“Stenting of the superficial femoral and proximal popliteal arteries with  
the Boston Scientific INNOVA self-expanding bare metal stent system” –  
Clinical Trial  
Boston Scientific Corporation, INNOVA  
4/28/2011-4/27/2014  
I: Marc L. Schermerhorn, MD

“GORE Flow reversal system extension study for ongoing collection of patient  
outcomes” – Clinical Trial  
W.L. Gore & Associates, Inc., FREEDOM  
5/6/2011-5/5/2016  
I: Marc L. Schermerhorn, MD

“Post approval study evaluating the long term safety and effectiveness of the  
endurant stent graft system” – Clinical Trial  
ENGAGE PAS  
8/26/2011-8/25/2016  
I: Marc L. Schermerhorn, MD

“Iliac artery treatment with the Invatec scuba cobalt chromium stent” –  
Clinical Trial  
Invatec, Inc., INTENSE  
8/12/2009-8/11/2011  
I: Marc L. Schermerhorn, MD

“Outcomes of stenting with Distal protection” – Clinical Trial  
Cordis Corporation, P06-3603  
7/27/2007-7/26/2011  
I: Marc L. Schermerhorn, MD

Clinical Trial  
Macquet Cardiovascular, LLC, FINEST  
6/7/2010-6/6/2011  
I: Marc L. Schermerhorn, MD

“GORE embolic filter in carotid stenting for high risk surgical subjects trial  
protocol GEF-06-08 Rev 1” – Clinical Trial  
W.L. Gore & Associates, Inc., GORE-EMBOLDEN  
5/7/2009-5/6/2011  
I: Marc L. Schermerhorn, MD

“Carotid wall stent monorail endoprosthesis FilterWire EZ embolic protection  
system” – Clinical Trial  
Boston Scientific Corporation, CABANA  
4/30/2009-4/29/2011  
I: Marc L. Schermerhorn, MD

Marc L. Schermerhorn, MD

“Carotid stenting for high surgical risk patients” – Clinical Trial  
Abbott Vascular, Inc., CHOICE, 06-717  
10/9/2007-10/8/2009  
I: Marc L. Schermerhorn, MD

#### Applications Submitted and Pending Review/Funding

“Laparotomy related complications in Medicare beneficiaries”  
NIH F32 (Mentor Marc L. Schermerhorn, MD)  
PI: Tommy Curran, MD

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### Accomplishments in the Past Year

#### Research Progress

##### AAA Repair

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 may 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.

With the Medicare database, Dr. Giles and I published a manuscript in the *Journal of the American College of Surgeons* demonstrating the differences between in-hospital mortality, 30-day mortality, and the combined 30-day and in-hospital mortality. Administrative databases often have access to only in-hospital data, which may bias in favor of endovascular repair given the shorter length of stay. We found that the absolute difference in mortality remained constant with each definition. However, the relative benefit of EVAR is overestimated when using odds ratios or relative risk with in-hospital mortality. We also showed that the period of increased risk of death after EVAR and open repair persists for at least 4 months.

We evaluated 30 day mortality and late survival after reintervention and readmission after EVAR and open AAA repair and presented our results at the plenary session of the SVS and published this in *JVS*.

We also evaluated the volume outcome effect at the hospital level for EVAR and open AAA repair and I presented this at the New England Vascular meeting and it was published in *Circulation*. We found that while there is a relatively low volume threshold above which centers demonstrate adequate outcomes with EVAR, there is a continued improvement in outcome with increasing volume of open AAA repair such that the busiest centers have the best results. This may impact referral patterns and supports the concept of regionalization for open AAA repair.

Dr. Bensley and I have recently submitted a manuscript to the American Surgical Association Annual Meeting and to the *Annals of Surgery* demonstrating age related trends in overall short-term AAA related mortality and AAA rupture. We found that patients <75 had a decrease in elective AAA repair and at the same time a decrease in rupture rate. However, in those >80 there was an increase in elective repair rate as well a reduction in rupture rate that was greater than that seen in the younger age group. We hypothesize



that the overall incidence of AAA may be decreasing and that an increase in elective repair in the elderly, likely related to the use of endovascular repair, has caused this greater reduction in elderly ruptures and short-term mortality.

Using our institution's experience with EVAR, Dr. Bensley showed that ultrasound guided percutaneous access for EVAR is a safe alternative to cut down with a very high technical success rate that percutaneous failure is predicted by small vessel size. Percutaneous access has a high success rate as well as decreased wound complications when compared to cut down access. Contrary to prior studies identifying that sheath size was a predictor of percutaneous failure, he has shown that it is actually access vessel size that predicts percutaneous failure. This data was presented at the NESVS annual meeting and has been accepted for publication in *JVS*.

In a similar study, Dr. Hurks examined the benefit of percutaneous access in the ACS NSQIP database. He has shown that percutaneous access is increasing nationally, however, contrary to what our institutional data has shown, the benefits of percutaneous access are not being realized nationally. In fact, patients with percutaneous access were found to have higher rates of DVT. This manuscript is under review for publication in the *European Journal of Vascular and Endovascular Therapy*.

Dr. Hurks has also used the NSQIP database to examine cardiovascular outcomes after AAA repair. He showed that traditional risk factors do not predict myocardial infarction in patients undergoing AAA repair. Interestingly, he found that nonwhite race showed an increased risk for MI, which could reflect differences in medical management or unequal access to care. His results suggest that risk factors for postoperative MI are different in this patient group, urging the need for further research and better risk assessment. This will be presented at the PVSS winter meeting and submitted for publication in *JVS*.

Using the VSGNE to study gender differences in AAA management and outcomes, Dr. Lo has found that women are undergoing EVAR at higher rates than previously reported, although these proportions are still lower than for men. Additionally, women present at an older age, rupture at smaller aortic diameters, and undergo elective repair at smaller diameters. Thirty-day mortality is higher for women after open repair but is comparable after EVAR. This abstract has been submitted for presentation at the SVS annual meeting.

#### Multiple specialties perform AAA repair

Dr. Hurks has used the NIS to look at how the proportions of specialties performing AAA repair has changed after the introduction of EVAR. He has shown that vascular surgeons are performing an increasing majority of AAA repairs driven by the increased utilization of EVAR, and that the majority of repairs are performed by high volume vascular surgeons at medium and high volume hospitals. He also noted that there were differences in mortality associated with specialty, surgeon volume, and hospital volume. This abstract has been submitted for presentation at the SVS annual meeting.

Dr. Sachs evaluated the change in rate of EVAR and open AAA repair in teaching and non-teaching hospitals over time as well as the ACGME resident and fellow exposure to these procedures and found that general surgery residents now get minimal exposure to aortic aneurysm repair while fellows exposure to open repair has decreased but substantially increased for EVAR. This was presented at NESVS and published in *JVS*.

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Thoracic Aneurysm and Dissection

Using the NSQIP data, Dr. Bensley has looked at the stroke risk of TEVAR with and without coverage of the left subclavian artery. He also examined if a left subclavian artery revascularization procedure affects this risk. He found an increased risk of stroke with coverage of the left subclavian artery and that a subclavian artery revascularization procedure did not decrease this risk if performed concomitantly, at a separate setting, or not at all. This data was presented at the annual meeting of the Society for Clinical Vascular Surgery and is under review for publication in the *Annals of Thoracic Surgery*.

Using the same database, Dr. Bensley also examined outcomes after open TAAA repair in NSQIP hospitals. While TAAA repair remains uncommon, he found that the 30-day mortality rate was half that previously reported with the NIS (national administrative database) and approaching those reported at high volume single institutions. This was presented at the annual meeting of the SVS and the manuscript will be submitted to *Annals of Vascular Surgery* for consideration of publication.

Laparotomy related complications after laparotomy and laparoscopy

Using the Medicare database, Dr. Bensley is analyzing the rate of adhesion related postoperative complications after various abdominal operations. All abdominal operations were reviewed and grouped according to invasiveness into the abdominal and pelvic cavities. Outcomes analyzed were incisional hernia repairs, operative complications (bowel resection and lysis of adhesions), and nonoperative admissions for bowel obstruction. He found that major abdominal operations carried the highest risk of adhesion related complications and that laparoscopic operations carried the lowest risk. Abdominal wall hernia related complications carried the highest risk for incisional hernia complications. The risk for complications was noted to extend well beyond the perioperative period. This abstract has been submitted to the American Surgical Association annual meeting and will be submitted to the *Annals of Surgery* for consideration for publication.

Lower Extremity Revascularization

Dr. Lo used the NIS to show that in patients with lower extremity PAD, women present with more advanced disease, at an older age, and are more likely to be treated with angioplasty than surgical bypass. Though women experience higher in-hospital mortality, amputation rates are comparable and have continued to trend downwards for both men and women. Furthermore, the NIS shows a downward trend in the rates of endovascular lower extremity revascularization but subsequent analysis of state data suggests that rather than an overall decrease in these procedures, more are being performed in an outpatient setting. This has been accepted for presentation at the SCVS annual meeting.

I was local PI for the Zilver PTX trial of paclitaxel coated SFA stents published in CCI showing improved patency with the drug coated stent.

Carotid Revascularization

Dr. Yoshida used the BIDMC vascular database to examine outcomes after CEA and CAS after stratification by high risk and symptom status. He found that current CMS high-risk CEA criteria place patients at an increased risk

for adverse events following CAS. This was presented at the annual meeting of the NESVS and will be submitted to JVS for consideration of publication.

Dr. Hurks has used the state inpatient databases to examine the effect of the Present on Admission variable on outcomes assessment after CEA and CAS. It is difficult to accurately determine symptoms status and outcomes after CEA and CAS using administrative data as strokes can be coded with diagnosis codes or with specific postoperative complication codes. The use of the POA indicator will allow us to more accurately identify symptoms present on admission to the hospital and strokes that are actual complications of their procedure. Using the POA indicator, he found that the vast majority of the diagnosis codes and a large part of the complication codes were present on admission. This suggests that these strokes were the indication for their intervention rather than complications. This has been submitted for presentation at the SVS annual meeting.

Using the VSGNE database, Dr. Bensley has looked at gender differences in patient presentation for CEA or CAS. Prior studies have suggested that asymptomatic women benefit less from carotid revascularization. He found that a greater proportion of women undergoing CEA or CAS were asymptomatic compared to men. However, the rates of stroke or death are comparable to randomized trials. This has been submitted for presentation at the SVS annual meeting.

Dr. Bensley has also used the BIDMC vascular database to determine the accuracy of administrative data versus clinical data in outcomes analysis for CEA and CAS. He found that administrative data grossly underestimates the proportion of symptomatic patients, while overestimating the proportion of physiologic high-risk patients. The accuracy of administrative data was a paltry 56% when determining postoperative stroke complications. This has been submitted for presentation at the SVS annual meeting.

Dr. Schermehorn published the results of the Gore flow reversal system for carotid stenting published in CCI as well as the CABANA trial, both demonstrating the efficacy of stent systems for treating carotid stenosis in high risk patients.

### Upcoming Projects

Five abstracts have been accepted to the 2012 SCVS annual meeting. Julia Glaser will be giving an oral presentation on the fate of the contralateral limb after amputation. Dr. Lo will be giving a mini presentation on the results from the NIS on gender differences on the presentation, management, and outcomes of lower extremity peripheral arterial disease. Dr. Siracuse will be giving a mini presentation on prosthetic graft infections involving the femoral artery – a 10-year experience. Dr. Bensley will be presenting an electronic poster on isolated iliac artery aneurysms – management and outcomes in the endovascular era. Patric Liang will be presenting an electronic poster on the rise and fall of renal artery angioplasty and stenting in the United States.

Additionally, 7 abstracts have been submitted to the 2012 SVS annual conference. These include the results from our institution's registry of tibial angioplasties performed for critical limb ischemia as well comparing the accuracy of administrative data versus clinical data in determining symptom status and postoperative complications with CEA and CAS. We also submitted 2 abstracts using the VSGNE to analyze gender differences in carotid revascularization and AAA repair, an abstract examined physician specialty and AAA repair and how the proportions of repairs per specialty have changed

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after the introduction of EVAR. The final abstract involved the use of the SVS registry to identify which high risk factors predict adverse outcome with carotid endarterectomy and stenting.

Proposals submitted to VSGNE's RAC committee include a study looking at the effect of protamine reversal on postoperative complications (specifically bleeding and stroke) and other outcomes following lower extremity bypass and carotid endarterectomy. Another project pending approval is studying gender differences in the potential cardioprotective effects of perioperative beta-blockade during and after major vascular operations.

**Individual Accomplishments**

Rob Hurks, MD

- First place in the Surgery Annual Research Competition for Residents and Postdoctoral Fellows, clinical research category, 2011.

**Invited Presentations**

"The Impact of Endovascular Repair on AAA Management and Outcome." Beth Israel Deaconess Medical Center, Center for Vascular Biology Research Translational Seminar Series. Boston, MA. January 18, 2011.

"The Impact of EVAR on AAA Management and Outcome." Beth Israel Deaconess Medical Center, Anesthesia Grand Rounds. Boston, MA.

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**Teaching, Training, and Education**

**Undergraduate Courses**

William J. von Liebig Research Training in Vascular Surgery  
Program Director: Frank W. LoGerfo, MD

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 atherosclerosis, IH, 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 2011, five students were enrolled in the program.

**Mentor:** Marc Schermerhorn, MD

**Student:** Patric Liang, Albert Einstein College of Medicine of Yeshiva University  
*Operative treatment trends for renal artery stenosis in the United States: surgical revascularization vs percutaneous transluminal angioplasty and stenting*

**Medical Students**

**Patric Liang.** Patric completed 2 months of outcomes research during his summer break. He will be presenting an electronic poster at the SCVS 2012

annual meeting on the rise and fall of renal artery angioplasty and stenting in the United States. He is also completing a project examining the incidence of splenic artery aneurysms and their treatment and outcomes in the NIS.

**Julia Glaser.** Julia completed 1 year in basic science research with Dr. Legerfo and while here took on a project detailing the fate of the contralateral limb after amputation. This work will be presented at the SCVS 2012 annual meeting.

**Lindsey Korepta.** Lindsey is a medical student from Michigan State University. She is currently doing a 2-month research elective with Dr. Schermerhorn studying the outcomes of patients receiving angioplasty vs. surgical bypass as first-line therapy for lower extremity critical limb ischemia using our institution's registry.

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### Graduate School and Graduate Medical Courses

#### Year-long Research Fellow in Vascular Outcomes

**Rob Hurks, MD.** Hurks completed one-year of outcomes research with Dr. Schermerhorn as part of his PhD training. He won first place in the BIDMC resident/fellow research competition. He will be presenting at the 2012 PVSS winter meeting. He has also submitted to abstracts to the SVS 2012 annual meeting. Additionally, he authored a chapter on the management of small AAA. His work has focused on cardiovascular outcomes after AAA repair, the affect the introduction of EVAR has had on the proportion of AAA repairs being performed by various physician specialties, and how the present on admission variable affects outcomes analysis for CEA and CAS. He has also examined percutaneous versus cut down access at a national level using the NSQIP database.

#### Vascular Residents

**Jeff Siracuse, MD.** Jeff will be presenting work looking at prosthetic graft infections at the SCVS annual meeting.

**Elizabeth Turner, MD.** Elizabeth is working on a project using the NIS to look at angioplasty versus open surgical revision in failed lower extremity bypass grafts.

**Prathima Nandivada, MD.** Prathima presented work at the NESVS looking at resident and fellow experiences in the endovascular era.

**Christina Feng, MD.** Christina will be working under Dr. Schermerhorn's mentorship during her 1-month intern research elective. She will be pursuing one of the VSGNE projects currently pending RAC approval.

## Bibliography (January – December 2011)

### Peer-Reviewed Publications in Print or Other Media

#### Research Investigations

Claire DG, Hopkins LN, Mehta M, Kasirajan K, Schermerhorn M, Schonholz C, Kwolek CJ, Eskandari MK, Powell RJ, Ansel GM; EMPiRE Clinical Study Investigators. Neuroprotection during carotid artery stenting using the GORE flow reversal system: 30-day outcomes in the EMPiRE Clinical Study.

Catheter Cardiovasc Interv 2011;77(3):420-9.

Giles KA, Landon BE, O'Malley JA, Cotterill P, Pomposelli F, **Schermerhorn ML**. Thirty-day mortality and late survival with reinterventions and readmissions after open and endovascular aortic aneurysm repair in Medicare beneficiaries. J Vasc Surg 2011;53(1):6-12.

O'Malley AJ, Cotterill P, **Schermerhorn ML**, Landon BE. Improving observational study estimates of treatment effects using joint modeling of selection effects and outcomes: the case of AAA repair. Med Care 2011;49(12):1126-32.

Sachs T, Pomposelli F, Hamdan A, Wyers M, **Schermerhorn M**. Trends in the national outcomes and costs for claudication and limb threatening ischemia: angioplasty vs bypass graft. J Vasc Surg 2011;54(4):1021-31.e1.

Sachs, T, **Schermerhorn ML**, Pomposelli F, Cotterill P, O'Malley J, Landon B. Resident and fellow experiences after the introduction of endovascular repair for abdominal aortic aneurysm. J Vasc Surg 2011;54(3):881-8.

**Schermerhorn ML**, Giles KA, Sachs T, Bensley RP, O'Malley AJ, Cotterill P, Landon BE. Defining perioperative mortality after open and endovascular aortic aneurysm repair in the US Medicare population. J Am Coll Surg 2011;212(3):349-55.

White CJ, Avula SB, Mintz RT, Iskander A, Chervu A, Feldman RL, **Schermerhorn ML**, Woo HH, Hopkins LN. Carotid artery revascularization with distal protection in high surgical risk patients in routine clinical practice: rationale and design of the CABANA safety surveillance program. Catheter Cardiovasc Interv 2011; 79(1):167-73.

#### Research Investigations (Submitted or in Press)

Asopa A, Jidge S, **Schermerhorn ML**, Hess PE, Matyal R, Subramaniam B. Preoperative pulse pressure and major perioperative adverse cardiovascular outcomes after lower extremity vascular bypass surgery. Anesth Analg 2011; in press.

Bensley RP, Hurks R, Huang Z, Pomposelli F, Hamdan A, Wyers M, Chaikof E, **Schermerhorn ML**. Ultrasound guided percutaneous EVAR success is predicted by vessel diameter. J Vasc Surg 2011; in press.

#### Abstracts, Poster Presentations, and Exhibits Presented at Professional Meetings

Bensley RP, Hurks R, Hamdan AD, Pomposelli FB, Wyers MC, Chaikof EL, **Schermerhorn ML**. Open repair of intact thoracoabdominal aortic aneurysms in the ACS-NSQIP. Poster presentation at the 2011 annual meeting of the SCVS, March 16-19, 2011, Orlando, Florida.

Bensley RP, Hurks R, Huang Z, Pomposelli F, Hamdan A, Wyers M, Campbell D, Chaikof E, **Schermerhorn ML**. Ultrasound guided percutaneous endovascular aortic aneurysm repair can be performed routinely with high success and minimal complications. Oral Presentation at the 2011 annual meeting of the NESVS, September 2011, Providence, Rhode Island

Bensley BP, Sachs T, Wyers MC, Hamdan AD, Pomposelli FB, Chaikof E, **Schermerhorn, ML**. Thoracic endovascular aortic aneurysm repair with and without coverage of the left subclavian artery in the 2005-2009 ACS-NSQIP. Oral presentation at the 2011 annual meeting of the SCVS, March 16-19, 2011, Orlando, Florida.



Nandivada P, Lagisetty KH, Pomposelli FB, Chaikof EL, **Schermerhorn ML**, Wyers MC, Hamdan AD. The impact of endovascular procedures on vascular fellowship training in lower extremity revascularization. Oral Presentation at the 2011 annual meeting of the NESVS, September 2011, Providence, Rhode Island

Siracuse JJ, Giles KA, Pomposelli FB, Hamdan AD, Campbell DR, Wyers MC, Nedeau AE, **Schermerhorn ML**. Infrainguinal bypass vs. endovascular interventions for primary treatment of claudication. Electronic poster at the 2011 annual meeting of the SCVS, March 16-19, 2011, Orlando, Florida.

Siracuse JJ, **Schermerhorn ML**, Nandivada P, Giles KA, Hamdan AD, Campbell DR, Wyers MC, Chaikof EL, Pomposelli FB. Morbidity of prosthetic graft infections. Poster presentation at the 2011 annual meeting of the SCVS, March 16-19, 2011, Orlando, Florida.

Yoshida S, Bensley RP, Hamdan AD, Pomposelli FB, Wyers MC, Chaikof EL, **Schermerhorn ML**. Increased risk of adverse events in physiologically high-risk patients undergoing carotid artery stenting. Poster presentation at the 2011 annual meeting of the SCVS, March 16-19, 2011, Orlando, Florida.

Yoshida S, Nabzdyk CS, Glaser JD, Bensley RP, Hamdan AD, Pomposelli FB, Wyers MC, Chaikof EL, **Schermerhorn ML**. Patients considered “High Risk” for carotid endarterectomy are at increased risk of adverse events following carotid artery stenting. Oral Presentation at the 2011 annual meeting of the NESVS, September 2011, Providence, Rhode Island

**Marc L. Schermerhorn, MD**



Beth Israel Deaconess Medical Center (BIDMC) is a patient care, teaching and research affiliate of Harvard Medical School and currently ranks third in National Institutes of Health funding among independent hospitals nationwide. The medical center is clinically affiliated with the Joslin Diabetes Center and is a founding member of the Dana-Farber/Harvard Cancer Center. BIDMC is the official hospital of the Boston Red Sox.



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