

# Words from the Chairman



**Dr. Josef E. Fischer**

When I came to the Beth Israel Deaconess Medical Center (BIDMC) four and a half years ago, I had in mind to rebuild the Department of Surgery into an academically-oriented Department. As many of you are aware, such rebuilding involved, first and foremost, staffing the Department with individuals to provide extraordinary patient care. I continue to be dedicated to this effort, which remains the hallmark of both the current (BIDMC) and the previous (University of Cincinnati) Departments of Surgery that I had the privilege to lead. However, an academic Department of Surgery also has another component, which is the pursuit of knowledge that is obtained by bench as well as by clinical research. I set a number of goals for Research in the Department of Surgery when I came to Boston. The first goal was that we would grow our research programs and increase our NIH funding to climb from, I think, number 16 or 17 in the country, to one of the top 5 Surgery Departments in total research support. This goal is difficult to quantify because the rankings are for combined Departments within a University and

not for individual Departments, like the situation we have here at Harvard. Although the ranking of BIDMC in total NIH-funded research is not presently known, what I do know is that we have grown substantially in the past years with the addition of new surgeons and investigators that are involved in basic and clinical research. Another goal I set concerning research was that each Division should have an NIH-funded laboratory, something which we are well on the way to achieving.

So, how are we doing in funding our basic and clinical research programs? I am pleased to say that our research holdings from the NIH have continued to grow each year. Last year we saw almost an 8% increase in NIH funding, which followed on the heels of a 13.4% increase in 2004, and a 22.5% increase in 2003. The total awarded funds for research last year, as you will see from the chart included in the report from Surgical Research that includes both NIH and non-NIH funding, was about \$12.6 million dollars. Since 2001 when I arrived at BIDMC, this represents a 23% increase in total funds awarded to our research programs in Surgery! Having productive and well-funded research laboratories in Surgery is an important part of our residency program too, so that our residents can go into the laboratory and carry-out first-class research with members of the Department of Surgery. Hence, we have gone a long way toward fulfilling our goal of sustained growth in research, both at the departmental and divisional levels, which could only be realized by the hard work and dedication of our research faculty, staff, and fellows over the past four and a half years.

I wish to thank all of the Division Chiefs and members of the Department, faculty and staff alike, for their continued superb efforts in making the Department of Surgery at the Beth Israel Deaconess Medical Center a true academic Department. My thanks are also extended to Drs. Per-Olof Hasselgren and Susan Hagen for putting together this book, and for their continued efforts to build and promote an especially strong academic program in Surgery.

## **Josef E. Fischer, MD**

Chairman, Department of Surgery and  
Surgeon-in-Chief  
Beth Israel Deaconess Medical Center

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# Division of Surgical Research



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

**Vice Chairman for Surgical Research  
George H. A. Clowes, Jr. Professor of  
Surgery**

Susan Hagen, PhD

Associate Director for Surgical Research  
Associate Professor of Surgery

Andrew French, BA

Administrative Coordinator

The Division of Surgical Research is an administrative division with an aim to facilitate both basic and clinical research in the Department of Surgery. In this section of the Annual Report, we provide an overall description of the goals and responsibilities of the Division of Surgical Research, a summary of funding and publications generated by researchers in the Department of Surgery, and other aspects of research within the Department. More detailed research updates are found for individual members of the different Divisions in subsequent sections of the Report.

The Division of Surgical Research has the following responsibilities. 1) Pre-award approval of all grants submitted by investigators in the Department of Surgery. Our responsibilities include assisting in the process of submission of grant applications and interaction with the BIDMC Office of Sponsored Programs. 2) Management of research space, including laboratory and office space, and shared research equipment. For this, we oversee the allocation of research space within the Department, maintain shared tissue culture facilities, and represent the Department at ReAc space sub-committee meetings. 3) Organizing monthly Surgical Research seminars. 4) Preparing the Department of Surgery Annual Research Report. 5) Organizing laboratory and shared equipment maintenance and telecommunications. 6) Supporting and mentoring junior faculty in the establishment of research laboratories. 7) Interacting with and providing information to Surgical Residents who plan to spend time in the research laboratory. 8) Obtaining visas for foreign scholars in Research and in preparing application for HMS appointments (Research Fellow-Instructor) to Harvard Medical School. 9) Making recommendations concerning research faculty appointments (Assistant-Full Professor) and reappointments in Surgery. 10) Assisting with the development of existing and new research areas within the Department of Surgery, including both short- and long-term strategic planning and recruitment.

## Department of Surgery Annual Research Report 2005

### Division of Surgical Research

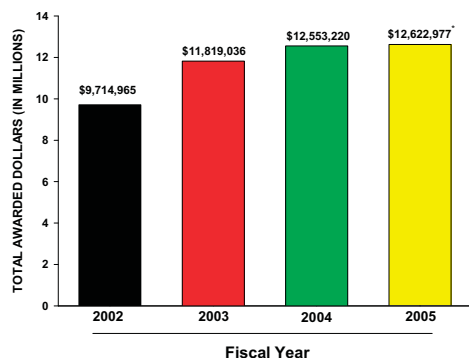
The Division of Surgical Research is headed by Per-Olof Hasselgren, MD, PhD, who is the Vice Chairman for Research in the Department of Surgery. Susan J. Hagen, PhD, is Associate Director. Dr. Hagen works closely with Dr. Hasselgren to accomplish the goals and mission for the Division. Andrew French is the Administrative Coordinator for Surgical Research. Andrew provides administrative support for the Division, under the supervision of Dr. Hagen. The Division of Surgical Research works closely with Research Administration Team 5, headed by Jennifer Sabbagh. Ruth Coburn and Jennifer Clark-Croes are Senior Research Administrators, and William Decaneas and JeeSoo Erickson are Research Administrators in Team 5. The Team 5 staff is responsible for pre-award grant assistance, post-award grant management, research-related purchases, compliance, staff payroll, and the management of new hires for research in Surgery.



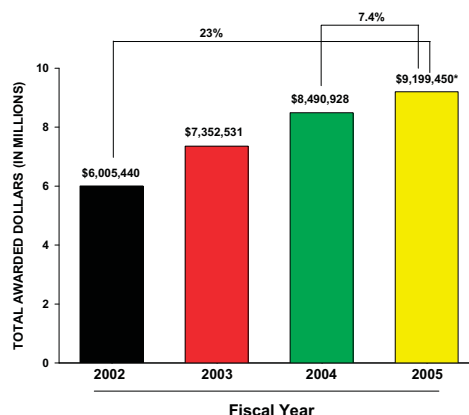
Andrew French

### Research Activity (Funding) for Fiscal Year 2005

Although it may be debated how the success and progress of a research program should be monitored, external funding is one tangible measure of the vitality of research. Based on that criterion, research programs in the Department continue to be successful. External research funding in the Department of Surgery increased by 0.5% from \$12,553,220 in fiscal year (FY) 2004 to \$12,622,977 in FY05 (Figure 1). This increase in total funding includes a significant, 7.4%, increase in NIH funding in FY05 (Figure 2). Approximately 79% of the awarded funding in FY05 was from federal sources, primarily from the NIH, and 21% from Other Sponsors. Again this year, there were numerous awards for clinical trials, which was about 7% of total funding for research in Surgery. It should also be noted that since 2002, NIH funding in Surgery has increased by 23% (Figure 2).

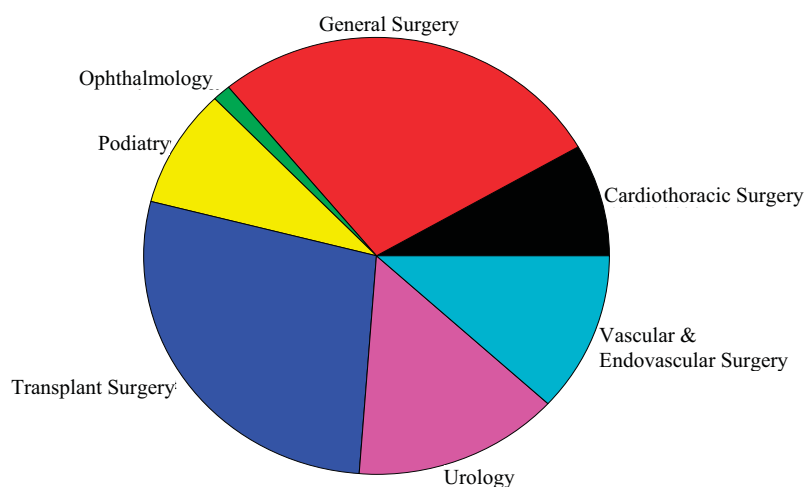


**Figure 1**  
Summary of total awarded funds from FY02-FY05. The funds are from NIH, Other Sponsors, and for Clinical trials.



**Figure 2**  
Summary of total awarded funds from the NIH from FY02-FY05.

Nine Divisions contributed to the research effort in Surgery in FY05 and 7 have significant external funding (Figure 3). General Surgery and Transplant Surgery Divisions continue to be the largest with \$3.4 million each in total research funding (Figure 3). Urology and Vascular Surgery each contribute about \$1.5 million and Cardiothoracic and Podiatry each contribute about \$1 million to total research funding (Figure 3). The Department of Surgery also holds 2 active NIH training grants, one in Cardiovascular Surgery (Dr. Sellke) and one in Vascular Surgery (Dr. LoGerfo). Investigators in Surgery at BIDMC also actively participate in the GI Surgery Training grant held at Brigham and Women's Hospital (Dr. Soybel). An additional NIH training grant for Surgery at BIDMC, submitted by the Transplant/Immunobiology Program (Dr. Hanto), is pending.



**Figure 3**  
**Total external funding in FY05 for each Division in Surgery.**

### **Research Facilities and Space**

This year, research in the Department of Surgery occupied approximately 32,000 square feet of laboratory space including wet labs, special purpose rooms (cold rooms, tissue culture rooms, and shared equipment rooms), and office space. Surgery (basic) research space included (in square feet) 8,139 at HIM, 12,556 in Dana/Research West, 917 in Slosberg-Landy, 1,664 at 21-27 Burlington Avenue, and 5,322 at Research North. Clinical research in Surgery included (in square feet) 443 in Palmer and 1,982 in Feldberg. The greatest numbers of researchers were located on the 7th and 8th floors of the Dana/Research West building on the East Campus, where General Surgery, Cardiothoracic Surgery, Neurosurgery, and Urology research laboratories are located. Vascular Surgery, Cardiothoracic Surgery, and Urology laboratories are located on the 1st and 10th floors of the Harvard Institutes of Medicine. Research related to Transplantation/ Immunobiology is located on the 3rd floor of Research North and 10th floor of the Harvard Institutes of Medicine. Finally, Surgical Nutrition research laboratories are located at the Burlington Avenue building and the Clinical Nutrition laboratories on Feldberg 8. Podiatry's clinical research effort remains in Palmer.

### **Research Seminars**

The Division of Surgical Research offered a seminar series with presentations from investigators within the Department of Surgery, from other Departments at BIDMC, and from other local institutions. Again this year, seminars were designed with a programmatic theme, with seminars each from Vascular/Cardiovascular, Transplant, Muscle Wasting and Metabolism, Epithelial Biology, and Urology. A summary of seminars that were presented in 2005 are listed in Table 1.

**Table 1. Seminars in Surgical Research**

<b>January 3, 2005</b>	<i>Simon Robson, MD, PhD</i> Associate Professor of Medicine, Harvard Medical School; Transplant/Liver/Vascular Biology Programs, Beth Israel Deaconess	"Vascular Injury, Extracellular Nucleotides, and E-NTPDases / CD39"
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<b>January 25, 2005</b> <b>*Special*</b>	<i>Ursula Seidler, MD</i> Professor of Internal Medicine and Gastroenterology, Medical School of Hannover, Germany	“The Emerging Role of PDZ-domain Binding Proteins in the Regulation of Intestinal Ion Transport”
<b>February 7, 2005</b>	<i>Frank Sellke, MD</i> Johnson and Johnson Professor of Surgery, Harvard Medical School; Chief, Division of Cardiothoracic Surgery, Beth Israel Deaconess	“Recent Advances in Surgical Coronary Angiogenesis”
<b>March 7, 2005</b>	<i>Daniel K. Podolsky, MD</i> Mallinckrodt Professor of Medicine, Harvard Medical School; Division Chief and Gastroenterology Director, Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital	“For What the Cell Tolls: TLR’s, Nods, and the Intestinal Epithelium”
<b>April 11, 2005</b>	<i>Nika N. Danial, PhD</i> Instructor in Pathology, Howard Hughes Medical Institute, Harvard Medical School; Staff Scientist, Dana Farber Cancer Institute	“Integration of Apoptosis and Glycolysis by the BCL-2 Protein BAD”
<b>May 2, 2005</b>	<i>P. Christian Schulze, MD, PhD</i> Instructor in Medicine, Harvard Medical School	“Mechanisms of Muscle Wasting and the Role of Local IGF-1”
<b>September 12, 2005</b>	<i>Charalabos Pothoulakis, MD</i> Professor of Medicine, Harvard Medical School; Director, Gastrointestinal Neuropeptide Center, Beth Israel Deaconess	“Mechanisms of Substance P in Intestinal Inflammation”
<b>November 14, 2005</b>	<i>Harold F. Dvorak, MD</i> Mallinckrodt Professor of Pathology, Emeritus, Harvard Medical School; Director, Center for Vascular Biology Research, Beth Israel Deaconess	“How Tumors Make Bad Blood Vessels and Stroma”

In addition to our regular seminar series, Surgical Research continued the series “Updates in Surgical Research” to highlight the research of Junior Faculty within the Department. Below, in Table 2, is a listing of the “Updates” Seminars that were held in 2005.

**Table 2. Updates in Surgical Research**

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<b>January 17, 2005</b>	<i>Jinrong Joe Zhou, PhD</i> Assistant Professor of Surgery, Harvard Medical School; Director, Nutrition Metabolism Laboratory, Beth Israel Deaconess	“Synergy Between Dietary Bioactive Components for Cancer Prevention”
<b>March 21, 2005</b>	<i>Michael Menconi, PhD</i> Assistant Professor of Surgery, Harvard Medical School; Director, Muscle Wasting Laboratory, Beth Israel Deaconess	“Calcium and Proteasome Function in Muscle Wasting”
<b>April 18, 2005</b>	<i>Aristidis Veves, MD, DSc</i> Associate Professor of Surgery, Harvard Medical School; Research Director, Microcirculation Laboratory, Beth Israel Deaconess	“Endothelial Function in the Microcirculation”



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<b>June 20, 2005</b>	<i>Jirong Bai, PhD</i> Instructor in Surgery, Harvard Medical School	“RNAi Knockdown of Predominant Bcl-Xl Overexpression Disables Anti-Apoptotic Mechanisms in Pancreatic Cancer Cells”
<b>September 26, 2005</b>	<i>Susan Hagen, PhD</i> Associate Professor of Surgery, Harvard Medical School; Associate Director for Research, Department of Surgery, Beth Israel Deaconess	“Regulation of Apoptosis by BAD and BCL-x During H. Pylori Infection”
<b>October 31, 2005</b>	<i>James D. McCully, PhD</i> Associate Professor of Surgery, Harvard Medical School	“Mechanisms of Ischemia / Reperfusion Injury”
<b>November 28, 2005</b>	<i>Aria Olumi, MD</i> Assistant Professor of Surgery, Harvard Medical School	“Transcriptional Regulation of c-FLIP(L) and Mechanisms of Improving Pro-Apoptotic Prostate Cancer Therapy”

**Resident’s Research Competition**

In 2005, Surgical Research conducted its second annual Residents’ Research Competition. All surgical residents, who are or have recently been in a research laboratory or who are involved in a clinical research project, were invited to submit a research abstract. From the 22 abstracts submitted, a ten-member committee of clinical and research faculty selected four finalists to present their work at Surgical Grand Rounds on June 8, 2005 after which the same committee voted to select a winner. The four finalists and winner of this year’s competition were:

**Brian Janz, MD.** “Development and Optimization of a Critical Care Alert and Display (CCAD) System using Retrospective ICU Databases”. Sponsor: Dr. Roger G. Mark, Massachusetts Institute of Technology.

**Shishir Maithel, MD.** “Ghrelin Antagonism Augments the Weight Loss and Decreased Food Intake Response in Novel Rat Models of Human Adjustable Gastric Banding and Roux-en-Y Gastric Bypass”. Sponsor: Drs. Daniel Jones (BIDMC Center for Minimally Invasive Surgery) and Lee M. Kaplan (MGH Weight Center).

**Jaime Mitchell, MD.** “Dietary Protein Deficiency Suppresses Proteolysis and Reduces Muscle Atrophy Caused by Catabolic Stress”. Sponsor: Dr. Nicholas Tawa, BIDMC Division of General Surgery.

**Virendra Patel, MD.** “A20 Promotes Regression of Neointimal Hyperplasia via a Novel NO-dependent Pro-apoptotic Function in Neointimal Smooth Muscle Cells”. Sponsor: Dr. Christiane Ferran, BIDMC Division of Vascular and Endovascular Surgery.

Dr. Maithel’s abstract and presentation won the Resident’s Research Competition this year.

**Faculty Accomplishments**

During 2005, research in the Department of Surgery was conducted by 48 faculty, 24 postdoctoral research fellows, 6 surgical residents, 28 research associates and assistants, 1 visiting scientist, 3 nurses, 1 dietitian, 1 medical writer, and 16 undergraduate, graduate, and medical students. Numerous research coordinators, administrative assistants, and administrative coordinators provided important administrative support for research-related efforts in Surgery. The details of staffing for research in Surgery accompany each Divisional report.

Many new grant applications were funded in 2005. New NIH grants, in the R01, R03, and R21 categories were awarded to Drs. Blackburn, Zhou, and Gaston. New research grants from other sources were awarded to Drs. Gaston and Veves. Drs. Levitsky and Sellke also successfully renewed their long-standing R01 grants. Ms. Anne Warren, an HMS medical student, received the prestigious Doris Duke Clinical Research Fellowship to work for 1 year with the Plastic and Reconstructive Division. Grants activity for new investigators also increased in 2005, with Drs. Archer, Parangi, and Bai submitting first-time R-category grant applications.

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### Division of Surgical Research

In 2005, many faculty members in Surgery were also active in national service. Drs. Hagen (GMPB) and Otterbein were appointed to NIH study sections and several faculty in Surgery served on ad hoc NIH study sections including Drs. Blackburn, Zhou, Hasselgren, Gaston, Ferran, and Veves. Drs. Ferran, Otterbein, and Veves also reviewed grant applications for the Juvenile Diabetes Foundation and for the American Diabetes Association. Dr. Olumi reviewed grant applications for the DOD and Dr. Zhou reviewed grant applications for the Natural Science Foundation of China. In 2005, Dr. Veves continued to be a journal editor for Wounds-A Compendium of Clinical Research and Practice and Dr. Olumi served on the editorial board of the Journal of Urology and for Investigative Urology. Dr. Blackburn was an associate editor for Obesity Research and on the editorial board for the journal Obesity Management. Dr. Slavin was an associate editor for the British Journal of Plastic Surgery.

In the national and international arena, Surgery faculty members were invited speakers around the world, from Israel (Slavin, Borud, Contreras, Lee) to the UK (Veves) to Belgium (Hasselgren), to Stockholm (Otterbein) to Brazil (Ferran) to India (Das). Dr. Levitsky delivered the prestigious William W.L. Glenn Lecture in Cardiac Surgery at the 2005 annual meeting of the AHA. Dr. Borud was featured nationally on Dateline NBC and Drs. DeWolf and Slavin were highlighted in Boston Magazine's list of the Best Doctors. Many honors were also bestowed-upon the faculty in Surgery this year. Dr. Sanda was the recipient of the Young Investigators Award from the Society of Urological Oncology and Dr. Olumi received the same award from the Society of Basic Urology. Drs. Archer and Parangi were elected to the Surgical Biology Club and Dr. Jones received the 2005 James IV Fellowship, providing travel funds to deliver lectures on minimally invasive surgery in the UK, China, and Australia. Dr. Borud was admitted to the NE Society of Plastic Surgeons and Dr. Das was elected Vice-chair for the Committee on Young Surgeons at the American College of Surgeons. Dr. Bach received an honorary Doctor of Medicine degree from the University of Vienna.

Researchers in Surgery also continued a strong commitment to teaching. This includes 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 continues to be actively involved in the William J von Leibig research training program for both medical and postdoctoral students. At Harvard Medical School, many investigators in Surgery teach in the Body, Cell Biology, Pharmacology, and/or GI Pathophysiology courses and nearly all of the Surgeons participate in the surgical clerkships. Dr. Jones was Course Director for the MIS course series and laboratory.

### **Bibliography (January – December 2005)**

The second means by which we monitor the success and progress of our research program is by productivity in terms of publications. Based on this second criterion, research programs in the Department also continue to be successful. In 2005, a total of 95 original articles were published and 52 articles were submitted or accepted for publication by faculty members in the Department of Surgery. This represents a 38% increase in published original articles and a 73% increase in submitted/accepted articles when compared to the previous year. The number of Reviews, Chapters, and Editorials was high again this year at 98 published or in press articles. Contributions to Books, Monographs, and Textbooks, as well as to Clinical Communications, Educational and Non-Print Materials, and Abstracts were also high again this year.

Below is a listing, in alphabetical order, of articles published by researchers in the Department of Surgery in 2005. **Bold** represents research Faculty in Surgery at BIDMC.

#### Original Articles

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# Division of Cardiothoracic Surgery



**Frank W. Sellke, MD**

**Chief, Division of Cardiothoracic Surgery  
Johnson and Johnson Professor of Surgery**

This year has been very productive for the Division of Cardiothoracic Surgery in terms of research. Frank Sellke renewed his oldest RO1 for an additional 4 years. Drs. Levitsky and McCully continue to examine mechanisms of ischemic preconditioning and myocardial protection. Drs. Sellke and Bianchi investigate changes in vascular function and signal transduction during cardiac surgery and myocardial ischemia, and therapeutic angiogenesis using protein growth factors in the setting of hypercholesterolemia. Dr. Ellis is looking at the changes in molecular characteristics in the GE junction leading to malignant transformation and Drs. Ralph Delatorre and Liddicoat examine minimally invasive techniques for valve repair. Dr. Kamal Khabbaz is investigating the effects of tissue acidosis on myocardial apoptosis and contractile function. The division continues to be one of the best-funded divisions of cardiothoracic surgery in the country in terms of NIH grants.

## **Division Members**

**Simon K. Ashiku Jr., MD**

**Instructor in Surgery**

### ***Dr. Sellke's Laboratory Group***

**Cesario F. Bianchi, MD, PhD**

Jun Feng, MD, PhD

Richard Clements, PhD

Munir Boodhwani, MD

Shigetoshi Mieno, MD

Steve Munevar, PhD

Yasunari Nakai, MD, PhD

Basel Ramlawi, MD

Neel Sodha, MD

Jiannyi Li, MB

Shu Hua Xu, PhD

**Assistant Professor of Surgery**

Instructor in Surgery

Research Fellow

Research Fellow

Research Fellow

Research Fellow

Research Fellow

Research Fellow

Research Fellow

Research Assistant

Research Assistant

**Malcolm DeCamp, MD**

**Visiting Associate Professor of Surgery**

**Ralph de la Torre, MD**

**Instructor in Surgery**

**F. Henry Ellis Jr., MD, PhD**  
Xiangjun Xu, MD, PhD

**Clinical Professor of Surgery, Emeritus**  
**Instructor in Surgery**

**Sidhu Gangadharan, MD, MD**

**Instructor in Surgery**

**Kamal Khabbaz, MD**

**Visiting Assistant Professor of Surgery**

**Sidney Levitsky, MD**  
**James D. McCully, PhD**  
Erin E. Tansey, BS

**Cheever Professor of Surgery**  
**Associate Professor of Surgery**  
**Research Associate**

**John R. Liddicoat, MD**

**Assistant Professor of Surgery**

**Robert L. Thurer, MD**

**Associate Professor of Surgery**

**Ronald M. Weintraub, MD**

**David Ginsburg Associate Professor of Surgery**

## F. Henry Ellis Jr, MD, PhD

### Basic Research

A tumor suppressor gene, p27, controls progression of cells from the G1 to S phase of the cell cycle. It is reduced or absent in resected specimens from patients with Barrett's Associated Adenocarcinoma (BAA). This loss of p27 is correlated with tumors of high grade, with increased depth of invasion, greater lymph node involvement, and a decreased postoperative survival rate. These findings influenced us to develop an experimental mouse model of BAA by performing an esophagojejunostomy, to promote reflux of alkaline and acid juices into the esophagus, along with the administration of a carcinogen (N-methyl N-benzyl nitrosamine). Subsequently, we showed that malignant transformation of the esophageal mucosa was enhanced in p27 knockout (KO) mice, but could be reduced by administration of flavopiridol, a CDK inhibitor, as a chemopreventive agent.



Dr. F. Henry Ellis

### **Current Employees**

Xiangjun Xu, MD

Instructor in Surgery

### **LIST OF CURRENT FUNDING**

Thelma and Jerry Stergios Fund for Thoracic Surgical Education and Research

### **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

#### Research Accomplishment

Having shown that flavopiridol (flavo) could act as a chemopreventive method to reduce the high cancer rate in p27 KO mice after esophagojejunostomy and carcinogen administration, we began studies designed to evaluate chemotherapeutic approaches to treating BAA after its development. Flavopiridol combined with gemcitabine (Gem) were administered to mice four months after esophagojejunostomy and carcinogen administration. Results of these showed a significant difference from the diluent (Control) group. We are currently adding two new groups of mice: one treated with flavo and the other with Gem alone. Preliminary results are shown below:

Findings	Diluent (Control, n=70)	Gem + Flavo (n=50)	P value	Gem (n=50)	P value	Flavo (n=81)	P value
Barrett's Esophagus	24%	6%	0.0116	8%	0.0274	7%	0.0057
Total Cancers	74%	26%	<0.0001	44%	0.0011	40%	<0.0001
Squamous Cell Carcinoma	43%	10%	<0.0001	30%	NS	21%	0.0048
Adeno Squam + Adenocarcinoma	32%	16%	NS	14%	0.0319	19%	NS

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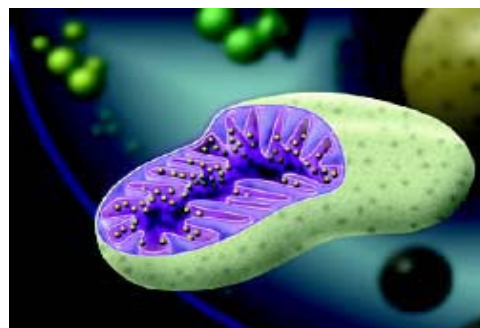
Lechpammer M, Xu, X, Ellis FH Jr., Bhattacharaya N, Shapiro GI, Loda M. Flavopiridol reduces malignant transformation of the esophageal mucosa in p27 knockout mice. *Oncogene* 2005;24(10):1683-8.



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

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. Study designs utilize models of stunning and ischemia/reperfusion injury in the isolated Langendorff perfused rabbit and the in situ blood perfused pig heart to determine the relative contribution of these pathways in the aged as compared to the mature cardiac surgical patient. The laboratory is also involved in the isolation and identification of genes associated with myocardial ischemia/reperfusion amelioration using differential display, selective subtraction hybridization, and microarray technology. For this, we use rabbit and pig heart cDNA libraries constructed in our laboratory and non-redundant cDNA's isolated, sequenced and putatively identified by our laboratory for microarray analysis.

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



Mitochondrion

**Current Employee**

Erin E. Tansey, BS

Research Associate

**LIST OF CURRENT FUNDING**

“Myocardial Protection: Reperfusion Injury Amelioration”

National Institutes of Health, RO1- **HL 29077**

Principal Investigator: Sidney Levitsky, MD

Collaborating Investigator: James D. McCully, PhD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Molecular Modulation in Myocardial Ischemia Reperfusion and Cardioprotection”

National Institutes of Health, RO1- **HL 59542**

Principal Investigator: James D. McCully, PhD

Collaborating Investigator: Sidney Levitsky, MD

**DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

**Individual Accomplishments**

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

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**Division of Cardiovascular Surgery**

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

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

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

Invited Presentations (Local, National, and International)

*Dr. Levitsky*

- "Protecting the Myocardial Cell during Coronary Revascularization." 2005 William W. L. Glenn Lecture in Cardiac Surgery, American Heart Association Scientific Sessions, 2005.
- "Endovascular Surgery." Educational Course sponsored by Society of Thoracic Surgeons, August, 2005.

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Original Articles (submitted or in press)

**McCully JD**, Toyoda Y, Wakiyama H, Rousou AJ, Parker RA, **Levitsky S**. Age and gender related differences in ischemia/reperfusion injury and cardioprotection: effects of diazoxide. *Ann Thorac Surg* 2005; submitted.

Rousou AJ, **Levitsky S**, **McCully JD**. Age and gender related differences in ischemia/reperfusion and the protection afforded by cardioplegia and diazoxide: role of mitochondrial oxygen consumption and mitochondrial calcium. *Am J Physiol. Heart Circ Physiol* 2005; submitted.

Reviews, Chapters, and Editorials

**Levitsky S**, **McCully JD**. Myocardial protection. In: Sellke FW, delNido PJ, Swanson SJ, editors. Sabiston and Spencer's Surgery of the Chest. 7<sup>th</sup> ed. Philadelphia: W. B. Saunders Company; 2005. p. 1081-1102.

Edwards FH, Welke KF, **Levitsky S**. Cardiac revascularization in specialty and general hospitals (letter to the editor). *N Engl J Med* 2005. 352:2755.

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

The goal of our research efforts is threefold. 1) To examine changes in coronary and peripheral microvascular reactivity and permeability and identify the respective cellular and molecular mechanisms of change, which occur as a consequence of cardiopulmonary bypass and cardioplegia in a porcine model and human atrial appendage and skeletal muscle. We use both *in vivo* and *in vitro* techniques in isolated microvessels and hearts. 2) To examine the use of therapeutic angiogenesis for the treatment of coronary artery disease (CAD). We identify causes for the lack of effect of exogenous growth factor therapy (implantation of sustained-release devices containing bFGF and/or VEGF) in a hypercholesterolemic porcine model with similarities to human CAD. 3) To characterize the gene expression profile of patients subjected to cardiopulmonary bypass and correlate differences in gene expression with clinical outcomes. We use cDNA microarray technology for this goal.

**Current Employees**

Jun Feng, MD, PhD	Instructor in Surgery
Richard Clements, PhD	Research Fellow
Munir Boodhwani, MD	Research Fellow
Shigetoshi Mieno, MD	Research Fellow
Steve Munevar, PhD	Research Fellow
Yasunari Nakai, MD, PhD	Research Fellow
Basel Ramlawi, MD	Research Fellow
Neel Sodha, MD	Research Fellow
Jiannyi Li, MB	Research Assistant
Shu Hua Xu, PhD	Research Assistant
Tanisha Wilson	Summer Student / Project Success
Atheena Dy	Summer Student / Project Success



**The Sellke Laboratory. Back: Drs. Feng, Nakai, Ramlawi, Bianchi, Sellke, Mieno, and Boodhwani. Front: Dr. Xu and Jiannyi Li.**

**LIST OF CURRENT FUNDING**

“Cardioplegia and Coronary Microvascular Reactivity”  
National Institutes of Health, NHLBI RO1 - **HL-46716**  
Principle Investigator: Frank W. Sellke, MD

“Surgical Intramyocardial Angiogenesis in a Swine Model”  
National Institutes of Health, NHLBI RO1 - **HL-69024-02**  
Principle Investigator: Frank W. Sellke, MD



**Department of Surgery Annual Research Report 2005**  
**Division of Cardiovascular Surgery**

“KLF15, TGFb1, and Smooth Muscle Biology”

National Institutes of Health, NHLBI RO1

Principle Investigator: Mukesh Jain, MD (Brigham and Women’s Hospital)

“Cardiovascular Surgery Research”

National Institutes of Health, T32 Training Grant -**HL076130-01**

Program Director: Frank W. Sellke, MD

“Research Training in Vascular Surgery”

National Institutes of Health, T32 Training Grant - **HL007734-11**

Program Director: Frank LoGerfo, MD

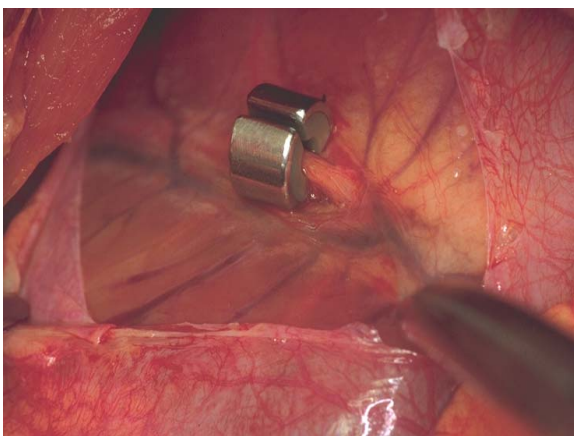
“Cardiovascular Research Training Grant”

National Institutes of Health, T32 Training Grant - **HL007374-24**

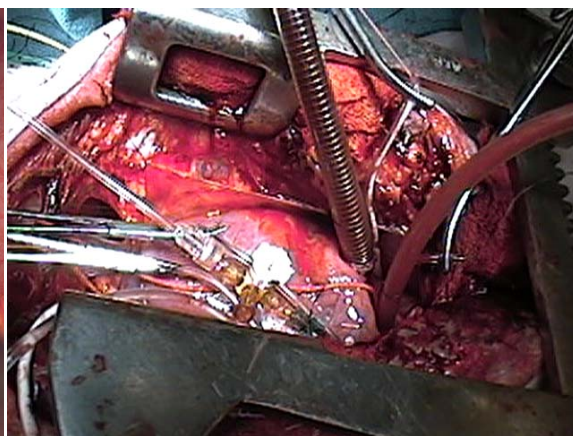
Program Director: James P. Morgan, MD, PhD



The laboratory uses two large animal operating rooms for survival (left) and non-survival (right) experimental protocols. Around 250 surgeries were performed between January 2005 and December 2005.



Ameroid Placement



Cardiopulmonary Bypass

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Diabetes and Vascular Function after Cardiac Surgery”

National Institutes of Health, NHLBI RO1 - **HL-83384-01**

Principle Investigator: Frank W. Sellke, MD

“Angiogenesis in a model of diabetes and endothelial dysfunction”

National Institutes of Health, NHLBI RO1

Principle Investigator: Frank W. Sellke, MD



## **REPORT OF TEACHING**

### Undergraduate and Medical School Courses

Dr. Cesario Bianchi continues as a member of the Teaching Faculty for Harvard Medical School, tutoring first year Harvard Medical / Dental Students (Human Body, Cell Biology).

The laboratory sponsors 1 or 2 high school students from Project Success, Harvard Medical School Office for Diversity and Community Partnership. Each student spends 10 weeks in the laboratory doing a research project.

### Graduate School and Graduate Medical Courses

Dr. Sellke does daily teaching rounds, instruction and assisting at surgery.

Dr. Sellke is Director of the Cardiothoracic Surgery Residency Training Program, where he is responsible for the organization and administration of conferences and training programs. He has 1 junior (PGY-6) and 1 senior (PGY-7) resident per year.

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Boodhwani M, Nakai Y, Mieno S, Voisine P, **Bianchi C**, Araujo EG, Feng J, Michael K, Li J, **Sellke FW**. Hypercholesterolemia impairs the myocardial angiogenic response in a swine model of chronic ischemia: Role of endostatin and oxidative stress. *Ann Thorac Surg* 2005; in press.

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**Sellke FW**, Laham RJ, Suuronen EJ, Ruel M. Angiogenesis for the treatment of inoperable coronary disease: The future. *Semin Cardiothorac Vasc Anesth* 2005; in press.

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**Sellke FW**, Del Nido PJ, Swanson SJ, editors. Sabiston and Spencer's Surgery of the Chest. 7<sup>th</sup> edition. Philadelphia: Elsevier Publishing; 2005.

# Division of General Surgery



**Mark Callery, MD**

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**Associate Professor of Surgery**

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**Director of Endocrine Surgery**

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Instructor in Surgery  
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Research Fellow  
Research Fellow, Surgical Resident  
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Administrative Coordinator

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Skills Lab Coordinator  
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**Leonardo Villegas, MD**

**Charles Vollmer, MD**

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Linglin Li, MS

**Assistant Professor of Surgery**

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**Instructor in Surgery**

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**Visiting Assistant Professor of Surgery**

**Assistant Professor of Surgery**

**Instructor in Surgery**

**Clinical Fellow in Surgery**

**Instructor in Surgery**

**Assistant Professor of Surgery**

Research Fellow  
Research Associate  
Clinical Fellow  
Research Technician



**Sonia Archer, MD**



**Dr. Sonia Archer**

My research focuses on deciphering the mechanisms involved in the beneficial effects of fiber on colon cancer. This work is of significant clinical and societal importance since colon cancer is the third most common cancer, and the second leading cause of cancer deaths in the U.S.A. Although both environmental and genetic factors play a role in its genesis, environmental factors appear to predominate in importance.

Butyrate, a product of fiber fermentation in the colon, is known to inhibit colon carcinogenesis and colon cancer cell growth both *in vivo* and *in vitro*. Cell growth occurs through cell cycle progression and cell cycle progression is controlled by a variety of protein cyclins and their associated kinases. These complexes are inhibited by small proteins, e.g. p21, which cause growth arrest. Our laboratory has shown that butyrate mediates this inhibition of colon cancer cell growth *in vitro* via transcriptional induction of the cell cycle inhibitor, p21. We have further defined the molecular mechanisms which are involved in the transcriptional induction of p21 by butyrate both *in vitro* and

*in vivo*. In addition, we have expanded the scope of this work to include examination of other cell cycle regulators, such as cyclin B1. Cyclin B1 is a cell cycle promoter which is increased in colon cancer cells and we are now actively involved in studies which address the regulation and importance of this cell cycle gene product in colon cancer cell growth as well as its regulation by butyrate.

Our long-term goal is to continue to advance the understanding of the molecular mechanisms involved in butyrate's (and fiber's) protection against colon carcinogenesis. My expectation is that we will eventually be able to translate these findings into diagnostic and therapeutic strategies against colon cancer.

**Current Employees**

Chong Gao, PhD

Postdoctoral Fellow

**LIST OF CURRENT FUNDING**

"Regulation of Cyclin B1 Gene Expression by Butyrate in Colon Cancer Cells"

Robert Wood Johnson, Minority Medical Faculty Development Award

Principle Investigator: Sonia Archer, MD

"Regulation of Cyclin B1 Gene Expression by Butyrate in Colon Cancer Cells"

Harvard Medical School, Minority Medical Faculty Development Bridge Award

Principle Investigator: Sonia Archer, MD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

"Molecular Mechanisms Underlying Butyrate-mediated Growth Inhibition in Colon Cancer Cells *in vivo* – Importance of the p21 Gene and Histone Hyperacetylation"

Dana Farber/ Harvard Cancer Center G.I. Cancer SPORE - Colorectal Adenoma Developmental Projects Program, National Institutes of Health

Principle Investigator: Sonia Archer, MD

### **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

#### Research Accomplishments

Over the past year, I have made significant advancements in determining the molecular mechanisms underlying the regulation of cyclin B1 gene expression by butyrate in colon cancer cells. This interesting work has continued to attract students and residents to come to the laboratory to participate.

At the national level, I was elected to the prestigious Surgical Biology I Club and continued active service in the Association for Academic Surgery. I also served as ad hoc reviewer for the journal, Tumor Biology.

#### Plans for the Coming Year

We will continue our work on the regulation of cyclin B1 by butyrate, both in *in vivo* and *in vitro* models. Our work has produced exciting data which has been submitted for publication. With the acquisition of additional grant funding (NIH R-O1), our long-term goal will be to continue to advance the understanding of the molecular mechanisms involved in butyrate's (and fiber's) protection against colon carcinogenesis. My expectation is that this will eventually be able to translate the findings into diagnostic and therapeutic strategies against colon cancer.

I will continue to teach the HMS GI Pathophysiology and Surgical Core Clerkship courses.

### **REPORT OF TEACHING**

#### Undergraduate and medical school courses:

I participated in a focused Discussion on Colon Cancer Genetics, Colon Cancer, and Polyps in the GI Pathophysiology Course for 2<sup>nd</sup> year Harvard Medical School Students.

I continue to serve as an advisor and mentor for minority students in the Biomedical Science Careers Student Project, as well as students who work in my laboratory. One student obtained a scholarship to Cornell University based on work performed in my laboratory.

#### Graduate school and graduate medical school course:

I continue to teach surgical residents in our General Surgery program at BIDMC.

#### CMR courses:

I served as a reviewer/editor for the Risk Management Foundation Colorectal Cancer Screening Guidelines.

### **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

#### Original Articles

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#### Original Articles (submitted or in press)

Lee MG, Nadig SN, **Archer SY**. The telescoping tumor: a report of appendiceal cystadenoma causing intussusception. 2005; submitted.



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

**Jin-Rong Zhou, PhD**

*Section of Surgical Nutrition-*

*Center for the Study of Nutritional Medicine (CSNM)*

*Nutrition Metabolism Laboratory (NML)*

Clinical Research (Center for the Study of Nutrition Medicine)

The Center for the Study of Nutrition Medicine (CSNM), directed by Dr. Blackburn, has 30-years of extensive experience conducting longitudinal studies particularly in multi-center settings. The CSNM is particularly well-equipped with the infrastructure to develop clinical investigation and outcomes assessment and provides sophisticated, scientific nutrition interventions that are utilized to support research, training and patient care in many disease states. The CSNM mission is in line with the medical center's "bench-to-bedside" mission.

Last February, the CSNM released a multidisciplinary evidence-based report on best practices in weight loss surgery—the findings of an expert panel sponsored by the Massachusetts Department of Public Health's Betsy Lehman Center for Patient Safety and Medical Error Reduction. Publication of this report put Massachusetts at the forefront of an accelerating national trend to impose standards and safeguards on the practice of bariatric surgery, a specialty that has grown in the U.S. from approximately 16,000 procedures a year in the early 1990s to more than an estimated 140,000 in 2004.



**Dr. George Blackburn**

In Massachusetts, the number of weight loss surgeries increased from 148 in 1996 to 3,036 in 2004, raising concerns about patient safety. The Lehman Center addressed these concerns by bringing together obesity experts and allied health professional from more than 80% of the sites performing weight loss surgery in the Commonwealth. Together they developed in-depth recommendations and guidelines based on a model of evidence-based medicine similar to that used by the U.S. Preventive Services Task Force and the National Institutes of Health. Their findings have informed health care policy and had far-reaching effects on both state and national levels.

To date, the report has been posted on the Agency for Healthcare Research and Quality (AHRQ) website, adopted by Blue Cross Blue Shield of Massachusetts, applied as a standard by the state's Board of Registration in Medicine, and used as the blueprint for the American College of Surgeons (ACS) Bariatric Surgery Center Network Accreditation Program. Other professional groups, including the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) and the American Society of Bariatric Surgeons (ASBS), have joined the ACS in launching similar programs. So have many managed care companies and third party payers, including: Aetna, Kaiser Permanente, Cigna, the California Association of Health Plans, Health America, and Blue Cross Blue Shields in South Dakota, Wisconsin, North Carolina, and Idaho.

These efforts mark a turning point in the practice of weight loss surgery, away from patchwork reporting and performance analysis and toward a national network of prospective, clinically-derived databases that can serve as a vehicle for quality improvement, much like current systems for coronary artery bypass graft surgery established by the Society for Thoracic Surgeons. The lone surgeon in bariatrics has given way to the multidisciplinary team involving nurse practitioners, triage nurses, dietitians, on-call expert consultants, and administrative support staff. In the last 10 years, weight loss surgery has become mainstreamed into the discipline of surgery, medical practice in general, and public awareness. In the coming years, quality assurance will be mainstreamed into bariatric surgery to ensure the delivery of appropriate, safe, and effective care.

Basic Research (Nutrition Metabolism Laboratory)

The Nutrition Metabolism Laboratory (NML), directed by Dr. Joe Zhou, studies the effects of dietary and nutritional components, such as soy phytochemicals, tea polyphenols, and other dietary/herbal supplements, on the prevention and treatment of cancer and obesity, and to elucidate the underlying molecular and cellular mechanisms. The NML is particularly interested in the *in vivo* evaluation of preventive activities of bioactive components in soy, tea, and other plant compounds by application of clinically relevant orthotopic and transgenic mouse tumor models. The NML has a particular interest in studying the molecular mechanisms by which dietary bioactive components



**Dr. Jin-Rong (Joe) Zhou**

modulate cell proliferation, apoptosis, and tumor angiogenesis. We also investigate the effect of a novel daidzein-rich isoflavone-aglycone extract from soy germ fermentation with Koji fungus (*Aspergillus awamori*) on the prevention of obesity and inflammation. We are further isolating and identifying other bioactive components in soy and tea that may be responsible for their cancer prevention activity.

Collaborative research with the investigators inside and outside the BIDMC involves studies in hormone-independent prostate cancer (Steve Balk, Department of Medicine, BIDMC), in the effect of adiponectin on breast cancer (Christos Mantzoros, Department of Medicine, BIDMC), in the protective role of L-glutamine on gastric atrophy and cancer progression during *H. pylori* infection (Susan Hagen, Department of Surgery, BIDMC), the effect of diet/nutrition on pancreatic cancer (Sareh Parangi, Department of Surgery, BIDMC), in molecular mechanism studies of prostate cancer progression modulated by dietary components (Sandra Gaston, Department of Surgery, BIDMC), in the modulation of gene expression by nutritional manipulations in prostate and breast cancer (Towia Libermann, Department of Medicine, BIDMC), in the effect of plant components and synthetic analogues on prostate cancer prevention by inhibition of DNA topoisomerase (David Lee, McLean Hospital/HMS), in the effect of peptides delivered by nano-particles on prostate cancer progression (Martin Yarmush, MGH), and in the effect of ER-beta modulation by phytoestrogens on prostate cancer (Paul Mak, Urology Department, University of Massachusetts Medical School). Our long-term goal of research is to identify the effective components in nature for prevention of cancer and obesity.

### **Current Employees**

#### *Center for the Study of Nutritional Medicine*

Lalita Khaodhiar, MD	Instructor in Medicine
Daniel S. Rooks, PhD	Assistant Professor in Medicine
G. Galicka-Piskorska, MD, PhD	Instructor in Medicine
Anne McNamara RN	Research Associate
Belinda Waltman, BS	Research Associate
Kristina Day, RD, LD	Research Dietician
Rita Buckley, MBA	Medical Writer
Barbara M. Ainsley, DTR	Administrative Assistant

#### *Nutritional Metabolism Laboratory*

Ajita V. Singh, PhD	Research Fellow
Derek Liu, PhD	Research Associate
Weijun Pan, MD, PhD	Clinical Fellow
Linglin Li, MS	Research Technician

### **LIST OF CURRENT FUNDING**

“Chemoprevention of Bladder Cancer by Soybean Bioactive Components”

National Institutes of Health, RO1-**CA92546**

Principle Investigator: Jin-Rong Zhou, PhD

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

“Genistein and Prevention of HER2-overexpressing Breast Cancer”

National Institutes of Health, NCI RO3-**CA112644**

Principle Investigator: Jin-Rong Zhou, PhD

“Prevention of Bladder Cancer Progression by Sulforaphane”

National Institutes of Health, NCI RO3-**CA112640**

Principle Investigators: Jin-Rong Zhou, PhD

“Effects of AglyMax on the Prevention and Treatment of Obesity and Prostate Cancer”

Nichimo Company, Japan

Principle Investigator: Jin-Rong Zhou, PhD

“Effects of Soy Products on Estrogen Insufficiency-induced Tamoxifen-nonresponsive Breast Cancer”

Susan Komen’s Breast Cancer Research Foundation

Principle Investigator: Jin-Rong Zhou, PhD

“Functional Erythropoietin Receptors Expressed by Human Prostate Cancer Cells”

Department of Defense, Idea Award

Principle Investigator: Arthur Sytkowski, MD

Co-Investigator: Jin-Rong Zhou, PhD

“New Strategies for Interpreting *in vivo* Prostate MRI/MRS Choline Spectra: Manipulating Gene Expression to Enhance Cancer Specificity”

US Department of Defense, Hypothesis Development Award

Principle Investigator: Sandra Gaston, PhD

Co-Investigator: Jin-Rong Zhou, PhD

“Light OJ-- Effect of Calcium/Vitamin D on Weight Loss”

The Beverage Institute of Health and Wellness

Principle Investigator: George Blackburn, MD, PhD

“Regular OJ-- Effect of Calcium/Vitamin D on Weight Loss”

The Beverage Institute of Health and Wellness

Principle Investigator: George Blackburn, MD, PhD

“Effects of Soy Isoflavones on Menopausal Hot Flashes”

Nichimo Co., Japan.

Principle Investigator: Hope Ricciotti, MD

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

Co-Investigator: Jin-Rong Zhou, PhD

“Exercise, Diet, and Sex Hormones in Postmenopausal Women”

National Institutes of Health, NCI R01-**CA105204**

Principle Investigator: Anne McTiernan, MD, PhD

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

“Low-Fat Diet in Stage II Breast Cancer: Outcome Trial”

National Institutes of Health, NCI R01-**CA45504**

Principle Investigator: Rowan Chlebowski, MD, PhD

Co-Investigator/Committee Chair: George Blackburn, MD, PhD

“The Boston Obesity Nutrition Research Center (BONRC)”

National Institutes of Health NIDDK, P30-**DK46200**

Principle Investigator: Barbara Corkey, PhD

Associate Director: George Blackburn, MD, PhD

“The Study of Health Outcomes of Weight Loss”

National Institutes of Health, NIDDK U01-**DK57154**

Principle Investigator: David Nathan, MD

Co-Investigator: George Blackburn, MD, PhD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Black Tea Bioactives for Prostate Cancer Prevention”

National Institutes of Health, NCI RO1-**CA118106**

Principle Investigator: Jin-Rong Zhou, PhD

“Soy and Radiation Combination for Breast Cancer Treatment”

National Institutes of Health, NCI RO1-**CA122773**

Principle Investigator: Jin-Rong Zhou, PhD

“Oldenlandia Diffusa for Prostate Cancer Treatment”

National Institutes of Health, NCCAM R21-**AT003341**

Principle Investigator: Jin-Rong Zhou, PhD

“Phytochemicals Combination for Breast Cancer Prevention”

National Institutes of Health, NCI R21-**CA122409**

Principle Investigator: Jin-Rong Zhou, PhD

“Soy as a Radiation Sensitizer in Prostate Cancer Treatment”

National Institutes of Health, NCI R21-**CA120649**

Principle Investigator: Jin-Rong Zhou, PhD

“Mechanisms of Androgen Independent Prostate Cancer”

National Institutes of Health

Principle Investigator: Steve Balk, MD, PhD

Co-Investigator: Jin-Rong Zhou, PhD

“Phytochemicals and Prostate Cancer Prevention and Treatment”

American Institute for Cancer Research

Principle Investigator: Paul Mak, PhD (University of Massachusetts Medical Center)

Co-Investigator: Jin-Rong Zhou, PhD

“A Home-based, Preoperative Exercise Intervention for Weight Loss Surgery Patients”

Harvard Clinical Nutrition Research Center

Principle Investigator: Daniel S. Rooks, PhD

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

“Functional Status Assessment in Severely Obese Adults Before and 6 months After Weight Loss Surgery”

CReFF Grant

Principle Investigator: Daniel S. Rooks, PhD

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

“Preoperative Exercise for Weight Loss Surgery”

National Institutes of Health, NIDDK RO3-**DK074444**

Principle Investigator: Daniel S. Rooks, PhD

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

“The effect of surgical weight reduction and associated medical interventions on microalbuminuria and hypertension in patients with morbid obesity”

Investigator Initiated External Sponsor Charitable Gift.

Principle Investigator: Grazyna Galicka-Piskorska, MD, PhD

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

“Thirty-Thirty: A Program of Preoperative Exercise Counseling”

American Society of Bariatric Surgeons

Principle Investigator: Daniel B. Jones, MD

Co-Investigators: George L. Blackburn, MD, PhD; Daniel S. Rooks, PhD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### Research Accomplishments and Presentations

In the area of clinical trials the following is an update on the status of our current trials:

- Women's Intervention Nutrition Study (WINS) - Protocol #: 2001-P-001549

Preliminary data from the WINS trial were presented in May at the ASCO meeting. Approval continuing review was obtained at BIDMC on June 13<sup>th</sup>, 2005.

- Women's Intervention Nutrition Study Extension - Protocol #: 2001-P-001549/7

Additional funding support was obtained from the National Cancer Institute to allow for a WINS Extension to complete the original study design follow-up duration. Notification from the IRB for approval of this extension was obtained at BIDMC on November 15<sup>th</sup>, 2005. Packages to study participants including a letter regarding current status of WINS Extension study, new consent form (2 copies, one for pt file, one for BIDMC file) and Health Status Forms were sent out in December. Follow-up will continue through 2006.

- Adiponectin in Relation to Breast Cancer - Protocol #: 20005p-000256

Exemption status was approved by the BIDMC Committee on Clinical Investigations on October 18<sup>th</sup>, 2005. Plasma samples were obtained in November from existing data from the Women's Intervention Nutrition Study (WINS). Measurement of adiponectin levels began in December using RIA and data will be analyzed using univariate and multivariate analysis. This will allow us to assess whether baseline serum adiponectin levels predict risk for developing breast cancer and whether the effect of low fat diet on breast cancer is direct and/or whether it is mediated through changes in adiponectin levels.

- Look AHEAD (Action for Health in Diabetes)

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

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

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

### DSE-Control Group

Two social retention events—"Night at the Pops" and "Holiday Party at Longwood Grille" were completed. Classes were organized throughout the year for nutrition, exercise and support. These classes showed improved attendance from previous years. We offered a class for Transition into Phase III- Year 5 and beyond and the first class ready to go for January 2006. We also did a seasonal Newsletter.

### Lifestyle Intervention Group

This year we tried a new initiative, which was "Reunion Groups". These groups have the aim to serve as a retention event for participants to meet with the original group members from the first year. We accomplished three weight loss campaigns/refreshers-1) Mission Possible II, 2) World Series, and 3) The After Dark Campaign. We also hosted a Holiday Weight Loss Challenge. This event was new for 2005 and was not a national campaign, but was done only at the Joslin. Participants signed a contract during the holiday season to either maintain or lose weight during a matter of 8 weeks. There was an incentive provided if successful. Results from the event are below.

**Department of Surgery Annual Research Report 2005**  
**Division of General Surgery**

Weight loss % seen below. National average is 53.3% @ 1 year, 40.8% @ 2 year.

	BI/Joslin April 05	BI/Joslin August 05
Percent with $\geq 7\%$ wt loss yr 1	51.3%	51.3%
Percent with $\geq 7\%$ wt loss yr 2	39.0%	38.2%

- **Effects of Soy Isoflavones on Menopausal Hot Flashes**

In collaboration with OB/GYN, we continue to study alternatives to hormone replacement therapy in postmenopausal women. We are investigating the effect of the novel daidzein-rich isoflavone-aglycone extract from soy germ fermentation on the severity and frequency of hot flashes in postmenopausal women. We are responsible for analyses of biomarkers in the blood and urine samples. The laboratory is equipped with two state-of-art HPLC systems to determine soy isoflavones and catecholamines for the proposed clinical study. The pilot and feasibility study as been accepted for publication and the recruitment for the full trial has been completed; we are analyzing the data and preparing manuscripts with the results.

- **Calcium Supplementation for Healthy Weight (CaSHew)**

The CSNM has been given the opportunity to collaborate with one of our Boston Obesity Nutrition Research groups at the Massachusetts General Hospital to investigate Calcium Supplementation for Healthy Weight (CaSHew). The hypothesis is adding calcium and vitamin D supplementation, via orange juice, to caloric restriction enhances weight loss and decreases visceral fat in adults with BMI in the range of 25 to 35 kg/m<sup>2</sup>. The primary objective of this proposal is to evaluate the effect of calcium and vitamin D supplementation (in form of calcium and vitamin D fortified orange juice beverage) in combination with caloric deficit diet on weight loss in overweight and obese adults. Visceral fat loss will be examined as a secondary outcome.

#### New Staff

We have two new investigators Grazyna Galicka-Piskorska, MD, Ph.D. an instructor in Medicine with the division of Nephrology; she will be looking at the effect of surgical weight reduction and associated medical interventions on microalbuminuria and hypertension in patients with morbid obesity. The other investigator Daniel S. Rooks, Ph.D. from the division of Rheumatology, Assistant Professor in Medicine will be investigating the role of preoperative exercise for weight loss surgery.

#### New Awards and Clinical Trials

Dr. Zhou will be co-investigator on a new grant, "New strategies for interpreting in vivo prostate MRI/MRS choline spectra: manipulating gene expression to enhance cancer specificity". The award is from the Department of Defense and is a Hypothesis Development Award.

Dr. Blackburn was awarded two new grants, "Regular OJ-- Effect of calcium/vitamin D on weight loss" and "Light OJ-- Effect of calcium/vitamin D on weight loss". The grants are from the Beverage Institute of Health and Wellness.

#### Individual Accomplishments

##### *George Blackburn, MD, PhD*

- Member of the NIH NIDDK Special Emphasis Panel ZDK1 GRB-1 M2. Clinical Nutrition Research Unit Core Centers, March 9-11, 2005.
- Member of the NIH - NIDDK Special Emphasis Panel Loan Repayment Study Section, April 2005.
- Member of the NIH -NIDDK study section ZDK1 GRB-4, December 8, 2005
- Invited Chairperson: Obesity Treatment Magellan Health Services, Avon CT.
- Associate Editor for *Obesity Research*.
- Editorial Board for *Obesity Management*.

##### *Jin-Rong Zhou, PhD*

- Member, Special Emphasis Panel ZRG1 ONC-K 07M.
- Scientific Advisory Board, 6th International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, Chicago, IL.



- Member, Psychosocial/CAM Treatment Review Panel, Susan G. Komen Breast Cancer Research Foundation
- Ad-hoc member, Cancer Etiology Study Section, NIH.
- Review member, National Key Programs, Natural Sciences Foundation of China
- Ad hoc reviewer, Molecular Nutrition and Food Research
- Ad hoc reviewer, Molecular Carcinogenesis Study Section, NIH.

Invited Presentations (Local, National and International)

*George Blackburn, MD, PhD*

- Best Practices: Patient Safety Issues and Weight Loss Surgery. Harvard Medical School CME; Beth Israel Deaconess Medical Center, Boston, MA. January, 2005.
- Hyperglycemia and the ICU. Surgical Grand Rounds, Mount Auburn Hospital, Cambridge, MA. January 2005.
- Obesity Medicine: Emergence of a New Discipline. American College Physicians, San Francisco, CA. April, 2005.
- Excess Visceral Fat and it's Connection with CVD. Pri-Med Updates, Norfolk, VA. April, 2005.
- Best Practices: Patient Safety Issues and Weight Loss Surgery. Danbury Hospital, Danbury, CT. May, 2005.
- Separating Fact from Fiction: Developments in Obesity-Related Research. 2nd Annual Forum on Obesity Policy, Regulation, and Litigation, Chicago, IL. May. 2005.
- Basic Principles of Obesity Therapy. Nastech Analyst Day, New York, NY. June, 2005.
- Obesity and Cancer. Harvard Medical School CME Long-term Weight Management, Boston, MA. June, 2005.
- Practitioner's Guide to the Dietary Guidelines for Americans. Harvard Medical School CME Patient Safety in Obesity Surgery, Boston, MA. July, 2005.
- Meal Replacements for Weight Management. Harvard Medical School CME Patient Safety in Obesity Surgery, Boston, MA. July, 2005.
- Prevention of Obesity. Obesity and Diabetes Seminar via Satellite to Nicosia, Cyprus. September, 2005.
- Research in Nutrition. BIDMC Dietetic Internship Research Day, Boston, MA. September, 2005.
- Obesity in 2005: Current State of the Nation. Contemporary Forums Obesity Treatment and Prevention Program, Boston, MA. September, 2005.
- Medication for Obesity Management. Contemporary Forums Obesity Treatment and Prevention Program, Boston, MA. October, 2005.
- Excess Visceral Fat and its Connection with CVD. Pri-Med Updates, Providence, RI. October, 2005.
- Use of Complementary and Alternative Medicine Therapies for Menopause Symptoms in the USA: Current and Future Expectations. 20th Annual Japan Menopause Society, Tokyo, Japan. November, 2005.
- Excess Visceral Fat and its Connection with CVD. Pri-Med Updates, Houston, TX. December, 2005.
- Obesity Treatment. Dietetic Interns Obesity Day, Boston, MA. December, 2005.
- Excess Visceral Fat and its Connection with CVD. Pri-Med Updates, Philadelphia, PA. December, 2005.
- Medication Management in Obesity Treatment. Magellan Health Services Advisory Board, Avon, CT. December, 2005.

*Dr. Jin-Rong Zhou, PhD*

- Synergy between dietary bioactive components for cancer prevention. BIDMC Department of Surgery, Boston, MA. January, 2005.
- Diet, Nutrition and Prostate Cancer Prevention. BIDMC Urology Club, Boston, MA. June, 2005.
- The Role of Dietary Modification in Cancer Prevention. BONRC, Boston, MA. May, 2005.

## REPORT OF TEACHING

### Undergraduate and Medical School Courses:

George Blackburn, MD, PhD

- Preventive Medicine & Nutrition, course number PM711.0; Second year HMS Tutor.

### CME Courses

George Blackburn, MD, PhD

- HMS, Department of Continuing Medical Education, Enhancing the Safety of Parenteral and Enteral Nutrition. Cambridge, MA. November 6-8, 2005 Course Director.
- HMS, Department of Continuing Medical Education, "Practical Approaches to the Treatment of Obesity: Obesity Medicine: Emergence of a New Discipline" Cambridge, MA. June 23-25, 2005 Course director.
- HMS, Department of Continuing Medical Education, Patient Safety in Obesity Surgery: Defining Best Practices. Boston, MA July 7-9, 2005. Co-Director. This course was a collaborative effort with Drs. Daniel Jones and Benjamin Schneider from Minimally Invasive Surgery at BIDMC.

## BIBLIOGRAPHY (JANUARY – DECEMBER 2005)

### Original Articles

Ricciotti HA, Khaodhiar L, **Blackburn GL**. Daidzein-rich isoflavone-aglycones for menopausal symptoms. *Int J Gynaecol Obstet* 2005; 89:65-6.

### Original Articles (submitted or in press)

Singh AV, Franke AA, **Blackburn GL**, **Zhou JR**. Soy phytochemicals prevent orthotopic growth and metastasis of bladder cancer by alteration of cancer cell apoptosis and tumor angiogenesis in a mouse model. *Cancer Res* 2005; in press.

### Proceedings of Meetings

**Blackburn GL**, Walker WA. Symposium introduction. Science-based solutions to obesity: what are the roles of academia, government, industry, and healthcare? *Am J Clin Nutr* 2005; 82 (suppl): 207S-210S.

**Blackburn GL**. Solutions in weight control: lessons from gastric surgery. *Am J Clin Nutr* 2005; 82 (suppl): 248S-252S.

**Blackburn GL**. Teaching, learning, doing – best practices in education. *Am J Clin Nutr* 2005; 82 (suppl): 218S-221S.

### Reviews, Chapters, and Editorials

**Blackburn GL**, Hu FB, Harvey AM. Evidence-based recommendations for best practices in weight loss surgery. *Obes Res* 2005; 13: 203-4.

**Blackburn GL**, Mun EC. Therapy insight: weight loss surgery and major cardiovascular risk factors. *Nat Clin Pract Cardiovasc Med* 2005;2:585-91.

**Blackburn GL**, Waltman BA. Authors' response. *J Am Diet Assoc* 2005; 105: 1519.

**Blackburn GL**, Waltman BA. Expanding the limits of treatment – new strategic initiatives. *J Am Diet Assoc* 2005; 105: S131-5.

**Blackburn GL**, Waltman BA. Obesity and insulin resistance. In: McTiernan A, editor. Cancer prevention and management through exercise and weight control. New York: Marcel Dekker, Inc; 2005. p.301-16.

**Blackburn GL**, Waltman BA. Physician's guide to the new dietary guidelines 2005: How best to counsel patients. *Cleve Clin J Med* 2005; 72:609-18.

**Blackburn GL**. Evidence-based approach to the evaluation of weight-loss programs. *Obes Manag* 2005; 1:134-135.

**Blackburn GL**. Diet, exercise, and behavioral treatment of obesity. In: Mantzoros CS, editor. Contemporary diabetes: obesity and diabetes. Totowa: Humana Press; 2005. p.445-55.

McCowen KC, **Blackburn GL**. Obesity and weight control. In: Wong ND, Black HR, Gardin JM, editors. Preventive cardiology a practical approach, 2nd Edition. New York: McGraw-Hill; 2005. p. 233-255.

**Zhou JR**. Flavonoids as inhibitors of tumor metastasis. In: Awad AB, Bradford PG, editors. Nutrition and cancer prevention. New York: Marcel Dekker, Inc; 2005. p.325-49.

**Zhou JR**. Soy-food and soy-drug interactions in prevention and treatment of cancer. In: Thompson LU, Ward WE, editors. Food drug synergy and safety. Boca Raton: CRC Press; 2005. p 125-46.

Reviews, Chapters, and Editorials (submitted or in press)

Gotto AM, **Blackburn GL**, Dailey GE, Garber AJ, Grundy SM, Weir MR. The metabolic syndrome: a call to action. *Coron Artery Dis* 2005; in press.

Khaodhiar L, McCowen KC, **Blackburn GL**. Risk assessment and treatment standards of obesity and overweight in relation to cardiovascular disease. In: Robinson MK, Thomas A, editors. Obesity and cardiovascular disease. New York: Marcel Dekker Inc. 2005; in press.

**Zhou JR**. Animal models in nutritional oncology. In: Heber D, Blackburn GL, Go VLW, Milner J, editors. Nutritional oncology (2nd Ed). San Diego: Academic Press Inc. 2005; in press.

Non-print Materials

**Blackburn GL**, Waltman BA. Selecting commercial weight loss programs (Electronic Letter). Available at: <http://www.annals.org/cgi/eletters/142/1/56>. Accessed April 14, 2005.

**Blackburn GL**, Waltman BA. Patient-oriented, clinician-guided weight management: a case study in the treatment of obesity. *Medscape Diabetes & Endocrinology*. October 31, 2005. Available at: <http://www.medscape.com/viewprogram/4676>.

Abstracts

**Zhou JR**, Mai Z, **Blackburn GL**. Identification of genes responsible for synergistic effect of genistein and tamoxifen combination on growth inhibition of HER2-overexpressing human breast cancer cells. *FASEB J* 2005; 19(5): A1461.



## Mark P. Callery, MD, FACS

Pancreatic cancer is an extraordinarily lethal disease. It is profoundly resistant to any therapy currently available. Our research focuses on the identification of the molecular mechanisms that underlie this phenomenon. We have undertaken three different approaches to reveal these mechanisms.

*Investigate the role of Bcl-X<sub>L</sub> in the chemoresistance of pancreatic cancer.* We have examined the expression and potency of three major death receptors TNF-R, TRAIL-R and Fas in mediating cytotoxicity in pancreatic cancer cell lines. We have analyzed the expression of major anti-apoptotic factors, cell cycle regulators, and death receptor decoys (DcRs) in comparison with normal pancreas tissues and five other human malignant tumor cell lines. By using RNA interference (RNAi) we demonstrate that predominant Bcl-X<sub>L</sub> overexpression plays a critical role in pancreatic cancer chemoresistance. We have utilized RNA interference (RNAi) to deplete Bcl-X<sub>L</sub> expression and further investigated its effects on chemoresistance of pancreatic cancer by using *in vitro* assay and *in vivo* mouse tumor xenograft models.



Dr. Mark Callery

*Investigate the role of HDAC-1 in tumorigenesis of pancreatic cancer.* Histone acetyltransferases (HATs) and HDACs affect gene expression by altering the acetylation status of histones and some transcription factors on target gene promoters. We have found that pancreatic cancer cell lines overexpress HDAC-1 compared to control tissues. Trichostatin A (TSA) treatment of pancreatic cancer cell lines identified TSA-resistant and sensitive phenotypes. To reveal the role that HDAC-1 may play in tumorigenesis of pancreatic cancer, we have constructed HDAC-1 knockdown cells and control counterparts by using RNAi. The effects of HDAC-1 knockdown on cancer cell proliferation and the growth of tumor xenograft *in vivo* are assessed.

*Development of optimal combinatorial chemotherapy.* Pancreatic cancer cells overexpress multiple anti-apoptotic factors and death receptor decoys, and are strongly resistant to radiation, and to 5-fluorouracil (5-FU)- or gemcitabine (Gem)-based chemotherapy regimens. Most pancreatic cancer cell lines are strongly resistant to the proteasome inhibitor PS-341, Hsp90 inhibitor geldanamycin (GA), histone deacetylase inhibitor TSA, or transcription inhibitor doxorubicine (Dox) when administered individually. We hypothesized that an optimal combination of anti-tumor drugs would maximize killing of pancreatic cancer cells of diverse sources at low drug doses. In order to achieve this goal, we have investigated the cytotoxic effects of PS-341, GA, TSA and Dox in eight invasive pancreatic cancer cell lines in the absence of pro-inflammatory cytokines, such as death receptor ligands. In particular, we have compared the efficacies of cytotoxicity of different combinatorial regimens among these drugs in pancreatic cancer cell lines. Through these analyses, we have identified an optimal drug combination that effectively kill most pancreatic cancer cell lines *in vitro*.

### Current Employees

Jirong Bai, DVM, PhD  
Aram Demirjian, MD

Instructor in Surgery  
Research Fellow

### LIST OF CURRENT FUNDING

Research Support  
Beth Israel Hospital Foundation  
Principal Investigator: Mark P. Callery, MD, FACS

“Research Training in Alimentary Tract Surgery”  
National Institutes of Health, T32 Training Grant  
Principal Investigator: David Soybel, MD; Training Fellow: Aram Demirjian, MD

### **APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Overcoming Chemoresistance in Pancreatic Cancer”

National Institutes of Health, RO1

Principle Investigator: Mark P. Callery, MD, FACS; Co-Principle Investigator: Jirong Bai, DVM, PhD

“Targeting Histone Deacetylase-1 to Defeat Pancreatic Cancer Chemoresistance”

National Institutes of Health, RO1

Principle Investigator: Jirong Bai, DVM, PhD; Co-Principle Investigator: Mark P. Callery, MD, FACS

“Identification of pancreatic cancer stem cells”

National Institutes of Health, R21 pilot grant

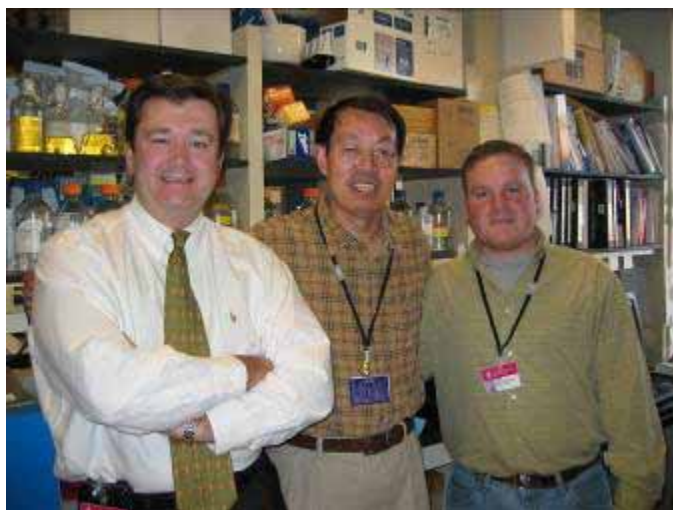
### **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

#### Research Accomplishments

During the past year, we have made the following important discoveries. We have demonstrated that different pancreatic cancer cell lines coexpress high-level TRAIL-R, Fas, and TNF-R1, but are strongly resistant to apoptosis triggered by the death receptors. Death receptor decoys DcR2 and DcR3 overexpression may partly contribute to the resistance of pancreatic cancer cells to TRAIL-R and Fas-mediated cytotoxicity. However, predominant Bcl-XL overexpression plays a vital role in the chemoresistance of pancreatic cancer. We have developed Bcl-XL RNAi knockdown retroviral vectors that cause a 100% depletion of endogenous Bcl-XL overexpression in transduced pancreatic cancer cells. The knockdown of predominant Bcl-XL overexpression significantly reduces the viability of pancreatic cancer cells to TNF- $\alpha$  and TRAIL mediated apoptosis by sublethal-dose PS-341 and GA or combined antitumor drugs including PS-341/Ga and PS-341/TSA regimens.

To investigate further the effects of Bcl-XL depletion on tumor growth, we subcutaneously injected Bcl-XL knockdown pancreatic cancer cells and control counterparts into athymic mice at rear flanks. The animals were maintained for 2 months to allow tumor engraftment. At the end of the experiment, tumor volumes and weight were measured for statistic comparison between Bcl-XL knockdown and control groups. We found that the knockdown of Bcl-XL significantly increased apoptosis, reduced angiogenesis and suppressed tumor growth in vivo.

Pancreatic cancer cell lines overexpress HDAC-1 compared to control tissues. Trichostatin A (TSA) treatment of pancreatic cancer cell lines identified TSA-resistant and sensitive phenotypes. To reveal the role that HDAC-1 may play in tumorigenesis of pancreatic cancer, we have constructed HDAC-1 knockdown cells and control counterparts by retroviral vector harboring RNAi constructs. By using in vitro proliferation assay, we found that HDAC-1 depletion in TSA-sensitive cells had no effects on proliferation of pancreatic cancer cells in the



The Callery Lab: Drs. Mark Callery, Jirong Bai, and Aram Demirjian

presence or absence of antitumor drugs under hypoxic or monoxic conditions. However, HDAC-1 knockdown enhanced TNF $\alpha$ -triggered proliferation of TSA-resistant pancreatic cancer cells in the presence of PS-341 and TSA/PS-341 under hypoxic conditions. In a preliminary study, we found that HDAC-1 knockdown increased the growth of xenografts derived from TSA-resistant cells in athymic mouse models. We have further purified cellular RNA from HDAC-1 knockdown and control cells for gene profiling assays in order to identify HDAC-1 regulated target genes in the future.

We have found that low-dose proteasome inhibitor PS-341 and histone deacetylase inhibitor trichostatin A (TSA) synergistically



induces cytotoxicity in a panel of eight diverse pancreatic cancer cell lines. Combining TSA with PS-341 caused RelA depletion, effectively disrupted NFκB signaling, suppressed the predominant endogenous anti-apoptotic factor Bcl-XL overexpression, and caused an average of 76% apoptotic cell death in six of eight pancreatic cell lines by triggering the intrinsic apoptosis pathway. TSA and PS-341 combinatorial therapy also caused the depletion of K-Ras, MEK1/2, phosphorylated-MEK1/2 and ERK1/2 protein kinases, and inactivated MAP kinase pathways. Conclusion: TSA and PS-341 combination effectively induced apoptosis in pancreatic cancer cells by inactivating NFκB signaling and MAP kinase pathways and may represent a novel antitumor chemotherapy.

Abstracts Presented at Local, National, and International Meetings

Bai J, Demirjian AN, Vollmer CM Jr, **Callery MP**. Developing novel biological therapies that drive apoptosis and overcome chemoresistance in pancreatic cancer cells [Poster session]. Annual Meeting, American Hepato-Pancreato-Biliary Association, Fort Lauderdale, FL. April 14-17, 2005.

Bai J, Demirjian AN, Vollmer CM Jr, **Callery MP**. Bcl-XL depletion sensitizes pancreatic cancer cells to ligand-mediated apoptosis. Annual Meeting, American Hepato-Pancreato-Biliary Association, Fort Lauderdale, FL. April 14-17, 2005.

**REPORT OF TEACHING**

Undergraduate and Medical School Courses

I was active in several courses and teaching activities at the Harvard Medical School.

Graduate School and Graduate Medical Courses

I act as a research mentor to Dr. Aram Demirjian, a surgery resident fellow, who joined my laboratory in June 2004 and works on a project entitled: NF-κB RelA and cRel differentially regulate chemoresistance in pancreatic cancer.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original Articles

Novitsky YW, Kercher KW, Czerniach DR, Kaban GK, Khera S, Gallagher-Dorval KA, **Callery MP**, Litwin DE, Kelly JJ. Advantages of mini-laparoscopic versus conventional laparoscopic cholecystectomy: results of a prospective randomized trial. *Arch Surg* 2005;140(12):1178-83.

Bai J, Sui J, Demirjian A, Vollmer CM Jr, Marasco W, **Callery MP**. Predominant Bcl-X<sub>L</sub> knockdown disables antiapoptotic mechanisms: tumor necrosis factor-related apoptosis-inducing ligand-based triple chemotherapy overcomes chemoresistance in pancreatic cancer cells in vitro. *Cancer Res* 2005; 65(6):2344-52.

Reviews, Chapters, and Editorials

**Callery MP**. Chemotherapy-related steatohepatitis: proceed with caution. *Gastroenterology* 2005;129(6):2114-5.

**Callery MP**. A new platform for gene discovery in pancreatic cancer. *Gastroenterology* 2005 Aug;129(2):763-4.

**Callery MP**. Laparoscopic colectomy for colon cancer: new answers, new questions. *Gastroenterology* 2005; 128(3):793-4.



## Susan J. Hagen, PhD

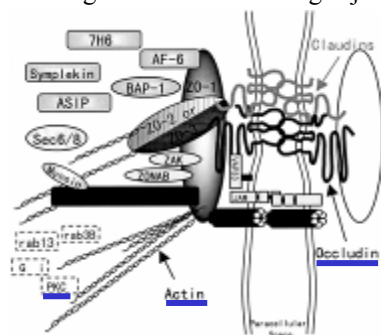
Our current NIH sponsored research is concerned with the regulation of gastric barrier function during health and disease, and our projects include mechanisms that regulate tight junction organization and permeability in the stomach, gastric mucosal restitution after injury, and cell death and survival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



Dr. Susan Hagen

### Tight junction Permeability

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



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

### Gastric Mucosal Restitution after Injury

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

### Cell Death

A new area of investigation in the laboratory is concerned with understanding pathways that regulate cell death and survival of gastric epithelial cells. These new studies were initiated because Th1 cytokines, liberated during HP infection, kill gastric epithelial cells rather than affecting tight junction integrity as occurs in other GI cells. In all inflammatory diseases of the stomach, including infection with HP, death of gastric chief and parietal cells within the gastric gland results in atrophy, which is the major initiating factor in the progression to gastric cancer. In work we submitted for publication in the past year, a novel idea was proposed that gastric chief and parietal cells have single, non-overlapping, cell death pathways that are regulated by unique factors and physiology. Chief cells express BCL-X, which is regulated by transcriptional mechanisms, whereas parietal cells express BAD, which is regulated by intracellular signaling pathways that result in serine phosphorylation. The lab is currently working to understand the regulation of these pathways using isolated cell models.

**Department of Surgery Annual Research Report 2005**  
**Division of General Surgery**

**Current Employees**

*Research Laboratory*

Songhua Zhang, MD, PhD

Regina Ragasa, BS

Andrew French, BA

Saeko Yanaka

Jacob Sanders

Research Fellow

Research Assistant

Administrative Coordinator

Student, Tokyo University

Student, Harvard University

*Core Facilities*

Dan Brown, MS

Justine Curley, MS

Suzanne White, BS

Wendy Litzkow, BS

Sr. Research Associate, Microscopy Core

Research Assistant, Microscopy Core

Histotechnologist Supervisor, Histology Core

Histotechnologist, Histology Core



**Core Facility Staff: Dan Brown, Justine Curley, Suzanne White, (Left) and Wendy Litzkow (Right)**

**LIST OF CURRENT FUNDING**

“GI Mucosal Barrier in Health and Surgical Disease”

National Institutes of Health, NIDDK - **DK15681-33**

Principal Investigator: Susan J. Hagen, PhD

“Biology of Alimentary Epithelia in Health and Disease”

National Institutes of Health, Harvard Digestive Diseases Center grant

Principal Investigator: Wayne Lencer, MD (Children’s Hospital)

Subcontract: “Imaging Core Facility B”

Subcontract Principal Investigator: Susan J. Hagen, PhD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Confocal Microscope for the BIDMC Imaging Core Facility”

NIH: Shared Instrument Grant Program

Principal Investigator: Susan J. Hagen, PhD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### Research Accomplishments

In the past year, we finished three projects and submitted the work for publication. Dr. Kimihito Tashima finished a paper where he outlined the procedure for preparing isolated cultures of gastric chief cells that grow into a confluent monolayer within 3 days. We pursued this line of investigation because no immortalized cell lines exist for gastric parietal or chief cells and, to date, it has not been possible to grow isolated chief cells in culture from rodent species. To accomplish the production of chief cell cultures, we determined that HGF is required. Although the physiological significance of this finding is not presently known, HGF facilitates better cell attachment after isolation and increases protein synthesis resulting in faster confluency and greater pepsinogen protein available for secretion. Confluent monolayers of chief cells also have a very high transepithelial resistance and low permeability making them suitable for further studies of barrier properties and regulation of tight junction structure. We then used the chief cell cultures to show how pro-inflammatory cytokines affect cell viability via the cell survival/death pathway regulated by BCL-X. In April of 2005, Dr. Tashima returned to Japan to take a position as an Associate Professor of Pharmacology.

In collaboration with Dr. Ursula Seidler, Professor of Gastroenterology and Hepatology at Hannover Medical School in Germany, we finished a paper to show the significance of Kir4.1 channels in membrane trafficking and acid secretion in gastric parietal cells. In brief, Kir4.1 channels are apical membrane channels in parietal cells that we propose function, in concert with KCNQ1 channels, to regulate K<sup>+</sup>-efflux and acid secretion after stimulation. We believe that the ion conductance channels contain heteromeric Kir proteins and that KCNQ1 functions in membrane depolarization after stimulation.

### Abstracts Presentations at Local, National, and International Meetings

Asli Muvaffak, PhD, a postdoctoral fellow in the lab in 2005, presented her work at both FASEB and AGA. Dr. Muvaffak's work on barrier properties using cell models of gastric surface cells was accepted for a poster presentation at both meetings. April-May, 2005.

Kimihito Tashima, PhD, a postdoctoral fellow in the lab in 2005, presented his work at the AGA. Dr. Tashima's work on the development of chief cell cultures and the role of inflammatory cytokines on chief cell barrier properties was accepted for poster presentation. May, 2005.

Susan Hagen, PhD, and collaborator Ursula Seidler, MD, had their work on Kir4.1 channels in gastric parietal cells accepted for oral presentation at an AGA Research Forum in 2005. The session was Gastric Cell Biology sponsored by the Esophageal, Gastric, and Duodenal Disorders section of the AGA. May, 2005.

### Administrative Accomplishments

I continued to work as Associate Director for Research in the Department of Surgery. Accomplishments this year were successful completion, in collaboration with Dr. Per-Olof Hasselgren, of the "Annual Research Report" and "Funding Sources for Residents". I was also able to fill the vacant Administrative Coordinator position in the Office for Surgical Research with a very capable and experienced administrator, Andrew French, who was past Office Manager for the Shad Fitness Center at the Harvard Business School.

I continued to direct the Morphology, Histology, and Confocal Microscopy Core Facilities and to provide oversight and consultation for imaging experiments in the hospital and for members of the Harvard Digestive Diseases Center. Accomplishments this year were that I applied for and was awarded, by the BIDMC, funds to purchase a new confocal microscope, a Zeiss LSM510 META, for the Morphology Core Facility. This instrument will replace our outdated Bio-Rad MRC1024 laser confocal system. I submitted a shared instrument grant application to the NIH in collaboration with 6 other PI's at the BIDMC to request funds for a live-cell confocal microscope. This instrument will be used for measuring intracellular pH and for doing FRET analysis in living cells. We obtained a good priority score and the application is pending a funding decision. I was also provided funds by Research and Academic Affairs to hire a new histotechnologist, Wendy Litzkow, to help with the ever increasing demand for service in the Histology Core Facility.



## Department of Surgery Annual Research Report 2005

### Division of General Surgery

#### Individual Accomplishments

I was asked to sit on 2 NIH study sections in 2005. The first invitation was to review applications for an ad hoc section set-up to review a program project grant application from the University of Illinois at Chicago. The second invitation was to review applications for the newly established Gastrointestinal Mucosal Pathobiology (GMPB) study section. Subsequently, I became a charter member of the GMPB study section for a 3 year term starting in October of 2005.

I was invited to serve as an abstract reviewer in the Esophageal, Gastric, and Duodenal Disorders section of the American Gastroenterological Association (AGA).

I was asked to be session chair: “H. pylori Biology and Gastric Immunology” at the 10th International Proton Transport Conference in San Diego CA. March, 2005.

#### Invited Presentations (Local, National, and International)

Invited Speaker: “Revisiting the Harvard Connection: Acid-base Balance and Bile Salts on Physiology of the Frog Gastric Mucosa”. Symposium in honor of Professor John Forte entitled “Cellular and Molecular Physiology of H<sup>+</sup>-transport in the GI Tract” at the University of California at Berkeley, Berkeley, CA. February, 2005.

Invited Speaker: “Cell Specific Pathways Regulate the Survival and Death of Gastric Epithelial Cells”. 10th International Proton Transport Conference. San Diego, CA. March, 2005.

Invited Speaker: “Identifying New Ion Transport Mechanisms that Regulate Restitution after Injury in the Stomach”. 2005 Annual Meeting of the American Gastroenterological Association Research Symposium, sponsored by the Esophageal, Gastric, and Duodenal Disorders section: Upper GI Tract Epithelial Repair. May, 2005.

#### Other Accomplishments

Lisa Marrone, a Research Scholars Institute (RSI) student from MIT who worked in the laboratory during the summer of 2005, won numerous awards for the work she did in the laboratory. First, Lisa’s final paper was ranked one of the 5 best in the RSI program in 2005 (chosen from 90 entries) and will be published by the RSI program in their advertising brochure. Second, Lisa’s paper was selected as an STS Intel semifinalist in a rigorous worldwide competition; the paper is pending consideration as a Finalist in the Intel competition. Her paper also won first place at the Greater Washington Area Junior Science and Humanities Symposium. After giving a presentation of her project before a panel of judges, she was awarded a trip to Albuquerque for the National Symposium and a large scholarship. Lisa was also recently accepted “Early Decision” to Yale University as an undergraduate student. This is an outstanding accomplishment, as Yale accepts only 10% of applicants and very few early decision applicants.

## **REPORT OF TEACHING**

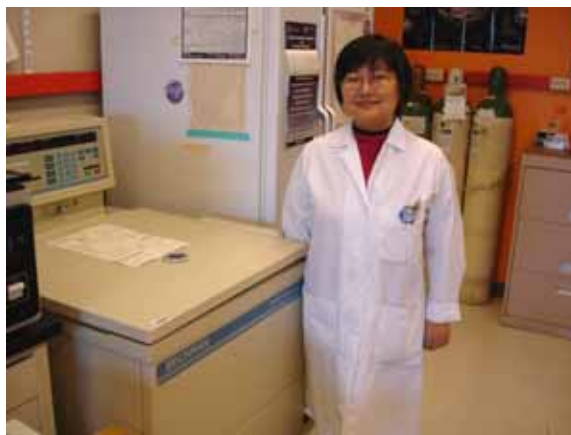
#### Undergraduate and Medical School Courses

I participated in the Body Block at Harvard Medical School from 9/01/2005- 10/31/2005 as co-director of the histology laboratory.

#### Summer and Medical Students

I was a mentor to Ms. Lisa Marrone from the Research Scholars Institute (RSI) at MIT. Lisa was in the laboratory for 5 weeks from June-August of 2005.

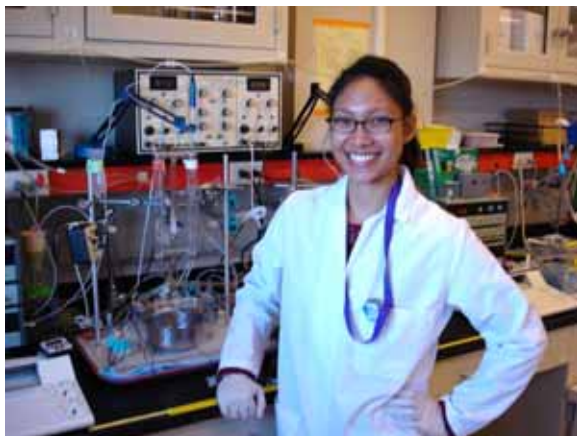
I was a mentor for Ms. Boram Cha, a PhD student from the Department of Pharmacology, Yonsei University College of Medicine in Seoul, Korea. Boram worked in the laboratory with Dr. Muvaffak for 3 months from June-August of 2005.



Dr. Songhua Zhang



I was, again in the summer of 2005, a mentor for Ms. Saeko Yanaka, who did a research rotation in the laboratory for 3 weeks in August of 2005. Saeko is a 2nd year undergraduate student at Tokyo University in Japan.



Regina Ragasa



Saeko Yanaka

#### **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

##### Original Articles (submitted or in press)

**Hagen SJ**, Yang DX, Taylor J, Tashima K, Fox JG. BAD and BCL-X<sub>L/S</sub> may regulate *Helicobacter pylori*-induced corpus glandular atrophy in the mouse stomach. 2005; submitted.

Tashima K, Muvaffak A, Nakamura E, **Hagen SJ**. Establishment of high resistance and low permeability cultures of chief cells from the rat stomach. 2005; submitted.

Kaufhold M-A, Fahrmann, Klocker N, Beil W, **Hagen SJ**, Seidler U. Localization, trafficking, and phosphorylation of the K<sup>+</sup>-channel, Kir4.1, in rat and rabbit parietal cells. 2005; submitted.

##### Educational Materials

**Hagen SJ**. Funding Sources for Residents; 2005. This document is published on the web at: <http://bidmc.harvard.edu/content/bidmc/Departments/Surgery/ResFund05.pdf>

##### Abstracts

**Hagen SJ**, Yang DX, Fox JG. Changes in BCL-X gene expression may regulate chief cell deletion during *H. pylori* infection of the stomach. *FASEB J* 2005; 19(4): A756.

Kaufhold M-A, Fahrmann, Klocker N, Beil W, **Hagen SJ**, Seidler U. Localization, trafficking, and phosphorylation of the K<sup>+</sup>-channel, Kir4.1, in rat and rabbit parietal cells. *Gastroenterology* 2005;128(4): 519A.

Muvaffak A, Tashima K, **Hagen SJ**. Effects of L-glutamine on ammonia-induced injury in rat gastric mucosa (RGM-1 cells cultured on Matrigel matrix with established barrier properties). *Gastroenterology* 2005; 128(4): 345A.

Muvaffak A, Tashima K, **Hagen SJ**. EGF, TGF- $\beta$ 2, and matrix proteins induce tight junction reorganization in rat gastric mucosal-1 (RGM-1) cells. *FASEB J* 2005; 19(4): A755.

Tashima K, Muvaffak A, Nakamura E, **Hagen SJ**. Establishment of high resistance and low permeability cultured chief cells from the rat stomach. *Gastroenterology* 128(4): 600A.

Tashima K, Muvaffak A, Sanders JN, **Hagen SJ**. Expression of the pro-apoptotic protein BCL-X<sub>S</sub> may facilitate chief cell death and gland atrophy during *Helicobacter pylori* infection. *Gastroenterology* 128 (4): 597A.



## Per-Olof Hasselgren, MD, PhD

The research efforts in our group are focused on the metabolic and inflammatory responses to injury and sepsis in skeletal muscle and intestinal mucosa. Sepsis and severe injury are associated with muscle wasting (Figure 1), mainly reflecting ubiquitin-proteasome-dependent degradation of the myofibrillar proteins actin and myosin. 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 pathway, 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

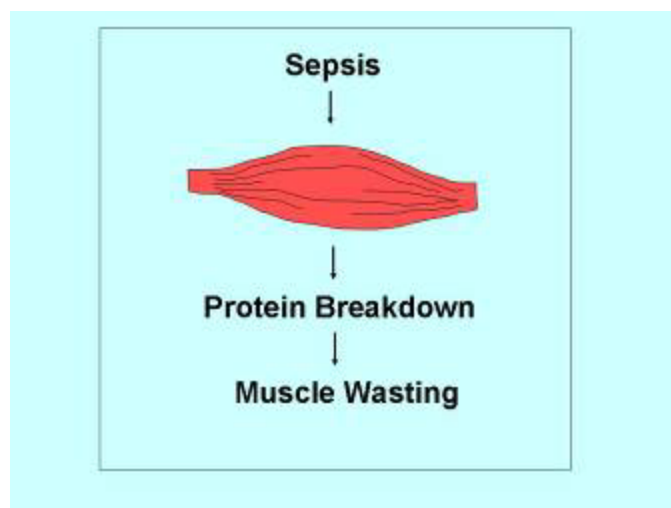


Figure 1

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 the activation of calcium-calmodulin protein kinase II and the PI3K/Akt/GSK3 $\beta$  signaling pathway. The long-term goal of the studies is to define molecular mechanisms responsible for sepsis-induced muscle proteolysis and to define molecule(s) that can be targeted to prevent or treat muscle wasting in sepsis and other catabolic conditions.

In other studies, the regulation of IL-6 production in gut mucosa and enterocytes is examined. IL-6 is a pleiotropic cytokine that can have both pro- and anti-inflammatory properties. In previous studies, we found evidence that mucosal IL-6 production is increased during sepsis and endotoxemia and in human enterocytes stimulated with IL-1 $\beta$  (Figure 2). In other experiments, we defined transcription factors (NF- $\kappa$ B, AP-1, CREB, and C/EBP) that are involved in the activation of the IL-6 gene in stimulated enterocytes. We have recently made the interesting

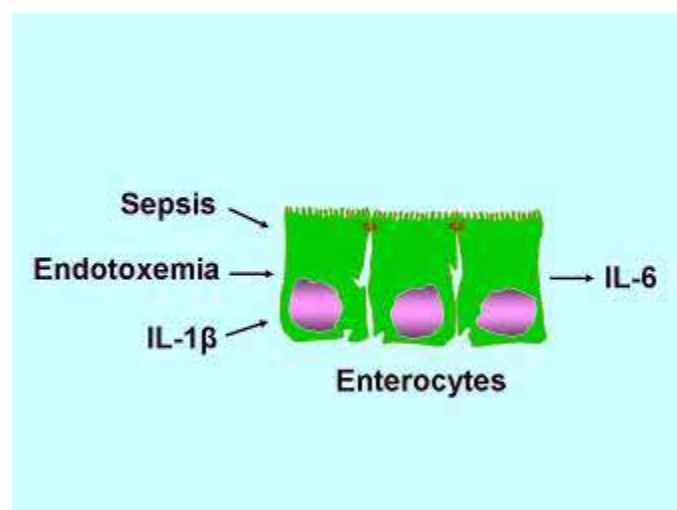


Figure 2

observation that the heat shock response upregulates the expression of IL-6 in stimulated enterocytes and in intestinal mucosa. In current experiments, we are defining signaling pathways that are involved in heat shock-induced potentiation of IL-6 production and have found evidence that the PI3K/Akt pathway may be important for this response. In more recent experiments, we have found evidence that probiotic bacteria may also potentiate IL-6 production in enterocytes and that this effect of probiotics is secondary to induction of the heat shock response. Because IL-6 may exert protective effects in enterocytes/gut mucosa, treatments that augment IL-6 production and understanding the mechanisms of stimulated IL-6 production may have important clinical implications.

**Department of Surgery Annual Research Report 2005**  
**Division of General Surgery**

**Current Employees**

Michael Menconi, PhD  
Moin Fareed, PhD  
Hongmei Yang, PhD  
Wei Wei, PhD  
Vitaliy Poylin, MD  
Natasha Reilly, BS  
Sally Gwin, BS

Assistant Professor of Surgery  
Instructor in Surgery  
Research Fellow  
Research Fellow  
Research Fellow, Surgical Resident  
Research Assistant  
Administrative Coordinator

**LIST OF CURRENT FUNDING**

“C/EBP and IL-6 Production in Mucosa and Enterocytes”

National Institutes of Health, NIDDK R01 - **DK60546**

Principle Investigator: Per-Olof Hasselgren, MD, PhD

“C/EBP, Atrogin-1, and Muscle Wasting”

National Institutes of Health, R01 - **NR08545**

Principle Investigator: Per-Olof Hasselgren, MD, PhD

Gastrointestinal Training Grant

National Institutes of Health, T32 Training Grant

Training Fellow: Vitaliy Poylin, MD; Mentor: Per-Olof Hasselgren, MD, PhD



**The Hasselgren Laboratory. Back: Drs. Hasselgren, Poylin, Menconi, and Fareed. Front: Natasha Reilly, Drs. Yang and Wei.**

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Muscle Protein Turnover and Amino Acid Uptake in Sepsis”

National Institutes of Health, R01–**DK37908** (Competing renewal)

Principle Investigator: Per-Olof Hasselgren, MD, PhD

Priority score: 133; Percentile: 2.0

“HAT and HDAC in Muscle Wasting”

Individual National Research Service Award

National Institutes of Health, F32

Principle Investigator: Hongmei Yang, PhD; Mentor: Per-Olof Hasselgren, MD, PhD

“Acetylation, Deacetylation, and p65 in Muscle Wasting”

Muscular Dystrophy Association

Principle Investigator: Per-Olof Hasselgren, MD, PhD

“The Role of PGC-1 $\beta$  in Muscle Wasting”

National Institutes of Health, R21

Principle Investigator: Michael Menconi, PhD; Co-Investigator: Per-Olof Hasselgren, MD, PhD

“GSK-3 $\beta$  and NF-kB/p65 Phosphorylation in Sepsis-induced Muscle Wasting”

National Institutes of Health, R21

Principle Investigator: Moin Fareed, PhD; Co-Investigator: Per-Olof Hasselgren, MD, PhD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### Administrative Accomplishments

- Organized Annual Residents' Research Competition, Department of Surgery, BIDMC. June, 2005
- Organized Clowes' Visiting Professorship in Surgical Research (Kevin Tracy, MD). November, 2005.
- Edited (with Dr Susan Hagen) the Department of Surgery Annual Research Report. 2005



Dr. Michael Menconi



Dr. Hongmei Yang

### Individual Accomplishments

- NIH study section, February 2005
- Visiting Professor, Departments of Surgery and Molecular Biology, Pennsylvania State University, Hershey, PA. May 17-18, 2005
- Invited speaker, “Cell Signaling in Muscle Wasting”, European Society for Parenteral and Enteral Nutrition (ESPEN), Brussels, Belgium. August 2005
- Guest Editor, Directed Issue on Muscle Wasting, International Journal of Biochemistry and Cell Biology. October 2005

## **REPORT OF TEACHING**

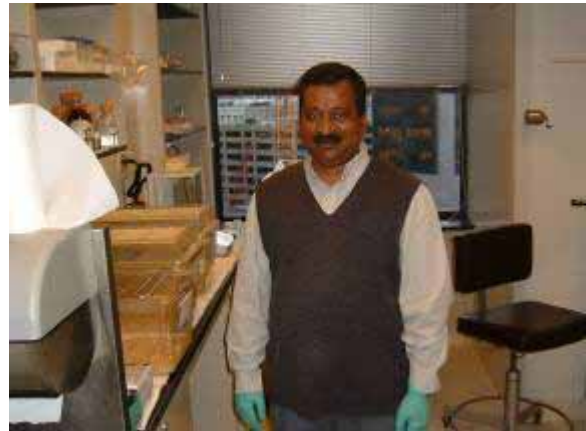
### Graduate School and graduate medical courses

Surgical Clerkship, Medical Students 3<sup>rd</sup> year, Harvard Medical School: Endocrine Surgery – Thyroid and Parathyroid





Dr. Wei Wei



Dr. Moin Fareed

### **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

#### Original Articles

Evenson AR, Fareed M, Menconi M, Mitchell JC, **Hasselgren PO**. GSK-3 $\beta$  inhibitors reduce protein degradation in muscles from septic rats and in dexamethasone-treated myotubes. *Int J Biochem Cell Biol* 2005;37:2226-38.

Fang CH, Li BG, James JH, King JK, Evenson AR, Warden GD, **Hasselgren PO**. Protein breakdown in muscle from burned rats is blocked by IGF-I and GSK-3 $\beta$  inhibitors. *Endocrinology* 2005;146:3141-49.

Li BG, **Hasselgren PO**, Fang CH. Insulin-like growth factor I inhibits dexamethasone-induced proteolysis in L6 myotubes through PI3K/GSK3 $\beta$  and PI3K/mTOR signaling pathways. *Int J Biochem Cell Biol* 2005;37:2207-16.

Mitchell JC, Grant F, Evenson AR, Parker JA, **Hasselgren PO**, Parangi S. Pre-operative evaluation of thyroid nodules with 18FDG-PET/CT. *Surgery* 2005;138:1166-75.

Wei W, Fareed M, Evenson A, Menconi M, Yang H, Petkova V, **Hasselgren PO**. Sepsis stimulates calpain activity in skeletal muscle by decreasing calpastatin activity but does not activate caspase-3. *Am J Physiol* 2005;288:R580-90.

Yang H, Mammen J, Wei W, Menconi M, Evenson A, Fareed M, Petkova V, **Hasselgren PO**. The expression and activity of C/EBP $\beta$  and  $\delta$  are upregulated by dexamethasone in skeletal muscle. *J Cell Physiol* 2005;204:219-26.

Yang H, Menconi M, Wei W, Petkova V, **Hasselgren PO**. Dexamethasone upregulates the expression of p300 and its interaction with C/EBP $\beta$  in cultured myotubes. *J Cell Biochem* 2005;94:1058-67.

#### Original Articles (submitted or in press)

Fareed MU, Evenson AR, Wei W, Menconi M, Poylin V, Petkova V, Pignol B, **Hasselgren PO**. Treatment of rats with calpain inhibitors prevents sepsis-induced muscle proteolysis independent of atrogene-1/MAFbx and MuRF1 expression. *Am J Physiol* 2005; in press.

#### Reviews, Chapters, and Editorials

**Hasselgren PO**, Attaix D. Muscle wasting: current progress and future aims. *Int J Biochem Cell Biol* 2005;37:1932.

**Hasselgren PO**, Menconi MJ, Fareed MU, Yang H, Wei W, Evenson AR. Novel aspects on the regulation of muscle wasting in sepsis. *Int J Biochem Cell Biol* 2005;37:2156-68.





Dr. Vitaliy Poylin



Natasha Reilly

Reviews, Chapters, and Editorials (submitted or in press)

**Hasselgren PO**, Hubbard WJ, Chaudry I. Metabolic and inflammatory responses to trauma and infection. In: Fischer JE, editor. Mastery of Surgery, 5<sup>th</sup> Edition. 2005; in press.



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

*Section for Minimally Invasive Surgery, Center for Minimally Invasive Surgery (CMIS)  
Simulation and Skills Center, Bariatric Program*

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 technical innovations in instrumentation for laparoscopic adjustable banding, robotic colonoscopy, and fibrin glue repair of inguinal hernia repair and current investigation is leading to a better understanding of hormonal regulation of obesity. CMIS has trained medical students, residents, research fellows, clinical fellows, and surgeons worldwide in advanced laparoscopic techniques.



**Dr. Dan Jones (left) in the OR doing a laparoscopic hernia repair.**

Education research is focused on establishing a technical skills laboratory validating new teaching tools and instituting curriculums for medical students and residents. At Harvard Medical School we have established educational programs as part of the Tele-conferencing, Simulation and Technical Skills Lab. First year students observe live surgery telebroadcasts that are available to student groups learning anatomy. During clerkships, students also interact with surgeons from the teleconference center in small groups. These unique learning approaches have challenged traditional pathways. The skills lab has recently been expanded with the addition of a mock operating theatre and mock ICU, and \$2.75 million in philanthropic gifts to create the Simulation and Skills Lab. Further information about the CMIS lab can be obtained at <http://www.bidmc.harvard.edu/mis>.



**MIS resident using the videotrainer to practice endostiching.**

In collaboration, with the Department of Chemical Engineering at MIT, we have investigated the use of alginate and collagen as materials, which can be modified to synthesize an injectable mesh. The goal is to develop a biodegradable liquid that will solidify upon injection into the hernia defect. Availability of an injectable liquid mesh cannot only make the hernia operation less invasive but also potentially eliminate the need for incisions. The project is currently funded through the Center for the Integration of Medicine and Innovative Technology (CIMIT), a research consortium of Harvard hospitals and MIT.

In collaboration with the Weight Loss Program at MGH, we have developed a rodent model to study the laparoscopic adjustable band technique compared to the gastric bypass surgery. Studies evaluate central gut neuroendocrine

changes after surgery, specifically ghrelin, the POMC pathway, and PYY 3-3. Bariatric efforts have also resulted in publication of evidence-based best practices in Massachusetts, hospital clinical care pathways, SAGES national consensus statement on the surgical treatment of morbid obesity, and led the American College of Surgeons Bariatric Network. More information about the obesity and weight-loss program in Surgery at BIDMC can be obtained at <http://www.bidmc.harvard.edu/wls>.

**Current Employees**

Noel Iridias  
Leo Villegas, MD  
Angi Walsh, RN  
Deb Zoll

Simulation and Skills Center Coordinator  
Skills Lab Coordinator  
Nurse Educator  
Administrator

**Department of Surgery Annual Research Report 2005**  
**Division of General Surgery**

Collaborators

Ben Schneider, MD	Section MIS, BIDMC
Vivian Sanchez, MD	Section MIS, BIDMC
Jonathan Critchlow, MD	Section MIS, BIDMC
Lee Kaplan, MD	Weight Loss Center, MGH
David Rattner, MD	Surgery, MGH
David Brooks, MD	Surgery, BWH
George Blackburn, MD, PHD	Surgery, BIDMC

Clinical MIS Fellows:

Christopher Boyd, MD	MIS Fellow
Thomas McIntyre, MD	MIS Fellow
Michael Edwards, MD	MIS Fellow
James Ellsmere, MD	MIS Fellow
Ronit Grinbaum, MD	MIS Fellow

**LIST OF CURRENT FUNDING**

“Liquid Inguinal Hernia Repair”

Center for the Integration of Medicine and Innovative Technology (CIMIT).

Principle Investigator: Ashish Patel, MD; Mentor: Daniel B. Jones, MD

“Educational Training Grant for the Center for Minimally Invasive Surgery (CMIS)”

United States Surgical / TYCO.

Principle Investigator: Daniel B. Jones, MD

“Rabkin Fellowship in Medical Education”

Principle Investigator: Daniel B. Jones, MD

“Objective Competency Assessment in MIS with Novel Performance Theory Based Methods”

Principle Investigator: Ben Schneider, MD; Collaborating Investigator: Daniel B. Jones, MD

“Task Performance Using Head Mounted Display”

Stryker Endoscopy.

Principle Investigator: Shishir Maitel, MD; Mentor: Daniel B. Jones, MD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Preventing Procedural Errors: Development and Validation of a Simulation Based Curriculum”

Risk Management Foundation, Healthcare Safety Research Institute. Collaborative Investigator: Daniel B. Jones, MD

“Physical Exercise After Gastric Bypass”

National Institutes of Health

Collaborative Investigator, Daniel B. Jones, MD

“Development of a Laparoscopic Band Simulator”

National Institutes of Health

Collaborative Investigator, Daniel B. Jones, MD

“Validation of Surgical Teleproctoring”

Stryker Endoscopy

Principle Investigator, Daniel B. Jones, MD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### **Research Accomplishments**

*Education:* As a major resource of the Harvard medical community, the Teleconferencing, Simulation and Technical Skills Lab established in 2003 has this year expanded with a mock operating room and mock ICU to the Simulation and Skills Center. We have sought accreditation as a Level 1, Comprehensive Learning Institute of the American College of Surgeons next year.

*MIS Fellows Research:* We have developed a laparoscopic adjustable band in rodents. This allows for hormonal comparison after gastric bypass procedure. Work by Dr. Ronit Grinbaum, a surgical resident in the MIS program at BIDMC, may lead to better understanding of weight loss and control of diabetes.



**Dr. Dan Jones teleconferencing a laparoscopic adjustable band.**

We are drawing on MIT electrical engineering expertise of Dr. James Ellsmere to develop technologies to better access the laparoscopic adjustable band for band fills. He is currently submitting a grant to CIMIT.

Dr. Michael Edwards, a surgical resident in the MIS program at BIDMC, is studying leptin in adipose tissue with the Division of Endocrinology at BIDMC.

### **Patents Pending**

- Laparoscopic adjustable band and bypass instrumentation. Daniel B. Jones, MD
- Laparoscopic adjustable band for rodents. Shishir Maitel, MD

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

Maithel SK, Stylopoulos N, Rattner, **Jones DB**, Kaplan LM. Roux-en-Y gastric bypass in rats alters hypothalamic weight regulation through a decrease in circulating ghrelin. SAGES; 2005.

Ellsmere J, Edwards M, Grinbaum R, Sanchez V, Schneider B, **Jones DB**. MIS Fellowship improves resident laparoscopic experience and does not lessen operative caseload. SAGES; 2005.

### **Individual Accomplishments**

SAGES Board of Governors

SSAT Foundation Trustee

Chair, Educational Resources Committee

Dinner Chair, Boston Surgical Society

ACS Bariatric Advisory Board

ACS Committee of Accreditation Learning Centers

The Fellowship Council Site Reviewer

James IV Travel Fellowship 2005 –

St Mary's Hospital Campus, London, England

Imperial College London, South Kensington, London, England

Hammersmith Hospital, London, England

Cardiff University Hospital, Cardiff, Wales

Ninewells Hospital and Medical School, Dundee, Scotland

University of Dublin, Adelaide & Meath Hospital, Dublin, Ireland

University College Dublin, St. Vincent's Hospital, Dublin, Ireland

Hong Kong University, Hong Kong, China

University of Sydney, Sydney, Australia

Center for Research and Education, Monash University, Melbourne, Australia.

**Department of Surgery Annual Research Report 2005**  
**Division of General Surgery**

Invited Presentations (Local, National and International)

De S, **Jones DB**. Importance of haptics in minimally invasive surgical simulation and training. SAGES Hollywood, FL. April 15, 2005.

Ellsmere J, **Jones DB**. MIS fellowship improves resident training. Poster presentation, BIDMC Research Day, Boston, MA, October 14, 2005.

**Jones DB** (moderator) Controversies in bariatric surgery. 5<sup>th</sup> Annual Minimally Invasive Surgery Summit. Steamboat Springs, CO. March 22, 2005.

**Jones DB** (moderator) Sugerman H, Blankenship J, Ponce J, OBrien P. Pregnancy and bariatric surgery panel discussion. Minimally Invasive Surgery Symposium, Squaw Valley, CA. February 26, 2005.

**Jones DB**, Provost D, Gagner M, Nguyen, DeMaria E. Stump the experts. 5<sup>th</sup> Annual Minimally Invasive Surgery Summit. Steamboat Springs, CO. March 22, 2005.

**Jones DB**, Schirmer B, Allen JW, Lagardere AO, Boone K (panel). Integrating exercise before and after bariatric surgery panel discussion. Minimally Invasive Surgery Symposium, Squaw Valley, CA. February 24, 2005.

**Jones DB**. Interface of surgery with technology, entrepreneurship and business. John Warren Surgical Society, Harvard Medical School, Boston, MA. May 12, 2005.

**Jones DB**. Laparoscopic gastric bypass: procedural and nursing considerations. Trends in MIS Nursing: Bariatric Surgery. Beth Israel Deaconess Medical Center, Boston, MA. February 12, 2005.

**Jones DB**. Bariatric surgery in elderly and adolescent. Advanced Bariatric Surgery: Laparoscopic Advances, Boston, MA. January 8, 2005.

**Jones DB**. Bariatric surgical management and development of centers of excellence. Beth Israel Deaconess Medical Center, Boston, MA. December 13, 2005.

**Jones DB**. Betsy Lehman Center for error reduction: bariatric surgery. 5<sup>th</sup> Annual Minimally Invasive Surgery Summit. Steamboat Springs, CO. March 23, 2005.

**Jones DB**. Current surgical procedures for obesity. Nutrition. Beth Israel Deaconess Medical Center, Boston, MA. December 5, 2005.

**Jones DB**. Determining best practices and implementing solutions. Patient Safety in Obesity Surgery: Defining Best Practice, Harvard Medical School, Boston, MA. July 10, 2005.

**Jones DB**. Developing best practices. AORN, Mass Chapter, Lahey Clinic, Burlington, MA. November 8, 2005.

**Jones DB**. Fibrin glue and staple-line reinforcement. SAGES Hollywood, FL. April 13, 2005.

**Jones DB**. James IV Report 2005. James IV Association, San Francisco, CA. October 18, 2005.

**Jones DB**. Laparoscopic gastric bypass and adjustable band. Norwalk, CT. August 16, 2005.

**Jones DB**. Laparoscopic gastric bypass versus band for morbid obesity. The Royal North Shore Hospital, Sydney, Australia. November 18, 2005.

**Jones DB**. Laparoscopic gastric bypass. 5<sup>th</sup> Annual Minimally Invasive Surgery Summit. Steamboat Springs, CO. March 21, 2005.

**Jones DB**. Laparoscopic gastric bypass. The Queen's Medical Center, Kapolei, HI. January 27, 2006.

**Jones DB**. Laparoscopic inguinal hernia repair. The Queen's Medical Center, Kapolei, HI. January 28, 2006.

**Jones DB**. Laparoscopic inguinal hernia. Beth Israel Deaconess Medical Center, Boston, MA. August 21, 2005.

**Jones DB**. Laparoscopic obesity surgery in America. Cardiff Hospital, Cardiff, Wales. June 27, 2005.

**Jones DB**. Laparoscopic obesity surgery in America. Hammersmith Hospital, London, England. June 24, 2005.



**Jones DB.** Laparoscopic obesity surgery. The University of Dublin, Trinity College, The Adelaide & Meath Hospital, Dublin, Ireland. July 4, 2005.

**Jones DB.** Laparoscopic obesity surgery. University College Dublin, St Vincent's University Hospital, Dublin, Ireland. July 6, 2005.

**Jones DB.** Laparoscopic obesity surgery: a team approach. Anesthesia Grand Rounds, Beth Israel Deaconess Medical Center, Boston, MA. Dec 14, 2005.

**Jones DB.** Laparoscopic obesity surgery: effective laparoscopic treatment. Imperial College, St Mary's Hospital Campus, London, England. June 20, 2005.

**Jones DB.** Laparoscopic surgery for obesity. Queen Mary Hospital, Hong Kong. November 14, 2005.

**Jones DB.** Mass DPH Betsy Lehman guidelines. Minimally Invasive Surgery Symposium, Squaw Valley, CA. February 26, 2005.

**Jones DB.** Moderator. Practical issues for the new investigator. Distinguishing Yourself as an Independent Clinical Investigator. Harvard Faculty Club, Cambridge, MA. May 13, 2005.

**Jones DB.** Obesity surgery. Clinical Physiology Grand Rounds. Harvard Medical School, Boston, MA. December 12, 2005.

**Jones DB.** Obesity: surgical management. Update in Medicine. Harvard Medical School, Boston, MA. December 14, 2005.

**Jones DB.** Obesity: Surgical management. Updates in Medicine. Boston, MA. Dec 10, 2005.

**Jones DB.** Role of laparoscopic adjustable band. Advanced Bariatric Surgery: Laparoscopic Advances, Boston, MA. January 7, 2005.

**Jones DB.** Safer surgery with simulation training. President's Society, Beth Israel Deaconess Medical Center, Boston, MA. February 15, 2005.

**Jones DB.** Skills training. Red Sox Mentors Program. Beth Israel Deaconess Medical Center, Boston, MA. March 18, 2005.

**Jones DB.** Space, simulators and models. Regional support for skills training through ACS accredited education centers. 91<sup>st</sup> Annual Clinical Congress, San Francisco, CA. October 17, 2005.

**Jones DB.** Status of minimally invasive surgery. Relative merits of open vs laparoscopic. Core Curriculum in Adult Primary Care Medicine. Boston University School of Medicine, Boston, MA. April 9, 2005.

**Jones DB.** Techniques of laparoscopic adjustable band. SAGES Hollywood, FL. April 13, 2005.

**Jones DB.** Videotrainers and simulators in surgical training in the United States. Ninewells Hospital and Medical School, Dundee, Scotland. June 29, 2005.

**Jones DB.** Videotrainers, simulation and virtual reality. Queen Mary Hospital, Hong Kong. November 15, 2005.

**Jones DB.** What is minimally invasive surgery? Crimson Summer Program, Beth Israel Deaconess Medical Center, Boston, MA. August 4, 2005.

Maithel S, Callery M, **Jones DB**, Scott D. Construct and face validity of three laparoscopic simulators: MISTVR, endotower and CELTS. SAGES Hollywood, FL. April 14, 2005.

Schneider B, Rivera LC, Villegas L, **Jones DB**. The effects of sleep deprivation: how much sleep is enough? SAGES; Hollywood, FL. April 15, 2005.

Villegas L, Claros L, **Jones DB**. Results of a change to mandatory laparoscopic skills criteria among surgical residents. SAGES; Hollywood, FL. April 13, 2005.

## **REPORT OF TEACHING**

### Undergraduate and Medical School Courses

At HMS; OSCE, Summer Premedical Institute course, Patient safety in obesity surgery course, and obesity surgery clinical physiology grand rounds.

### Course Director

MIS course series with lab in bariatric nursing and obesity surgery.

For combined BIDMC, MGH, BWH surgeons and faculty: MIS video sessions on numerous laproscopic techniques including adjustable band, gastric bypass, colectomy, adrenalectomy, myotomy, inguinal hernia, cholecystectomy, ventral hernia, appendectomy, and nissen.

## **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

### Original articles

Hamza MA, Schneider BE, Recart A, White P, Ogunnaika B, Provost D, Villegas L, **Jones DB**. Heated and humidified insufflation during laparoscopic gastric bypass surgery: effect on temperature, postoperative pain, and recovery outcomes. *J Laparosc Adv Surg Tech* 2005;15(1):6-12.

Kelly J, Tarnoff M, Shikora S, Thayer B, **Jones DB**, Forse RA, Fanelli R, Lautz D, Buckley F, Munshi I, Coe N. Best care recommendations for surgical care in weight loss surgery. *Obes Res* 2005;13:227-233.

Korndorffer JR, Clayton JL, Tesfay S, Brunner WC, Sierra R, Dunne JB, **Jones DB**, Rege RV, Touchard BS, Scott DJ. Multicenter construct validity for Southwestern laparoscopic video trainer stations. *J Surg Res* 2005;128(1):114-119.

Villegas L, **Jones DB**, Lindberg G, Chang C, Fleming J. Laparoscopic hepatojejunostomy via PTFE-covered stent successfully achieves internal drainage of common bile duct obstruction. *HPB* 2005; 7:149-154.

### Original Articles (in press)

Hoover SJ, Berry MP, Jackes L, Baykal A, **Jones DB**, Anthony T, Naftalis EZ, Peters G, Huth JF, Rege RV, Leitch AM. Ultrasound-guided breast biopsy curriculum for surgical residents. *J Laparosc Adv Surg Tech* 2005; in press.

Maithel SK, Villegas L, Stylopoulos N, Dawson S, **Jones DB**. Simulated laparoscopy using a head-mounted display vs traditional video monitor: an assessment of performance and muscle fatigue. *Surg Endosc* 2005; in press.

Maithel SK, Sierra R, Korndorfer J, Callery M, Neuman PF, Dawson S, **Jones DB**, Scott DJ. Construct and face validity comparison of three laparoscopic surgery simulation trainers: MIST-VR, Endotower, and CELTS. *Surg Endosc* 2005; in press.

Wee CC, **Jones DB**, Davis RB, Bourland AC, Hamel MB. Understanding patient's value of weight loss and expectations for bariatric surgery. *Obes Surg* 2005; in press.

### Reviews, Chapters, and Editorials

Grunwaldt L, Schweisberg S, Rattner D, **Jones DB**. Is laparoscopic inguinal hernia repair an operation of the past? *J Am Coll Surg* 2005; (4): 616-620.

**Jones DB**. The circular stapler for the gastrojejunostomy in laparoscopic gastric bypass. *Obes Surg* 2005; 15(8): 1102-1103.

Jones SB, **Jones DB**: Preoperative evaluation of the healthy laparoscopic patient. In Whelan RL, Fleshman J, editors. The SAGES manual of peri-operative care in minimally invasive surgery. New York: Springer-Verlag; 2005. p. 1-7.

Lee MG, **Jones DB**. Applications of fibrin sealant in surgery. *Surgical Innovation* 2005; 12(3): 203-213.

Lee MG, **Jones DB**. Staple-line buttressing material in gastric bypass surgery. *Expert Rev Med Devices* 2005; 2(5): 599-603.

Nguyen NT, Cohen R, **Jones DB**, Higa K, Provost DA, Wilson EB. Is lap gastric bypass the next gold standard? *Contemp Surg* 2005; 61(3): 128-135.

Rattner DW, Schwaitzberg SD, Grunwaldt L, **Jones DB**. Reply, laparoscopic inguinal hernia repair. *JACS* 2005; 201(3):487-488.

Sanchez V, Provost D, DeMaria E, Blackburn G, **Jones DB**. Reoperative bariatric surgery. In Callery MP, editor. Handbook of reoperative general surgery. Malden: Blackwell Publishing; 2005. p. 67-83.

Schneider BE, Nguyen NT, **Jones DB**. Techniques of laparoscopic gastric bypass. In Sugerman H, Nguyen NT, editors. Management of morbid obesity. New York: Taylor and Francis; 2005. p. 129-137.

Scott DJ, **Jones DB**. Virtual reality training and teaching tools. In Eubanks S, Swanstrom LL, Soper NJ, editors. Mastery of endoscopic and laparoscopic surgery. New York: Lippincott, Williams, and Wilkins; 2005. p.146-162.

Watson M, Hamilton EC, **Jones DB**. Laparoscopic common bile duct exploration. In Van Heerden JA, Farley DR, editors. Operative techniques in general surgery. Philadelphia: Elsevier; 2005. p. 23-38.

#### Reviews, Chapters, and Editorials (in press)

Blackburn G, **Jones DB**. Surgical treatment of obesity and diabetes. *Curr Diabetes Rep* 2006; 6(2). In press.

**Jones DB**, Schneider BE. Introduction to morbid obesity. In: Fischer JE, editor. Mastery of surgery. New York: Lippincott, Williams, and Wilkins; 2006, in press.

McIntyre T, **Jones DB**. Training methods for minimally invasive bariatric surgery. *Surg Tech Int* 2005; in press.

Mun E, V Sanchez V, **Jones DB**. Postoperative assessment, documentation, and follow-up. In: Schauer PR, editor. Laparoscopic obesity surgery. New York: Springer-Verlag; 2005, in press.

Schneider BE, **Jones DB**. Transabdominal transgastric gastrojejunoscopy. In: Schauer PR, editor. Laparoscopic obesity surgery. New York: Springer-Verlag; 2005, in press.

Schwaitzberg SD, **Jones DB**, Grunwaldt L, Rattner DW. Laparoscopic hernia in the light of the Veterans Affairs Cooperative Study 456: more rigorous studies are needed. *Surg Endosc* 2005; in press.

Scott D, **Jones DB**. Hernias and abdominal wall defects. In: Norton JA, Bollinger RR, Chang AE, Lowry SF, Mulvihill SJ, Pass HI, Thompson RW, editors. Surgery scientific basis and current practice. 2<sup>nd</sup> ed. New York: Springer-Verlag; 2005, in press.

#### Books, Monographs, and Textbooks (in press)

**Jones DB**, Maithel S, Schneider BE. Atlas for minimally invasive surgery. Woodbury (CT): Cine-Med; 2005, in press.

#### Nonprint materials

Bessler M, Champion K, Cohen R, Felix E, Gagner M, Hamad G, Herron D, Higa K, **Jones DB**, Nguyen N, Paya M, Shikora S. Laparoscopic roux-en-Y gastric bypass: SAGES pearls [DVD]. Woodbury (CT): Cine-Med; 2005.

**Jones DB**, Schneider B, Blackburn G. Patient safety in obesity surgery: defining best practices [DVD]. Woodbury (CT): Cine-Med; 2005.

Provost DA, Scott DJ, **Jones DB**. Laparoscopic roux-en-Y gastric bypass. Film and Video Festival, American College of Surgeons. San Francisco; October 19, 2005.

#### Abstracts

McIntyre TP, **Jones DB**. Does a patient contract improve follow-up with bariatric patients? *Surgery for Obesity and Related Diseases* 2005. 1(3); 274.



## Sareh Parangi, MD

### Basic Research

1. Angiogenesis and pancreatic tumor progression.
2. Use of antiangiogenic drugs in combination to treat tumors.
3. Antiangiogenic gene therapy.
4. Molecular effects of Thrombospondin on endothelial cells in vivo and in vitro
5. Development of an orthotopic model of thyroid cancer, and treatment with antiangiogenic agents

The main focus of my research centers on the analysis of angiogenesis during tumor progression in a variety of tumors. Focus is on development and use of models that are close to human diseases such as the orthotopic pancreatic and thyroid cancer models. Projects involve use of genetically engineered pancreatic cancer models as well as orthotopic models to test novel antiangiogenic therapies. Gene therapy with antiangiogenic agents is also used to affect tumor progression in both orthotopic pancreatic cancer and thyroid cancer models. Detailed analysis of the effects of thrombospondin on endothelial cells is also an aim of our studies.



Dr. Sareh Parangi

### **Current Employees**

Xue Feng Zhang, PhD

Caitlin Connolly

Pravin Pant

Postdoctoral fellow

Research Technician

Clinical Research assistant (part time)

### **LIST OF CURRENT FUNDING**

“Antiangiogenic Gene Therapy in a Mouse Model of Pancreatic Cancer”

American College of Surgeons Faculty Research Fellowship

Principle Investigator: Sareh Parangi, MD

“Antiangiogenic Therapy of Pancreatic Cancer”

National Cancer Institute, K08 grant

Principal Investigator: Sareh Parangi, MD.

“Antiangiogenic Therapy of Thyroid Cancer”

American Thyroid Association, Thyroid Cancer Award

Principal Investigator: Sareh Parangi, MD

“Role of IGF-1 in Pancreatic Cancer”

American Cancer Society

Co-investigator: Sareh Parangi, MD

“Inhibition of Angiogenesis by Thrombospondin –1”

National Cancer Institute, Program Project Grant, “Temporal and Spatial Regulation of Angiogenesis”

Project 3; Co-investigator: Sareh Parangi, MD

“Multivoxel MRs of Human Breast Cancers at 3T”

National Institutes of Health

Co-investigator: Sareh Parangi, MD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### **Research Accomplishments**

I submitted several abstracts and articles (listed below).

I submitted a 2 year R21 grant proposal to the NIH October of 2005.

I submitted a 4 year grant proposal to the American Cancer Society in October of 2005.

I collaborated with cytopathology on an IRB approved study concerning fine needle aspiration of follicular thyroid lesions for molecular differentiation of follicular thyroid cancer from follicular adenoma.

I developed an orthotopic model of thyroid cancer in mice and was successful in obtaining funding through the American Thyroid Association to study antiangiogenic therapy in this animal model.

I helped to establish the use of a data base for analysis of endocrine surgery patients at BIDMC.

I evaluated the Role of PET/CT scanning in patients with thyroid nodules in the preoperative setting.

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

Grant FD, Mitchell JC, Evenson AR, Parker JA, Hasselgren PO, **Parangi S**. Pre-operative evaluation of thyroid nodules with 18FDG-PET/CT. American Association of Endocrine Surgeons. April 2005. Cancun, Mexico.

Zhang XF, Galardi E, Duquette M, Lawler J, **Parangi S**. Comparison of thrombospondin type I repeats antiangiogenic therapy with gemcitabine in an orthotopic pancreatic cancer model. Poster at the American Association of Cancer Research. April 2005. Anaheim, CA.

Grant FD, Mitchell JC, Evenson AR, Parker JA, Hasselgren PO, **Parangi S**. Pre-operative evaluation of thyroid nodules and identification of thyroid cancer by <sup>18</sup>FDG-PET/CT. Society of Nuclear Medicine, 52<sup>nd</sup> Annual Meeting. May 2005. Toronto, Canada.

Evenson A, Mitchell JC, Wei W, Poylin V, **Parangi S**, Hasselgren PO. The gene expression of calpains and the muscle wasting –associated ubiquitin ligases atrogen-1 and murf-1 is not altered in patients with primary hyperparathyroidism. Oral Presentation at the 52<sup>nd</sup> annual meeting of the Massachusetts Chapter of the American College of Surgeons. November 2005. Dedham, Massachusetts.

Zhang XF, Connolly C, Duquette M, Lawler J, **Parangi S**. Continuous administration of the three thrombospondin-1 type 1 repeats recombinant protein improves the potency of therapy in an orthotopic human pancreatic cancer model. Antiangiogenesis and Drug Delivery to Tumors, Bench to Bedside AACR Meeting. November 2005. Boston, Massachusetts.

### **Individual Accomplishments**

I was elected as a regular member of the American Association of Clinical Endocrinologists.

I was asked to become a member of the Nominating Committee for the American Thyroid Association.

I became an official certified instructor in ultrasound, certified by the American College of Surgeons National Ultrasound Faculty for teaching head and neck ultrasound to residents and faculty. I was also an instructor in the Head and Neck Ultrasound Course at the American College of Surgeons meeting in October of 2005.

I became a member of the prestigious Surgical Biology Club III.

I hired a Clinical Research assistant per diem for help with clinical research projects.

### **Invited Presentations (Local, National and International)**

February 2005: “Prognostic Factors in Thyroid Cancer.” Millenium Hospital, Ecuador.

February 2005: “Novel Horizons in Thyroid Cancers.” Millenium Hospital, Ecuador.

May 2005. “Novel Horizons in Thyroid Cancer.” Deaconess Glover Hospital Medical Grand Rounds. Needham, Massachusetts.

October 2005. “Incidentally Detected Thyroid Nodules, An Epidemic.” Milton Hospital, Milton, Massachusetts.



December 2005: “Incidentally Detected Thyroid Nodules, An Epidemic.” St. Luke’s Hospital, New Bedford, Massachusetts.

## **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

### Original Articles

Grant FD, Mitchell JC, Evenson AR, Parker JA, Hasselgren PO, **Parangi S**. Pre-operative evaluation of thyroid nodules with <sup>18</sup>FDG-PET/CT. *Surgery* 2005; 138(6): 1166-1176.

Mitchell J, **Parangi S**. The thyroid incidentaloma: an increasingly frequent consequence of radiologic imaging. *Semin Ultrasound CT MR* 2005;26(1):37-46.

Mitchell J, **Parangi S**. Angiogenesis in benign and malignant thyroid disease. *Thyroid* 2005;15(6 ):494-510.

Ren B, Wang Y, Ndebele K, Chen F, Wang Y, **Parangi S**. Multiple signaling is involved in endostatin-mediated apoptosis in ECV 304 endothelial cells. *Front Biosci* 2005; 10:1089-97.

Zhang XF, Galardi E, Duquette M, Delic M, Lawler J, **Parangi S**. Anti-angiogenic treatment with thrombospondin-1 three type I repeats recombinant proteins in an orthotopic human pancreatic cancer model. *Clin Cancer Res* 2005; 11(6):2337-44.

Zhang XF, Galardi E, Duquette M, Lawler J, **Parangi S**. Antiangiogenic treatment with three thrombospondin-1 type 1 repeats versus gemcitabine in an orthotopic human pancreatic cancer model. *Clin Cancer Res* 2005;11(15): 5622-5630.

### Original Articles (submitted or in press)

Kim Min P, Vin Yael, **Parangi S**. Image of the month “Gallstone Ileus”. *Arch Surg* 2005; in press.

Osborn C, **Parangi S**. Partial thyroidectomy: illustrated reflections for surgical residents. *Curr Surg* 2005; in press.

Upalakalin JN, Collins LC, Tawa N, **Parangi S**. Carcinoid tumors in the breast. *American Journal of Surgery*. In press.

Warren AG, **Parangi S**. Image of the month “Acute and Chronic Cholecystitis”. *Arch Surg* 2005; in press.

### Reviews, Chapters, and Editorials (in press)

Mitchell J, Hollenberg A, **Parangi S**. The role of the endothelium in normal and pathologic thyroid function. In: Aird W, editor. *Endothelial Biomedicine*. London, England: Cambridge University Press. 2005; in press.

**Parangi S**, Lawler J. The thrombospondins. In: Aird W, editor. *Endothelial Biomedicine*. London, England: Cambridge University Press. 2005; in press.

### Educational materials

DVD of Thyroid Surgery and Recurrent Laryngeal nerve monitoring for teaching of Harvard Medical Students, February 2005, Skills Lab, Beth Israel Deaconess Medical Center.

### Nonprint materials

Updated and maintained website for the Thyroid Center at Beth Israel Deaconess Medical Center, last updated November 2005. <http://www.bidmc.harvard.edu/thyroidcenter>.



## Nicholas E. Tawa, Jr., MD, PhD

### Basic Research

Our work focuses on the mechanisms by which dietary protein or amino acid deficiency reduces muscle proteolysis. In the past year, we have performed experiments demonstrating that pre-conditioning with a low protein diet prevents the rise in protein breakdown and loss of muscle size induced by catabolic stimuli, including denervation, fasting, or free radical exposure. Under these circumstances, low protein diets appear to block the activation of the muscle-specific ubiquitin-protein ligase atrogen, which normally is induced under catabolic conditions.

### Clinical research

Principal Investigator, Dietary polyunsaturated fatty acid and markers of inflammation in patients receiving home parenteral nutrition, Beth Israel Deaconess Medical Center

Co-Investigator, SPOR Award for Cutaneous Oncology, NIH, Bethesda, MD

Co-Investigator, Phase I trial of serial decitabine and dacarbazine in subjects with metastatic melanoma. Sponsor: National Institutes of Health, Bethesda, MD.

### **Current Employees**

Jamie Mitchell, MD

Research Fellow

### **LIST OF CURRENT FUNDING**

Beth Israel Deaconess Medical Center, Donor Gifts  
Principle Investigator: Nicholas E. Tawa, MD, PhD

“Brigham and Womens Hospital T32 Training Grant”  
National Institutes of Health, T32 Training Grant  
Principal Investigator: Nicholas E. Tawa, MD, PhD; Trainee: Jamie Mitchell, MD

### **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

#### Individual Accomplishments

- Lecturer, Association of Operative Registered Nurses, New England Baptist Hospital, Boston, MA
- Operative Nursing Grand Rounds, Beth Israel Deaconess Medical Center
- Lecturer, Cancer Celebration of Life, Beth Israel Deaconess Medical Center

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

Mitchell, JC and **Tawa, NE**. Dietary protein deficiency inhibits activation of muscle proteolysis by hydrogen peroxide. 66th Annual Meeting, Society for Surgical Oncology, 2005.

Mitchell, JC and **Tawa, NE**. Dietary protein deficiency reduces expression of multiple components of the ATP-dependent proteolytic pathway in muscle. J Am College of Surgeons 2005, 201: S35.

Wu, BP, Atkins, MB, Koon, H, Donohoe, K, **Tawa, NE**, Tahan, SR. Histopathologic features of sentinel lymph node metastasis associated with positive completion node dissection in cutaneous melanoma. American College of Pathology, 2005.

#### Invited Presentations (Local, National and International)

Mitchell, JC and Tawa, NE. Dietary protein deficiency inhibits activation of muscle proteolysis by hydrogen peroxide. 66th Annual Meeting, Society for Surgical Oncology, 2005.

**Department of Surgery Annual Research Report 2005**  
**Division of General Surgery**

Plans for the Coming Year

*Basic Research*

Determining the basis for the suppression of muscle proteolysis which occurs in conditions of dietary protein deficiency and prolonged fasting is our main goal. We have now shown that protein deficiency represents a low insulin state, with an accompanying, predictable inhibition of Akt/mTOR kinase signaling in muscle. A suppression of Akt signaling would normally result in activation of the transcription factor FOXO, with subsequent induction of atrogen and a rise in ubiquitin-proteasome mediated proteolysis. However, in protein deficient animals, FOXO's ability to induce a rise in atrogen in muscle is profoundly suppressed. We will further explore the intracellular mechanisms for this adaptation, including the role of endocrine signals, specifically the interaction between insulin signaling and thyroid and adrenal status in protein deficient animals. The role of specific intracellular signaling mechanisms involving Sirt-1 and HIF, which may modify FOXO action and which have relevance to other physiological states such as caloric restriction and aging, will also be assessed.

*Clinical Research*

Role of sentinel lymph node mapping for predicting the natural history of non-melanoma cutaneous malignancies of the trunk and extremities.

Prognostic indicators for thin invasive melanomas.

Novel mapping techniques for sentinel lymph node biopsy.

**REPORT OF TEACHING**

Undergraduate and medical school courses

- Lectured on topics of general surgery, nutrition, surgical oncology, and trauma to HMS surgical clerkship students and to Residents in training.
- Led weekly didactic nutrition conference for hospital dietitians, nurses, and related personnel.

Graduate School and graduate medical courses

- Teaching of Surgical Residents and Fellows by didactic rounds and clinics, preceptorships, and formal lectures.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original Articles (submitted or in press)

Mitchell JC, Hasselgren PO, **Tawa NE Jr.** Leucine inhibits proteolysis in response to dexamethasone and activates the mTor kinase signaling pathway in skeletal muscle. 2005; submitted.

Mitchell JC, Rambo L, Warren M, Goldberg AL, **Tawa NE Jr.** Adaptation to dietary protein deficiency suppresses muscle atrophy caused by fasting, denervation, or oxygen free radicals. 2005; submitted.

**Tawa NE Jr.**, Emu B, Goldberg AL. Thyroid hormones regulate ATP-dependent proteolysis, proteasome content, and ATP-dependent protease activity in skeletal muscle. 2005; submitted.

**Tawa NE Jr.**, Warren M, Goldberg AL. Dietary protein deficiency and prolonged fasting reduce thyroid status and sodium-dependent respiration in rat skeletal muscle. 2005; submitted.

Upalakalin JN, Collins LC, **Tawa NE Jr.**, Parangi, S. Neuroendocrine (Carcinoid) Tumors in the Breast. 2005; submitted.

# Division of Plastic and Reconstructive Surgery



**Sumner Slavin, MD**

**Chief, Division of Plastic and  
Reconstructive Surgery  
Associate Professor of Surgery**

## **Division Members**

**Loren J. Borud, MD**

**Instructor in Surgery**

**Mauricio A. Contreras, MD**

**Instructor in Surgery**

**Bernard T. Lee, MD**

**Instructor in Surgery**

**Donald Morris, MD**

**Assistant Clinical Professor of Surgery**

**Michael Tantillo, MD**

**Instructor in Surgery**

**Adam M. Tobias, MD**

**Instructor in Surgery**

**Joseph Upton, MD**

**Associate Clinical Professor of Surgery**

**Linda M. Dicenzo, RN**

**Nurse Manager**

**Jennifer Forgione**

**Administrative Coordinator**

**Geoffrey Brahmer**

**Educational Coordinator**

**Anne G. Warren**

**HMS IV, Doris Duke Clinical Research  
Fellow**





**Divisional Research Report by Sumner Slavin, MD**  
*Plastic Surgery Research Center*

Basic Research

*Perforator Identification using Near-Infrared Imaging (NIR).* In collaboration with Dr. John Frangioni at the BIDMC, NIR techniques are being investigated in the laboratory to transcutaneously visualize the location of major arterial and venous perforating vessels to aid in flap design (see Figure 1). Already, data gathered in a pig model shows promise for future work.

Clinical Research

*Lymphedema.* The Lymphedema Treatment Center continues to develop under the direction of Drs. Slavin and Borud. Now open two afternoons a month, the Clinic treated 183 patients in the last 2.5 years and also serves as a focal point for much needed residency education in the area of the diagnosis and treatment of lymphedema. No other medical institution in Boston (and few in the U. S.) provides residency education in this area of patient care.



**Figure 1:** (left) View of region of skin in porcine perforator model; (right) Near-infrared real-time image following ICG contrast infusion shows intraoperative non-invasive means of identifying perforators for flap design.

Clinical data on lymphedema is leading to research projects and papers by attending physicians and residents. Drs. Slavin and Borud are currently managing the preparation of manuscripts involving the treatment of both lymphedema and lipedema. Several manuscripts are in press; others have been submitted for publication. Abstracts by both attending physicians and faculty have also been presented at regional, national, and international meetings.

Research involving the use of bioimpedance analysis to document lymphedema is being conducted in collaboration with Anne Warren, a clinical research fellow from HMS. Pilot studies performed using the bioimpedance device has shown it to be a sensitive, reliable tool for evaluating and measuring lymphedema non-invasively. Planned future studies include using the technology to document clinical response to the surgical treatment of lymphedema.

*Massive Weight Loss / Body Contouring.* Dr. Borud has established a database of patients undergoing body contouring following massive weight loss. To date, over 150 patients have been treated with major body contouring procedures, including panniculectomy, brachioplasty, mastopexy, neck lift, lower body lift, and thigh lift. Already, analysis of this experience has resulted in numerous local, regional, and national presentations.

*Peter Jay Sharp Foundation Program for Reconstructive and Aesthetic Breast Surgery.* Through the efforts of Drs. Slavin, Tobias, Lee, Borud, and staff, development continues on the Peter Jay Sharp Foundation Program for Aesthetic and Reconstructive Breast Surgery. In the past two years, 120 perforator and S-GAP flaps have been performed for breast reconstruction. Clinical data from these cases is now being compiled and analyzed for future perforator flap studies, including some in the following areas:

- BRCA and bilateral mastectomy with DIEP Flap reconstruction;
- Fluorescein for evaluation of skin sparing mastectomy flaps;
- Vitamin E coagulopathy: a case report and literature review;
- Pedicled perforator flaps in massive weight loss patients;
- Indocyanine evaluation of deep inferior epigastric perforator anatomy: an animal study in pigs.

**Current Employees**

Loren J. Borud, MD

Mauricio A. Contreras, MD

Bernard T. Lee, MD

Instructor in Surgery

Instructor in Surgery

Instructor in Surgery

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**Current Employees, cont.**

Adam M. Tobias, MD	Instructor in Surgery
Joseph Upton, MD	Associate Clinical Professor of Surgery
Linda M. Dicenzo, RN	Nurse Manager
Jennifer Forgione	Administrative Coordinator
Geoffrey Brahmer	Educational Coordinator
Anne G. Warren	HMS IV, Doris Duke Clinical Research Fellow

**LIST OF CURRENT FUNDING**

“Lymphatic Regeneration within Porous VEGF-C Hydrogels for Secondary Lymphedema”

Department of Defense

Principal Investigator: Mauricio A. Contreras, MD

“Program for Aesthetic and Reconstructive Breast Surgery”

Peter Sharp Foundation

Principal Investigator: Josef E. Fischer, MD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Gene Expression in Secondary Lymphedema Due to Breast Cancer Treatment”

American Cancer Society

Principal Investigator: Sumner A. Slavin, MD

**DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

Research Accomplishments

*Peter Jay Sharp Foundation Program for Aesthetic and Reconstructive Breast Surgery.* In the past two years, 120 perforator and S-GAP flaps have been performed by Drs. Lee and Tobias for breast reconstruction. The program has also been active in resident education. A nurse manager, Linda Dicenzo, RN, was hired to work with patients and to develop the infrastructure of the program, including the ordering of clinical equipment. In the year, the Division practice moved into a new space, and developed key networks and working relationships with the BIDMC breast center, bariatric surgeons, and local area VNA's. Throughout the year, both public relations and educational materials for patients were developed including a website ([www.bostondiep.com](http://www.bostondiep.com)), Sharp Foundation brochures, and an educational CD-ROM for patients.

At the end of the year, a Harvard-wide fellowship was submitted to the GME to establish an unaccredited Reconstructive and Aesthetic Breast Fellowship at the BIDMC. Dr. Sheila Barnett, Director of Graduate Medical Education, BIDMC, has said that the fellowship submission is a “model proposal” for unaccredited fellowships in the medical center. The start of the breast fellowship is planned for July 1, 2006. Recruitment has begun.

*Robert M. Goldwyn, M.D., Distinguished Visiting Lectureship with Harvard Medical School.* Dr. Slavin, with help from Geoffrey Brahmer, continued to raise funds for the lectureship. To date, the fund has accrued \$96,000 in donations. It is the goal of this project to establish a yearly visiting professor lectureship in Plastic and Reconstructive Surgery at the BIDMC. A second solicitation is planned for 2006.

*Lymphedema.* Drs. Slavin and Borud continue to expand their efforts in the lymphedema clinic, involving more residents in clinical research, special projects, and presentations each year. Our scientific collaboration continues with Dr. Håkan Brorson, M.D., a surgical investigator in Malmo, Sweden. In 2005, Dr. Brorson, a world expert in the surgical treatment of lymphedema, came to the BIDMC to operate with Dr. Slavin on a patient from Israel with extreme lipedema. Another clinical collaboration for lymphedema was developed with Laura Jacobs, M.D., Ph.D., a physical medicine and rehabilitation expert. Dr. Jacobs is the inventor of

the Normatec, an external pneumatic compression device which has been effective with lymphedema, lipedema, chronic vascular disease, and open wounds.

In January, 2005, Dr. Slavin and Dr. Borud spoke to the Massachusetts HMO Medical Directors on lymphedema, patient care needs, and the difficulties of obtaining payment from insurance companies. This presentation was a result of advocacy on behalf of patients in the General Court of Massachusetts for Senate Bill 848, which passed the Massachusetts State Senate. Mary Beth Heffernan, Governmental Director, BIDMC, and Geoffrey Brahmer were actively involved in organizing and planning the meeting. The entire Division, including residents and medical students, was active on behalf of patients with lymphedema, both Jennifer Forgione and Linda Diczko, RN, worked closely with patients for information and referral, appointment scheduling, patient education, and follow-up.

*Hand Surgery.* Dr. Upton led a hand dissection workshop at HMS on February 17, 2005. The workshop was organized by the BIDMC Division of Plastic Surgery and the Department of Orthopaedics. In addition to Drs. Borud, Day, and Upton from the BIDMC, Harvard faculty members from the MGH and Children's Hospital also led specific components of the session, teaching about 30 residents and interns in a total dissection of the upper limb: plexus nerve, flexor mechanisms, extensor mechanisms, wrist and interphalangeal joints, arterial anatomy and intrinsic muscles. The Division also closely collaborated with the Department of Orthopaedic Surgery to develop a proposal for a second ACGME hand fellow at the BIDMC. The proposal is expected to be approved by the ACGME in January, 2006.

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

Cooper J, **Slavin SA, Borud LJ**. Lymphocele following medial thigh lift. Annual meeting, Presented at the International Symposium, Plastic Surgery at the Red Sea, Eilat, Israel. March 2005.

Cooper J, **Slavin SA, Borud LJ**. Lymphocele following medial thigh lift. Annual meeting, Presented at the International Symposium, American Society of Aesthetic Plastic Surgeons, New Orleans, LA. April 2005.

**Borud LJ**, Grunwaldt L, Janz BA, Mun E. Components separation combined with abdominal wall plication for repair of large abdominal wall hernias following bariatric surgery. American Society of Plastic Surgeons, Annual Meeting, Chicago, IL. September 2005.

**Borud LJ**, Grunwaldt L, Janz BA, Mun E. Components separation combined with abdominal wall plication for repair of large abdominal wall hernias following bariatric surgery. American Society of Plastic Surgeons, Annual Meeting, New England society of Plastic Surgeons, Washington, DC. November 2005.

Taghinia AH, Shapiro FE, **Slavin SA**. The Safety and efficacy of dexmedetomidine anesthesia in facial aesthetic surgery. Presented at the Northeastern Society of Plastic Surgeons annual meeting, Washington, DC. November 2005.

#### Individual Accomplishments

##### *Dr. Slavin*

- Dr. Slavin was the Invited Special Lecturer for 6 major national meetings, including the Breast Reconstruction Master Series, Annual Meeting – American Society of Plastic Surgeons, Chicago, September, 2005.
- Dr. Slavin established the Robert M. Goldwyn, M.D., Visiting Distinguished Lectureship with Harvard Medical School.
- Dr. Slavin served as an Associate Editor, British Journal of Plastic Surgery.
- Dr. Slavin was the North American Committee Chairman, International Symposium: Plastic Surgery at the Red Sea, Eilat, Israel, March 9-12, 2005.
- Dr. Slavin led 6 cosmetic surgery seminars for the residents in the Harvard Plastic Surgery Residency Program.
- Dr. Slavin served as a member of the Breast Committee, American Society of Plastic Surgeons.
- Dr. Slavin was a Senior Examiner for the Board Examination Committee, American Board of Plastic Surgeons, and was an examiner-participant at the Annual Certifying Examination in Phoenix, AZ, October, 2005.

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- Dr. Slavin represented the Division of Plastic Surgery, BIDMC, on the Executive Committee, Harvard Plastic Surgery Executive Board.
- Dr. Slavin held meetings and actively encouraged and mentored faculty, residents, and medical students to increase their annual output in presentations, research projects, and manuscripts.
- Dr. Slavin was selected by his peers for “Best Doctors in America,” 2005-2006.
- Dr. Slavin served as Director of the Lymphedema Clinic, BIDMC, and provided oversight and mentoring for all of the programs, research, and clinical activities of the Division of Plastic Surgery.

*Dr. Borud*

- Dr. Borud was admitted to the Northeastern Society of Plastic Surgeons.
- Dr. Borud represented the Division of Plastic Surgery, BIDMC, on the Executive Committee, Harvard Plastic Surgery Executive Board.
- Dr. Borud served on the Bariatric Task Force Committee, American Society of Plastic Surgeons.
- Dr. Borud was featured in a nationally televised Dateline NBC Segment on overseas plastic surgery.
- Dr. Borud visited several prominent post-bariatric body contouring specialists in 2005 to share ideas and establish new collaborations, including Dr. Al Aly in Iowa, and Drs. Dennis Hurwitz and Peter Rubin in Pittsburgh.
- Dr. Borud served as Co-Director of the BIDMC Lymphedema Clinic.

*Dr. Lee*

- Dr. Lee was invited to be editor, Encyclopedia of Flaps, 3rd edition.
- Dr. Lee was appointed Co-Director of the Peter J. Sharp Foundation Program for Reconstructive and Aesthetic Breast Surgery.

*Dr. Tobias*

- Dr. Tobias became a Diplomate of the American Board of Plastic Surgery after passing the American Board of Plastic Surgery Oral Exam in November 2005.
- Dr. Tobias was named Director of the Peter Jay Sharp Foundation Fellowship in Aesthetic and Reconstructive Breast Surgery. He was actively involved in program management, organization and development including staffing, website development, patient database, educational media, and the creation of the Breast Fellowship Program.
- Dr. Tobias completed development of a new clinical pathway at BIDMC for Deep Inferior Epigastric Perforator (DIEP) Flap Breast Reconstruction, which is scheduled for implementation in 2006.

*Anne Warren*

- Anne Warren was selected as Doris Duke Clinical Research Fellow, HMS IV, for 2005-2006.
- Anne Warren co-authored and submitted 4 manuscripts in a six month time period – 3 of the 4 papers are currently in press.

*Geoffrey Brahmer*

- Geoffrey Brahmer organized, with Jennifer Forgione, the hand dissection workshop and laboratory, HMS, February 2, 2005.
- Geoffrey Brahmer was the North American Organizer, International Symposium, Plastic Surgery at the Red Sea, Eilat, Israel, March 9-12. He also received a Special Recognition Award by the Israel Society of Plastic Surgeons.
- Geoffrey Brahmer organized and international plastic surgery meeting, American-Israeli Plastic Surgery, American Society of Plastic Surgeons, Annual Meeting, September, 2005.
- Geoffrey Brahmer organized 6 cosmetic training sessions for plastic surgery residents.
- Geoffrey Brahmer drafted and submitted the Breast Fellowship Proposal.
- Geoffrey Brahmer drafted the Combined Orthopaedic/Plastic ACGME Hand Fellowship Proposal.

*Linda M. Diconzo*

- Linda Diconzo provided nursing support and patient care (pre-op and post-op) to DIEP patients, lymphedema patients, and other plastic surgery patients.
- Linda Diconzo established networks with VNA, Breast Care centers, and bariatric surgeons.
- Linda Diconzo managed the development and operations of the plastic surgery office and clinics.
- Linda Diconzo helped develop the website and the dissemination of educational materials for patients.

*Jennifer Forgione*

- Jennifer Forgione organized the logistics and the implementation of Pneumatic medicine and Physical Therapy in the Lymphedema Clinic.
- Jennifer Forgione managed the Perforator Flap Program, with Linda Dicenzo, including the establishment of better clinical networks for patient care.
- Jennifer Forgione administered statistics and managed the lymphedema data base. She also worked closely with lymphedema patients, and their families, in the following areas: patient education, information & referral, travel arrangements, setting up lymphoscintigraphy, clinical appointments, and follow-up.
- Jennifer Forgione, through networking, helped organize the hand dissection workshop and laboratory at HMS.
- Jennifer Forgione attained certification and membership in the Association of Plastic Surgery Assistants, Chicago, American Society of Plastic Surgeons, September, 2005.
- Jennifer Forgione observed a full Lymphoscintigram in the Nuclear Medicine Department at the Dana Farber Cancer Institute in Boston Mass.

Invited Presentations (Local, National and International)

*Dr. Slavin*

“Oncoplastic Techniques: Improving Cosmesis in all Four Quadrants following Breast Conservation.” Invited speaker; Miami Cancer Symposium: Lymphedema – Current Concepts and New Perspectives, Miami, FL. February, 2005.

“The Evolution of TRAM Flap Breast Reconstruction.” Invited lecturer; International Symposium: Plastic Surgery at the Red Sea, Eilat, Israel; Chair, Breast Reconstruction Panel. March, 2005.

Breast Reconstruction Master Series. Invited special lecturer; Annual Meeting – American Society of Plastic Surgeons, Chicago, IL. September, 2005.

“Latissimus Dorsi Volume-Added Flap [Videotape Session]” Invited discussant; Annual Meeting – American Society of Plastic Surgeons, Plastic Surgery 2005, Chicago, IL. September, 2005.

“Breast Reconstruction Flap Techniques and the Treatment of Lymphedema.” Invited speaker; 11th Annual Perspectives in Breast Cancer, Boston, MA. October, 2005.

*Dr. Borud*

“Lymphedema: Medical Issues and Insurance Coverage”. Invited speaker; HMO Medical Directors Meeting. Commonwealth of Massachusetts, Needham, MA. January, 2005.

“Lymphedema”. Tufts New England Medical Center Surgery Grand Rounds Speaker, Boston, MA. February, 2005.

“Hernia Repair Following Massive Weight Loss”. Invited speaker; Plastic Surgery at the Red Sea, Eilat, Israel. March, 2005.

“Component Separation”. Invited speaker; Plastic Surgery Division Rounds, BIDMC. May, 2005.

*Dr. Contreras*

“Promoting Lymphangiogenesis *in vivo* Utilizing Alginate Gels with VEGF-C and Angiopoietin-2.”. Invited speaker; AIVS 2005, Lech am Arlberg, Austria. March, 2005.

“*In vivo* Lymphangiogenesis: VGF-C & Angiopoietin-2 Alginate Gels.” Invited speaker; Era of Hope 2005, Philadelphia, PA. June, 2005.

*Dr. Lee*

“Body Contouring After Bariatric Surgery”. Invited speaker; Caritas Good Samaritan Medical Center, Brockton, MA. January, 2005.

“Breast Reconstruction: State of the Art.” Invited speaker; Harvard Medical International- Video Conference to Chennai, India, Boston, MA. March, 2005.

“Wound Care for the Primary Care Physician.” Invited speaker; Core Curriculum Program in Adult Primary Care Medicine (CME Course), Dedham, MA. April 9, 2005.

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*Dr. Tobias*

“Breast Reconstruction: State of the Art.” Invited speaker; Nursing Inservice CC6, BIDMC. September, 2005.

*Dr. Upton*

Congenital Hand Anomalies Study Group Symposium, Pretoria, South Africa. March 1-3, 2005.

2005 Visiting Professor, Mayo Clinic, Rochester, MN. October 28-29, 2005.

*Geoffrey Brahmner*

“Images of the Body”. Invited speaker; Plastic Surgery Division Rounds, BIDMC. March, 2005.

“Images of the Body” Invited speaker; Woburn Arts Guild, Woburn, MA. May, 2005.

*Anne Warren*

“Bioempedence Analysis in Lymphedema”. Invited speaker; PASTEUR Summer Series, HMS. Summer, 2005.

“Lymphedema/Lipedema.” Invited speaker and panelist, Harvard Plastic Surgery Grand Rounds, Lymphedema Clinic: Diagnosis and Management, Shriners Burns Hospital, Boston, MA. January 11, 2006.

**REPORT OF TEACHING**

Undergraduate and Medical School Courses

Medical students were introduced to the diagnosis, treatment, and management of lymphedema at the lymphedema clinic. From this experience, one medical student prepared a presentation on lymphedema.

The Division of Plastic Surgery was active in teaching student clerkships and 4th year medical students for HMS course, SU514M.1. Five student clerks rotated through the service, each student spending 1 month in the Division. In addition, starting July 1, 2005, the Division was part of the Dept. of Surgery’s elective rotation for 2-week rotations of Harvard Medical Students, HMS III’s.

The Division was selected to be the host site for the Doris Duke Clinic Research Fellow, HMS, 2005-2006. Drs. Borud, Caterson, Cooper, Goldwyn, and Slavin have all served as mentors to the fellow, as well as Geoffrey Brahmner.

Graduate School and Graduate Medical Courses

Dr. Lee organized and led an in-service review for the Harvard Plastic Surgery Program, including study hand-outs, and 4 lectures covering Aesthetic/Breast, Hand, Craniofacial, and the Integument. This effort lead to a significant improvement in average test scores from 39% (no scores above 90%) to 50% (2 scores above 97%) in 2005.

Dr. Borud was an instructor in the BIDMC “Microsurgical Training Course,” July and August, 2005.

Drs. Slavin and Borud introduced surgical interns and plastic surgery residents to the special challenges and approaches in clinically treating patients with lymphedema. Residents are now involved in writing papers and abstracts for publication and presentations.

Drs. Tobias and Lee introduced surgical interns and plastic surgery residents to the special challenges and approaches in microsurgery and working with perforator flaps. Residents are now involved in writing papers and abstracts for publication and presentations.

Drs. Slavin, Borud, and Lee provided 6 demonstrations and training sessions in the use of plastic surgery fillers for both aesthetic and reconstructive purposes.

Drs. Upton and Borud, with other Harvard faculty surgeons, provided a hand dissection and laboratory to residents and interns. Dr. Upton was the lead instructor and session chairman, and Dr. Borud gave a presentation entitled “Flexor Mechanisms of the Hand.”



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Original Articles

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**Upton J**. Invited discussion: the true triPLICATION of the thumb: a case of unclassified thumb polydactyly. *Ann Pl Surg* 2005; 55 (3):324-6.

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**Borud LJ, Warren AG**. Modified vertical abdominoplasty in the massive weight loss patient following bariatric surgery. *Plastic Reconstr Surg* 2005; in press.

Garfein ES, **Borud LJ, Warren AG, Slavin SA**. Learning from a lymphedema clinic: an algorithm for the management of localized swelling. *Plast Reconstr Surg* 2005; in press.

Greene AK, **Slavin SA, Borud LJ**. Treatment of lower extremity lymphedema with suction assisted lipectomy. *Plast Reconstr Surg* 2005; in press.

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**Contreras MA, Slavin SA**, Promoting lymphangiogenesis *in vivo* utilizing alginate gels with VEGF-C and angiopoietin-2. Proceedings: *Era of Hope* 2005; 66:P9-3.

Reviews, Chapters, and Editorials

**Borud LJ, Upton J**. Embryology of the hand and upper limb. In: Mathes S, Hentz VR, editors. *Plastic Surgery*. 2<sup>nd</sup> ed. Philadelphia: Elsevier Inc; 2005.

Hagan R, **Upton J**. Reconstruction of the pediatric mutilated hand. In: Weinzwieg N, Weinzwieg J, editors. *The Mutilated Hand*. Philadelphia: Elsevier; 2005. p. 485-508.

Marler, J, **Upton J**. Management of vascular anomalies. In: Mathes S, Hentz VR, editors. *Plastic Surgery*. 2<sup>nd</sup> ed. Philadelphia: Elsevier Inc; 2005.

Pap S, **Upton J**. Microsurgical cross-hand transfer. In: Weinzwieg N, Weinzwieg J, editors. *The Mutilated Hand*. Philadelphia: Elsevier; 2005. p. 461-466.

**Slavin SA**. Discussion: Pneumothorax as a complication of breast augmentation. *Plast Reconstr Surg* 2005; 116:1127.

**Upton J**. Retrospective study of open versus percutaneous surgery for trigger thumb in children. *Plast Reconstr Surg* 2005; 115(7):1971-1972.

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**Upton J, Labow B.** Congenital anomalies of the upper extremity. In: McCarthy JG, Galiano RD, Boutros S, editors. *Current Therapy in Plastic Surgery*. Philadelphia: Saunders Co; 2006. p. 625-639.

**Upton J, Littler JW.** Digital pollicization for traumatic thumb loss. In: Weinzwieg N, Weinzwieg J, editors. *The Mutilated Hand*. Philadelphia: Elsevier; 2005. p. 143-162.

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Educational Material

**Tobias A, Lee B.** Education CD for breast reconstruction patients.

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Website for Sharp Foundation Program; Education for breast reconstruction patients.

<http://www.sharp.foundation.edu>

# Division of Podiatry



**John Giurini, DPM**

**Chief, Division of Podiatry  
Associate Clinical Professor of Surgery**

## **Division Members**

**Philip Basile, DPM**

**Instructor in Surgery**

**Thanh T. Dinh, DPM**

**Instructor in Surgery**

**Michael K. Gavigan, DPM**

**Clinical Instructor in Surgery**

**Thomas Lyons, DPM**

**Clinical Instructor in Surgery**

**Barry I. Rosenblum, DPM**

**Clinical Assistant Professor of Surgery**

**Aristidis Veves, MD, DSc**

**Associate Professor of Surgery**

Lalita Khaodhiar, MD

Instructor in Medicine

Thanh T. Dinh, DPM

Instructor in Surgery

Thomas Lyons, DPM

Instructor in Surgery

Christina Lima

Research Coordinator

Lydia Longoria

Research Coordinator

Christina Marc

Research Coordinator



**Aristidis Veves, MD, DSc**

*Joslin-Beth Israel Deaconess Foot Center and Microcirculation Lab*

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

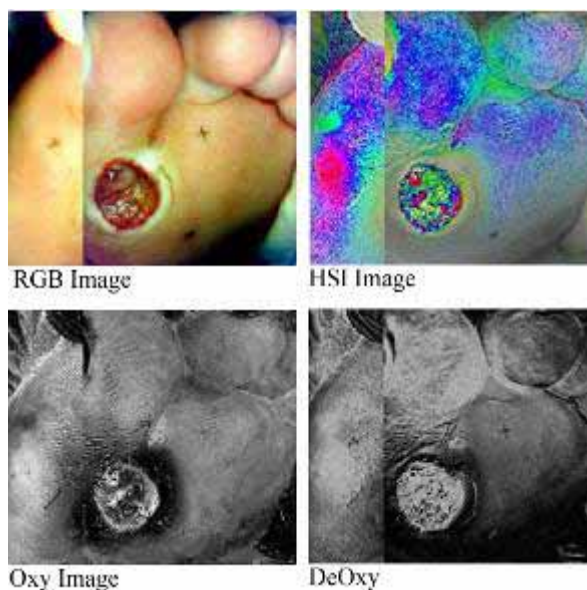
I am interested in the relationship between functional changes in the vascular reactivity and structural changes of the skin. Other interests include the effect of c-nociceptive fiber dysfunction of wound healing and the diabetes-related impairment of angiogenesis.

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

My group is also interested in the etiology of diabetic foot problems and the pathophysiology of foot ulcer 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. We also plan to evaluate the degree of oxygenation in the ulcer bed by using hyperspectral imaging to quantify the amount of oxy- and deoxy-hemoglobin in the ulcer distribution (Figure 1).

In collaboration with the department of Radiology, we also 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.

Finally, research in my Lab, in collaboration with Roy Freeman, MD, examines the natural history of the progression of peripheral neuropathy in diabetic patients.



**Figure 1: Use of Hyperspectral Imaging (HSI).** Visual image of a foot ulcer in the upper left panel, the oxyhemoglobin (OxyHb) and deoxyhemoglobin (DeoxyHb) in the lower two panels. The HSI image (a color representation of the OxyHb and DeoxyHb images) is depicted in the upper right panel.

**Current Employees**

Lalita Khaodhiar, MD  
Thanh T Dinh, DPM  
Thomas Lyons, DPM  
Christina Lima  
Lydia Longoria  
Christina Marc

Instructor in Medicine  
Instructor in Surgery  
Instructor in Surgery  
Research Coordinator  
Research Coordinator  
Research Coordinator

**LIST OF CURRENT FUNDING**

“Vascular and Metabolic Changes in the Diabetic Foot”

National Institutes of Health/Heart and Lung Institute

Principal Investigator: Aristidis Veves, MD, DSc

“Natural History of Small Fiber Diabetic Neuropathy”

National Institutes of Health

Principle Investigator: Aristidis Veves, MD, DSc

“Micro- and Macrovascular Abnormalities and Diabetic Foot Ulceration”

American Diabetes Association

Principal Investigator: Aristidis Veves, MD, DSc

“Imaging of Angiogenesis in Diabetic Animal Models”

Juvenile Diabetes Research Foundation

Principal Investigator: Aristidis Veves, MD, DSc

“Effect of Valsartan in Endothelial Function”

Novartis Pharma

Principle Investigator: Aristidis Veves, MD, DSc

“Imaging Early Markers of Diabetic Microvascular Complications in Peripheral Tissue”

National Institutes of Health - NIDDK

Principle Investigator: George L. King, MD (Joslin Diabetes Center)

Principal Investigator on the BIDMC subcontract: Aristidis Veves, MD, DSc

“Restoring Diabetic Tactile Sense Using Mechanical Noise”

National Institutes of Health

Principle Investigator: Jason Harry, PhD

Principal Investigator on the BIDMC subcontract: Aristidis Veves, MD, DSc

“Hyperspectral Imaging to Assess and Predict Foot Ulceration”

National Institutes of Health

Principle Investigator: Jenny Freeman, MD

Principal Investigator on the BIDMC subcontract: Aristidis Veves, MD, DSc

“Sleep Apnea and Obesity: Cardiovascular Risk Assessment”

National Institutes of Health

Principle Investigator: Atul Malhotra, MD

Principal Investigator on the BIDMC subcontract: Aristidis Veves, MD, DSc

“Ambulatory Foot Temperature in Diabetic Neuropathy”

National Institutes of Health

Principle Investigator: Seward Rutkove, MD

Co-Investigator: Aristidis Veves, MD, DSc

**DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

**Research Accomplishments**

During the last academic year we continued one investigator-initiated clinical study that is related to vascular dysfunction in diabetes and is funded by Novartis Pharma Inc. In addition, we continued the study that is funded by the three-year clinical research grant from the American Diabetes Association and the three-year NIH grant. The main aim is to study the relationship between vascular abnormalities and diabetic foot ulceration. We also continued a 5-year NIH grant that will investigate the natural history of peripheral neuropathy. In addition, I am the principle investigator for the BIDMC in a SBIR (R44) NIH grant awarded to Jason Harry



from Afferent Inc. and a SBTT (R41) NIH grant awarded to Jenny Freeman from HyperMed Inc. Finally, I was awarded a grant from Juvenile Diabetes Foundation and I participate as co-investigator in two NIH-funded studies.

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

Robert L. Greenman, Lalita Khaodhiar, Christina Lima, Thanh Dinh, John M. Giurini, **Aristidis Veves**. Foot small muscle atrophy precedes the development of clinical neuropathy: a phosphorus MRI study. Presented at the annual meeting of the American Diabetes Association, San Francisco, CA; 2005.

Ernest Yankee, Michael Miller, Thomas Serena, peter Sheehan, Lawrence Lavery, Robert Kirsner, Amber Reese, **Aristidis Veves**. Recombinant human lactoferrin (rhLF) may promote healing of diabetic neuropathic ulcers. Presented at the annual meeting of the American Diabetes Association, San Francisco, CA; 2005.

Thanh Dinh, Svetlana V. Panasyuk, Brain H. Tracey, Lalita Khaodhiar, Thomas E. Lyons, Barry I. Rosenblum, John M. Giurini, Jenny E. Freeman, **Aristidis Veves**. The use of medical hyperspectral imaging (MHSI) to identify patients at risk for developing diabetic foot ulcers. Presented at the annual meeting of the American Diabetes Association, San Francisco, CA; 2005.

Gautam Shrikhande, Lalita Khaodhiar, Salvatore Scali, Christina Lima, Matthew Hubbard, Katherine Dudley, Eva Csizmadia, Frank W. Logerfo, Om Ganda, John M. Giurini, Christiane Ferran, **Aristidis Veves**. Valsartan improves resting skin blood flow in type 2 diabetic patients and reduces PARP activation. Presented at the annual meeting of the American Diabetes Association, San Francisco, CA; 2005.

#### Individual Accomplishments

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

I was invited again this year to review grants for the American Diabetes Association. I started reviewing grants during the spring review in April 2003.

I was an ad hoc member of the following NIH study sections: NHLBI Mentored Patient Oriented Research Career Development Award Panel for K23, K24 and K25 applications and R13 Conference Grants; NHLBI Special Emphasis Panel; Specialized Centers of Clinically-Oriented Research in Vascular Injury, Repair, and Remodeling.

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 following journals: Diabetes, Diabetologia, Diabetes Care Diabetic Medicine, Journal of Diabetes and its Complications, Circulation, and New England Journal of Medicine.

I became a member of the Wentworth Institute of Technology Electromechanical Engineering Industrial Professional Advisory Committee.

#### Professional and Educational Leadership

I was a Series Editor for *Contemporary Diabetes*, Humana Press, Totowa, NJ.

#### Invited Presentations (Local, National and International).

"Vascular Abnormalities and Wound Healing." Diabetic Vascular Disease and Wound Complications. European Tissue Repair Society and Vascular Medicine Research Group, University of Southampton, UK. March, 2005.

"Diabetes and Vascular Disease." IX Congress of Vascular Problems, Risk Factor And Diabetic Foot. Buenos Aires, Argentina. May, 2005.

"Pathogenesis and Treatment of the Diabetic Foot Ulcer." IX Congress of Vascular Problems, Risk Factor And Diabetic Foot. Buenos Aires, Argentine. May, 2005.

"Animal Models in Wound Healing (Organizer, Chair and Introduction)." American Diabetes Association 65th Annual Scientific Sessions. San Diego, CA. June, 2005.



**Dr. Aristidis Veves**

**Department of Surgery Annual Research Report 2005**  
**Division of Podiatry**

“Vascular and Metabolic Changes in the Diabetic Foot – Progress Report RFA HL-03-003).” Clinical Research in Peripheral Arterial Disease Grantees' Meeting, Chicago, IL. June, 2005.

“Microcirculation in the Diabetic Foot.” Brigham and Women’s Plastic Surgery Research Team Meeting. Boston, MA. September, 2005.

“Microcirculation Abnormalities in Charcot Neuroarthropathy.” *The Diabetic Foot. Update 2005: A Multidisciplinary Approach*. Department of Orthopedics, The University of Texas Health Science Center at San Antonio, Texas. September, 2005.

“Tissue Oxygenation and Foot Muscle Metabolism Abnormalities in Diabetes”. Wound Healing: Science and Industry. St. Thomas, VI. December, 2005.



**The Veves Lab: Christina Lima, Lydia Longoria, Drs. Veves, Khaodiar, and Dinh.**

**REPORT OF TEACHING**

Educational Activities

I was involved in the training of the podiatry residents. More specifically, I was responsible for lecturing about the principles of clinical research and supervised the residents when they wrote a research proposal. Finally, I helped in reviewing important papers that were published and were relevant to diabetic foot problems.

Drs. Gautam Shrikhande, MD and Salvatore Scali, MD, surgical residents who are doing research this academic year, participated in two of our studies.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original articles

Buras J, Reenstra Wr, Orlow D, Horton Es, **Veves A**. Changes in adiponectin levels related to treatment with troglitazone do not affect endothelial function in type 2 diabetes. *Obes Res* 2005; 13:1167-74.

Economides PA, Khaodiar L, Caselli A, Caballero AE, Keenan H, Bursell S, King GL, Johnstone MT, Horton ES, **Veves A**. The effect of vitamin E on the endothelial function of the micro- and macro-circulation and the left ventricular function of type 1 and 2 diabetic patients. *Diabetes* 2005; 54:204-211.

Greenman RL, Khaodiar L, Lima C, Dinh T, Giurini JM, **Veves A**. Foot small muscle atrophy is present before the detection of clinical neuropathy. *Diabetes Care* 2005; 28:1425–1430.

Greenman RL, Panasyuk S, Wang X, Lyons TE, Dinh T, Longoria L, Giurini JM, Freeman J, Khaodiar L, **Veves A**. Early changes in the skin microcirculation and muscle metabolism of the diabetic foot. *Lancet* 2005; 366:1711-17.

O'Neill MS, **Veves A**, Zanobetti A, Sarnat JA, Gold DR, Economides PA, Horton ES, Schwartz J. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. *Circulation* 2005; 111:2913-20.

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Caselli A, Spallone V, Marfia GA, Battista C, Pachatz C, **Veves A**, Uccioli L. Validation of the nerve axon reflex for the assessment of small nerve fibers' dysfunction. *J Neurol Neurosurg Psych* 2005; submitted.

O'Neill MS, **Veves A**, Sarnat JA, Zanobetti A, Gold DR, Economides PA, Horton ES, Schwartz J. Air pollution and inflammation in Type 2 diabetes: A mechanism for susceptibility. *Diabetes* 2005; submitted.

Priplata AA, Patriiti BL, Niemi JB, Hughes R, Gravelle DC, Lipsitz LA, **Veves A**, Stein J, Bonato P, Collins JJ. Vibrating insoles and enhanced balance control in patients with diabetic neuropathy and patients with stroke. *Ann Neurol* 2005; in press.

Shrikhande G, Scali S, Lima C, Hubbard M, Dudley K, Csizmadia E, Logerfo Fw, Ganda O, Giurini JM, Ferran C, **Veves A**. Valsartan improves resting skin blood flow in type 2 diabetic patients and reduces PARP activation. *J Vasc Surg* 2005; in press.

Reviews, Chapters, and Editorials

Dinh T, **Veves A**. Microcirculation of the diabetic foot. *Curr Pharmaceut Design* 2005; 11:2301-09.

Hile C, **Veves A**. Microcirculation of the diabetic foot. In: Johnstone MT, Veves A, editors. Diabetes and Cardiovascular Disease. 2<sup>nd</sup> ed. Totowa, NJ: Humana Press; June 2005. p. 403-418.

Khaodhiar L, **Veves A**. Therapeutic interventions to improve endothelial function in diabetes. In: Johnstone MT, Veves A, editors. Diabetes and Cardiovascular Disease. 2<sup>nd</sup> ed. Totowa, NJ: Humana Press; June 2005. p. 465-485.

Malik RA, **Veves A**. Diabetic neuropathy. In: Johnstone MT, Veves A, editors. Diabetes and Cardiovascular Disease. 2<sup>nd</sup> ed. Totowa, NJ: Humana Press; June 2005. p. 381-401.

Skljarevski V, **Veves A**. Impact of diabetes on vasculature – focus on the nervous system. *Curr Diabetes Rev* 2005; 1:245-253.

Reviews, Chapters, and Editorials (in press)

Dinh D, **Veves A**. The efficacy of Apligraf in the treatment of diabetic foot ulcers. *Ann Plastic Surg* 2005; in press.

Dinh T, **Veves A**. Microcirculation of the diabetic foot. In: Mantzoros C, editor. Obesity and Diabetes. Totowa, NJ: Humana Press. 2005; in press.

Khaodhiar L., **Veves A**. Cutaneous blood flow, laser doppler measurement. In: Webster J, editor. Encyclopedia Of Medical Devices and Instrumentation. Hoboken, NJ: John Wiley & Sons, Inc. 2005; in press.

Books, Monographs, and Textbooks

Johnstone MT, **Veves A**. Diabetes and Cardiovascular Disease. 2<sup>nd</sup> ed. Totowa, NJ: Humana Press; June 2005.

Books, Monographs, and Textbooks (in press)

**Veves A**, Giurini JM, LoGerfo FW. The Diabetic Foot: Medical and Surgical Management. 2<sup>nd</sup> ed. Totowa, NJ: Humana Press; 2005; in press.

**Veves A**, Malik RA. The Clinical Management of Diabetic Neuropathy. 2<sup>nd</sup> ed. Totowa, NJ: Humana Press; 2005, in press.



# Division of Transplant Surgery



**Douglas W. Hanto, MD, PhD**

## **Division Members**

**Fritz H. Bach, MD**

Hideyasu Sakihama, MD  
Hongjun Wang, PhD  
Eva Czismadia  
Julienne Carty

**Scott R. Johnson, MD**

**Seth J. Karp, MD**

Karen Ho, MD  
Myung Hee Yoon, MD  
Nicole Nesbitt

**Khalid Kwaja, MB, BS**

**Anthony Monaco, MD**

**Takashi Maki, MD, PhD**  
Kanetoshi Sato, MD  
Rita Gottschalk

**Leo E Otterbein, PhD**

Beek Yoke Chin, MD, PhD  
Martin Bilban, PhD  
Kyoichiro Maeshima, MD, PhD  
Jeffery Scott, PhD  
David Gallo  
Eva Czismadia

**Chief, Division of Transplantation**  
**Lewis Thomas Professor of Surgery**

**Lewis Thomas Distinguished Professor of Surgery**

Instructor in Surgery  
Instructor in Surgery  
Research Assistant  
Administrative Assistant

**Instructor in Surgery**

**Assistant Professor of Surgery**

Surgical Resident/Research Fellow  
Visiting Instructor in Surgery  
Research Assistant

**Instructor in Surgery**

**Peter Medawar Professor of Surgery**  
**Associate Professor of Surgery**

Research Fellow  
Research Assistant

**Visiting Assistant Professor of Surgery**

Instructor in Surgery  
Research Fellow  
Research Fellow  
Research Fellow  
Research Associate/HMS Associate  
Research Assistant





**Fritz H. Bach, MD**

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

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

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

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

**Current Employees**

Hideyasu Sakihama, MD	Instructor in Surgery
Hongjun Wang, PhD	Instructor in Surgery
Eva Czismadia	Research Technician
Julienne Carty	Administrative Assistant II

**LIST OF CURRENT FUNDING**

“HemeOxygenase-1: Protection Against Chronic Rejection”  
National Institutes of Health, NHLBI  
Principle Investigator: Fritz H. Bach, MD

“Transplantation of Protected Porcine Islets”  
Riva Foundation/Harvard Medical School  
Principle Investigator: Fritz H. Bach, MD

“Heme Oxygenase as a Therapeutic for Rheumatoid Arthritis”  
Riva Foundation/Harvard Medical School  
Principle Investigator: Fritz H. Bach, MD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Heme Oxygenase-1 and Induction of Tolerance”

National Institutes of Health

Principle Investigator: Fritz H. Bach, MD

**DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

Research Accomplishments

The major research accomplishments relate to the work we have done showing the importance of HO-1 expression in tolerance induction that relies on T regulatory cells. We have also defined in some detail the migration of progenitor cells of the bone marrow to an allografted segment of allogeneic aorta and the effects of carbon monoxide on that process and the subsequent intimal proliferation.

Honors and Awards

Doctor of Medicine, Honoris Causa, 2005 University of Vienna

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original Articles

McDaid J, Yamashita K, Chora A, Ollinger R, Strom TB, Li XC, **Bach FH**, Soares MP. Heme oxygenase-1 modulates the allo-immune response by promoting activation-induced cell death of T cells. *FASEB J* 2005;19(3):458-60.

Wang H, Lee SS, Dell'agnello C, Tchipashvili V, D'Avilla J, Czismadia E, Chin BY, **Bach FH**. Bilirubin can induce tolerance to islet allografts. *Endocrinology* 2005; 147(2):762-8.

Mazzola S, Forni M, Albertini M, Bacci ML, Zannoni A, Gentilini F, Lavitrano M, **Bach FH**, Otterbein LE, Clement MG. Carbon monoxide pretreatment prevents respiratory derangement and ameliorates hyperacute endotoxic shock in pigs. *FASEB J* 2005;19 (14):2045-7.

Ollinger R, Bilban M, Erat A, Froio A, McDaid J, Tyagi S, Csizmadia E, Graca-Souza AV, Liloia A, Soares MP, Otterbein LE, Usheva A, Yamashita K, **Bach FH**. Bilirubin: a natural inhibitor of vascular smooth muscle cell proliferation. *Circulation* 2005;112(7):1030-9.

**Bach FH**. Heme oxygenase-1: a therapeutic amplification funnel. *FASEB J* 2005;19(10):1216-9.

Wang H, Lee SS, Gao W, Czismadia E, McDaid J, Ollinger R, Soares MP, Yamashita K, **Bach FH**. Donor treatment with carbon monoxide can yield islet allograft survival and tolerance. *Diabetes* 2005;54 (5):1400-6.

Berberat PO, A-Rahim YI, Yamashita K, Warny MM, Csizmadia E, Robson SC, **Bach FH**. Heme oxygenase-1-generated biliverdin ameliorates experimental murine colitis. *Inflamm Bowel Dis* 2005 11(4):350-9.

Nakao A, Neto JS, Kanno S, Stolz DB, Kimizuka K, Liu F, **Bach FH**, Billiar TR, Choi AM, Otterbein LE, Murase N. Protection against ischemia/reperfusion injury in cardiac and renal transplantation with carbon monoxide, biliverdin and both. *Am J Transplant* 2005; 5(2):282-91.

**Douglas W. Hanto, MD, PhD**

Basic Research

My current laboratory research is focused on understanding the mechanisms of antibody-mediated rejection in ABO incompatible allografts and the development of accommodation post-transplant. We are examining the ability of endothelial cells, the target of antibody-mediated rejection, to upregulate protective genes (genes that are anti-inflammatory, anti-apoptotic and anti-proliferative in some cases), including those encoding heme oxygenase-1 (HO-1), A20, Bcl-2, and Bcl-xL. Expression of protective genes in the endothelial cells and smooth muscle cells protects these cells from undergoing activation that leads to inflammation and graft rejection. We hypothesize that treatment of the donor and recipient by inducing HO-1 or administering a product such as CO or biliverdin will protect the endothelial cells from antibodies and complement. We are testing our approach in a rodent model and will follow this with large animal models (pig and cynomolgus monkeys) in which ABO incompatible animals are tested. This work is being done in collaboration with Fritz Bach, M.D., and Leo Otterbein, Ph.D. in our division.

A second area of focus is the development of a non-human primate model of liver transplantation and the testing of novel tolerogenic immunosuppressive regimens. We are developing method for the successful transplantation of the liver in cynomolgus monkeys. We are planning to examine the ability of interleukin-2 and interleukin-15 fusion proteins and rapamycin (with or without donor specific transfusions) to induce a permanent state of tolerance as has been shown in a monkey islet cell transplant model. The mechanism is limitation of the early expansion of activated T cells, accentuation of their subsequent apoptotic clearance, amplifying their depletion by antibody dependent mechanisms, while preserving CD4+CD25+ T cell dependent immunoregulatory networks. The balance between cytopathic and regulatory T cells is thereby tipped toward regulatory cells. We believe this may be a potent and effective means of inducing tolerance in the non-human primate model of liver transplantation and will have clinical applicability. This work is being done in collaboration with Terry Strom, M.D., Maria Koulmanda, Ph.D., and Scott Johnson, M.D.

Clinical Research

We are engaged in a number of prospective and retrospective clinical studies involving transplantation (kidney, liver, pancreas, and islet), dialysis access, and nontransplant hepatobiliary surgery. We have had a longstanding interest in the development of malignancies after transplantation, particularly post-transplant lymphoproliferative diseases (PTLD), and also in the risk of transmission of malignancy to recipients from donors with cancer. We have also been interested in antibody mediated rejection in kidney and liver allograft recipients and the development of therapeutic strategies to permit ABO incompatible transplants and transplants in highly sensitized patients. With the introduction of several new immunosuppressive drugs over the past several years, we are examining changes in immunosuppressive protocols to minimize the side-effects of chronic corticosteroid and calcineurin inhibitor toxicity. The ability to safely transplant HIV+ patients is another significant focus of our clinical research activities as part of a multi-center NIH sponsored trial. We are co-investigators in an NIH/NIAID Clinical Trials in Organ Transplantation study of novel immunosuppressive protocols. We are beginning a clinical study in liver transplant recipients using transcriptional profiling to analyze the allograft response in patients that are likely to have predictive value for post-transplant liver function and risk of rejection, with the ultimate goal of being able to individualize the degree of immunosuppression. There are many other ongoing clinical studies examining several issues, including: risk of infectious complications with thymoglobulin induction in kidney transplant recipients; use of donors after cardiac death for kidney, liver, and pancreas transplantation; safety and efficacy of older live kidney donors; role of surgical procedures for bleeding varices in the transplant era; results of total hepatectomy and backtable resection for hepatic malignancies; incidence and outcome of colon cancer after kidney and liver transplantation; antiviral prophylaxis in kidney transplantation; delayed steroid withdrawal utilizing anti-IL2R monoclonal antibody post-transplant; induction post-liver transplant with anti-CD52 monoclonal antibody; use of FTY720, a novel new immunosuppressive drug, in kidney transplantation.

**LIST OF CURRENT FUNDING**

“A Pilot Study to Determine the Safety and Efficacy of Infusion of Donor Specific Cytokine-Mobilized Peripheral Blood Bone Marrow Stem Cells (Pbscs) into Renal Allograft Recipients to Induce Donor Specific Hyporesponsiveness/ Unresponsiveness Evidenced By Reduction in Prednisone and Other Immunosuppressive Maintenance Drug Requirements”

SangStat Medical Corporation

Co-Investigator: Douglas W. Hanto, MD, PhD

“A One-Year, Multicenter Partially Blinded, Double-Dummy, Randomized Study to Evaluate the Efficacy and Safety of FTY720 Combined with Reduced-Dose or Full-Dose Neoral and Corticosteroids Versus Mycophenolate Mofetil (MMF, Cellcept) Combined with Full-Dose Neoral and Corticosteroids in De Novo Adult Renal Transplant Recipients”

Novartis Pharmaceuticals Corporation

Co-Investigator: Douglas W. Hanto, MD, PhD

“Delayed Induction with Zenapax for Successful Steroid Elimination”

Roche Laboratories

Co-Investigator: Douglas W. Hanto, MD, PhD

“Open Label, Prospective, Randomized Controlled, Multi-Center Study Assessing Fixed Dose vs Concentration Controlled Cellcept Regimens for Patients Following a Single Organ Renal Transplantation in Combination Full Dose and Reduced Dose Calcineurin Inhibitors”

Roche Laboratories

Co-Investigator: Douglas W. Hanto, MD, PhD

“Solid Organ Transplantation in HIV: Multi-Site Study”

National Institutes of Health, NIAID **A1052748**

Site Principle Investigator: Douglas W. Hanto, MD, PhD

“Clinical Trials in Organ Transplantation”

National Institutes of Health, NIAID

Co-Investigator: Douglas W. Hanto, MD, PhD

“A Prospective, Open-Label, Multi-Center Randomized Trial of the Efficacy and Safety of Long Term Calcineurin Inhibitor Free Maintenance Regimen with Mycophenolate Mofetil and Sirolimus in Recipients of an Orthotopic Liver Transplant.”

Roche Laboratories

Co-Investigator: Douglas W. Hanto, MD, PhD

“Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial-Extended Criteria Donors.”

Bristol-Myers Squibb

Co-Investigator: Douglas W. Hanto, MD, PhD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“T32 Training Grant in Transplant Immunology”

National Institutes of Health, NIAID T32 Training Grant

Principle Investigator: Douglas W. Hanto, MD, PhD

“Novel Calcineurin Inhibitor for De Novo Renal Transplant Recipients.”

Isotechnika

Co-Investigator: Douglas W. Hanto, MD, PhD

“Novel Early Dialysis Access Vascular Graft.”  
Boston Scientific  
Co-Investigator: Douglas W. Hanto, MD, PhD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### Abstract Presentations at Local, National, and International Meetings

Blumberg E, Olthoff K, Roland M, Ragni M, **Hanto D**, Sherman K, Lu A, Dove L, Light J, Redfield R, Stock P. Expanded criteria donors can be used successfully for transplantation of HIV infected individuals. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1294.

Blumberg E, Olthoff K, Roland M, Ragni M, **Hanto DW**, Sherman K, Lu A, Dove L, Light J, Redfield R, Stock P. Expanded criteria donors can be used successfully for transplantation of HIV infected individuals. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1294.

Cherikh WS, **Hanto DW**, Kauffman HM, Swinnen LJ. Impact of induction and maintenance immunosuppression on postransplant lymphoproliferative disorder in primary kidney transplant recipients with Epstein-Barr virus negative or positive serostatus. American Society of Transplant Surgeons State of the Art Winter Symposium 2005. Miami Beach, FL, January 21-23.

Cherikh WS, **Hanto DW**, Kauffman HM, Swinnen LJ. Impact of induction and maintenance immunosuppression on postransplant lymphoproliferative disorder in primary kidney transplant recipients with Epstein-Barr virus negative or positive serostatus. American Society of Transplant Surgeons State of the Art Winter Symposium 2005. Miami Beach, FL, January 21-23.

Cherikh WS, Kauffman HM, **Hanto DW**, Swinnen LJ. Association of immunosuppression and postransplant lymphoproliferative disorder (PTLD) in primary kidney transplant recipients with Epstein-Barr virus (EBV) negative and positive serostatus. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #390.

Cherikh WS, Kauffman HM, **Hanto DW**, Swinnen LJ. Association of immunosuppression and postransplant lymphoproliferative disorder (PTLD) in primary kidney transplant recipients with Epstein-Barr virus (EBV) negative and positive serostatus. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #390.

Cherikh WS, Kauffman HM, Shames BD, Cheng Y, **Hanto DW**. Association of different immunosuppressive regimens with postransplant de novo malignancies in liver recipients. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #930.

Cherikh WS, Kauffman HM, Shames BD, Cheng Y, **Hanto DW**. Association of different immunosuppressive regimens with postransplant de novo malignancies in liver recipients. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #930.

Johnson SR, Cherikh WS, Pavlakis M, Kauffman HM, **Hanto DW**. Retransplantation after post transplant lymphoproliferative disorder (PTLD). American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1032.

Johnson SR, Cherikh WS, Pavlakis M, Kauffman HM, **Hanto DW**. Retransplantation after post transplant lymphoproliferative disorder (PTLD). American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1032.

Khwaja K, Johnson S, Zaheer A, Pavlakis M, Karp S, Monaco A, Bratton C, **Hanto DW**. Donor kidney volume/recipient weight ratio affects renal function after living donor kidney transplantation. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1263.

Khwaja K, Johnson S, Zaheer A, Pavlakis M, Karp S, Monaco A, Bratton C, **Hanto D**. Donor kidney volume/recipient weight ratio affects renal function after living donor kidney transplantation. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1263.

Wong M, D’Agata E, Curry M, Johnson SR, Nagy S, Khwaja K, Karp S, **Hanto D**. Evolution of antimicrobial resistance in bacteria and yeast in a newly established liver transplant program. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1383.

**Department of Surgery Annual Research Report 2005**  
**Division of Transplant Surgery**

Wong M, D'Agata E, Curry M, Johnson SR, Nagy S, Khwaja K, Karp S, **Hanto D**. Evolution of antimicrobial resistance in bacteria and yeast in a newly established liver transplant program. American Transplant Congress 2005. Seattle, WA, May 21-25. Abstract #1383.

Invited Presentations (Local, National, and International)

Transplant Conference; "Liver and Intestinal Transplantation: Summary Analysis of Data from the SRTR (Scientific Registry of Transplant Recipients) 1994-2003"; Beth Israel Deaconess Medical Center, Boston, MA; February 8.

Charles Witte Legacy Lecture; "Translational Research: What Is It?"; University of Arizona, Department of Surgery, Tucson, AZ; March 2.

The Medical Student Research Program Seminar; "The Surgeon as Translational Scientist: Bench to OR. Adventures of a UA Medical Student/Researcher: From Tucson to Boston." University of Arizona, Department of Surgery, Tucson, AZ; March 2.

Harvard-MIT Division of Health Sciences and Technology, BioMatrix Program; "Ethical Issues in Transplantation"; BioMatrix Members' Meeting "Whose Organ Is It, Anyway?"; Massachusetts Institute of Technology, Cambridge, MA; October 18.

Japan Society for Transplantation, 41st Annual Meeting; "ABO-incompatible Transplants and Accommodation by Upregulation of Protective Genes: a Hypothesis"; Niigata, Japan; October 29.

Japan Society for Transplantation, 41st Annual Meeting; Special Lecture; "Post-transplant Lymphoproliferative Diseases: Current status and When to Transplant"; Niigata, Japan; October 30.

Kobe University Lecture; "Current Status: ABO-incompatible Organ Transplantation and Post-transplant Lymphoproliferative Diseases"; Kobe, Japan; October 31.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

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**Hanto DW**, Fishbein TM, Pinson CW, Olthoff KM, Shiffman ML, Punch JD, Goodrich NP. Liver and intestine transplantation: summary analysis, 1994-2003. *Am J Transplantation* 2005;5:916-33.

Johnson SR, Khwaja K, Pavlakis M, Monaco AP, **Hanto DW**. Older living donors provide excellent quality kidneys: a single center experience. *Clin Transplant* 2005;19:600-606.

Johnson SR, Pavlakis M, Khwaja K, Karp S, Curry M, Monaco A, **Hanto DW**. Intensive care unit extubation does not preclude extrarenal organ recovery from donors after cardiac death. *Transplantation* 2005;80:1244-50.

Kauffman HM, Cherikh WS, Cheng Y, **Hanto DW**, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005;80(7):883-9.

Lerner AB, Sundar E, Mahmood F, Sarge T, **Hanto DW**, Panzica PJ. Four cases of cardiopulmonary thromboembolism during liver transplant without the use of antifibrinolytic drugs. *Anesth Analg* 2005;101:1608-12.

Wray CJ, Lowy AM, Matthews JB, Park S, Choe KA, **Hanto DW**, James LE, Soldano DA, Ahmad SA. The significance and clinical factors associated with a sub-centimeter resection of colorectal metastases. *Annals Surg Oncol* 2005;12(5):374-80.

Reviews, Chapters, and Editorials

**Hanto DW**. Section Editor, Liver Transplantation. Current opinion in organ transplantation 2005;10(2).

Kauffman HM, Cherikh WS, McBride MA, Cheng YA, Delmonico FL, **Hanto DW**. Transplant recipients with a history of a malignancy: risk of recurrent and de novo cancers. *Transplantation Rev* 2005;19(1):55-64.

Reviews, Chapters, and Editorials (submitted or in press)

**Hanto DW**, Johnson SR. Liver transplantation. In: Baker RJ, Fischer JE, editors. *Mastery of Surgery*. 5th ed. Philadelphia: Lippincott, Williams and Wilkins; 2005; in press.



**Hanto DW**, Johnson SR, Karp JS, Khwaja K. Liver transplantation. In: Norton JA, Barie PS, Bollinger RR, Chang AE, Lowry SF, Mulvihill SJ, Pass HI, Thompson RW, editors. *Surgery: Basic Science and Clinical Evidence*, 2nd Edition. New York: Springer-Verlag Inc.; 2005; in press.

Clinical Communications

Lima MA, **Hanto DW**, Curry MP, Wong MT, Dang X, Koralnik IJ. Atypical radiological presentation of progressive multifocal leukoencephalopathy following liver transplantation. *J NeuroVirology* 2005;11:46-50.

Truog RD, Lowney J, **Hanto D**, Caplan A, Brock D. Soliciting organs on the Internet. *Med Ethics* (Burlington, Mass) 2005;12:5-8.

Non-print Materials

**Hanto DW**. Family disagreement over organ donation. Commentary. *Virtual Mentor* 2005;7(9). At: [http://www.ama-assn.org/ama1/pub/upload/mm/384/cc2\\_0905.pdf](http://www.ama-assn.org/ama1/pub/upload/mm/384/cc2_0905.pdf).

Patti ME, McMahon G, Mun EC, Bitton A, Holst JJ, Goldsmith J, **Hanto DW**, Callery M, Arky R, Nose V, Bonner-Weir S, Goldfine AB. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. *Diabetologia*. Online First, 30 September 2005. <http://www.diabetologia-journal.org>.

Abstracts

Paranjape C, Johnson SR, **Hanto DW**. Hepatic trisegmentectomy should be preceded by portal vein embolization to decrease the risk of post-operative liver failure. *J Gastrointest Surg* 2005;9:556.



## Seth J. Karp, MD

### Basic Research

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

Multiple projects are ongoing in the laboratory. The first involves a screen for genes that are important for liver development and regeneration. We identified a number of transcription factors and members of important signaling pathways that are differentially regulated during liver development and regeneration. These are currently being analyzed using real time PCR, in situ hybridization, gene-trap knockouts, RNA inhibition, and transgenic overexpression.

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

Other research involves the role of BMP signaling in liver regeneration using inducible gene targeting of specific members of the BMP family after 2/3 hepatectomy.

### Clinical Research

Clinical research is concerned with predictors of graft survival from donation after cardiac death organs (DCD). We are reviewing the database of the New England Organ Bank to determine whether we can predict whether which factors make an organ unsuitable for transplantation.

### **Current Employees**

Karen Ho, MD  
Myung Hee Yoon, MD  
Nicole Nesbitt

Surgical Resident/Research Fellow  
Visiting Instructor in Surgery  
Research Technician



**Dr. Seth Karp**

### **LIST OF CURRENT FUNDING**

“The Role of Activin Signaling in Liver Growth and Regeneration”

National Institutes of Health, K08 Award

Principle Investigator: Seth J. Karp, MD

“Lineage Analysis in the Developing and Regenerating Liver”

American Society for Transplant Surgery Faculty Development Award

Principle Investigator: Seth J. Karp, MD

### **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

#### Individual Accomplishments

- Assignment to the Vanguard Committee of the American Society of Transplant Surgeons (ASTS).
- Organizer for the ASTS basic science research course for 2006.

**Department of Surgery Annual Research Report 2005**  
**Division of Transplant Surgery**

Patent Disclosures

Karp SJ, Garfein E, Frangione J, Onishi S. Methods for localizing a site of bleeding using near infrared imaging.

**REPORT OF TEACHING**

Graduate School and Graduate Medical Courses

I am involved in operative and ward teaching of fellows and residents.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original Articles

Ugarte R, Kraus E, Montgomery RA, Burdick JF, Ratner L, Haas M, Hawxby AM, **Karp SJ**. Excellent outcomes after transplantation of deceased donor kidneys with high terminal creatinine and mild pathologic lesions. *Transplantation* 2005;80(6):794-800.

Wijgerde M, **Karp S**, McMahon J, McMahon AP. Noggin antagonism of BMP4 signaling controls development of the axial skeleton in the mouse. *Dev Biol* 2005;286(1):149-57.

Johnson SR, Pavlakis M, Khwaja K, **Karp SJ**, Curry M, Curran CC, Monaco AP, Hanto DW. Intensive care unit extubation does not preclude extrarenal organ recovery from donors after cardiac death. *Transplantation* 2005;80(9):1244-50.

**Anthony P. Monaco, MD**

**Takashi Maki, MD, PhD**

*Transplantation and Cellular Immunology Laboratory*

#### Basic Research

*Induction of tolerance to allografts.* The major goal of this project is to study the allograft tolerance induced by donor bone marrow cell infusion combined with immunosuppression by polyclonal anti-T cell antibody (ALS) and rapamycin in a mouse skin allograft model.

*Treatment of overtly diabetic NOD mice.* The major goals of this project are to study the effectiveness of ALS and FTY720 in preventing and curing autoimmune diabetes in NOD mice, a mouse model of type 1 diabetes. We also study the effectiveness of allogeneic islet transplantation under the tolerance induction protocol using donor bone marrow infusion to treat autoimmune diabetes.

*Induction of tolerance to allografts in non-human primates.* The major goal of this preclinical study is to study the induction of tolerance to kidney and islet allografts in non-human primates using anti-thymocyte globulin, rapamycin and donor bone marrow cells.

#### **Current Employees**

Kanetoshi Sato, MD

Postdoctoral Fellow

Rita Gottschalk

Research Technician

#### **LIST OF CURRENT FUNDING**

"Induction of Unresponsiveness to Allografts"

National Institutes of Health

Principal Investigator: Anthony P. Monaco, MD

"Treatment of Overtly Diabetic NOD Mice"

National Institutes of Health

Principal Investigator: Takashi Maki, MD, PhD

"Induction of Tolerance to Allografts in Non-human Primates"

National Institutes of Health

Principle Investigator: Anthony P. Monaco, MD

Co-Principle Investigator: Takashi Maki, MD, PhD

"Prevention and Reversal of Autoimmune Diabetes by FTY720"

Novartis Pharma AG

Principle Investigator: Takashi Maki, MD, PhD

#### **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

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

Khwaja K, Jonhnsen S, Zaheer A, Pavlakis M, Karp S, **Monaco A**, Bratton C, Hanto D. Donor kidney volume/recipient weight ratio effects renal functin after living donor kidney transplantation. American Transplant Congress. May 21- 25, 2005. Seattle, WA.

Minamimura K, Yagita H, **Monaco AP**, **Maki T**. Tolerance induction in sensitized recipients. American Transplant Congress May 21- 25, 2005. Seattle, WA.

**Maki T**, Minamimura K, Gao W. Antilymphocyte serum spares and activates regulatory T cells that suppress alloresponse. American Transplant Congress May 21- 25, 2005. Seattle, WA.

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Invited Presentations (Local, National and International)

**Maki T.** “IACUC Issues” and “CMV Prophylaxis”, Non-human Primate Transplantation Tolerance Models. Presented at the Immune Assays and Analysis Workshop, Emory Transplant Center, Atlanta, GA. September 20 – 21, 2005.

**Maki T.** “Use of Antilymphocyte Serum for Treatment of New Onset Type-1 Diabetes”. Presented at the Genzyme Corporation Annual Meeting in Cambridge, MA. October, 2005.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original Articles

Avihingsanon Y, Ma N, Pavlakis M, Chon WJ, Uknis ME, **Monaco AP**, Ferran C, Stillman I, Schachter AD, Mottley C, Zheng XX, Strom TB. On the intraoperative molecular status of renal allografts after vascular reperfusion and clinical outcomes. *J Am Soc Nephrol* 2005;16(6):1542-8.

Gautam A, Morrissey PE, Gohh R, Yango A, **Monaco AP**. Experience with sirolimus for calcineurin minimization/elimination in pancreas-after-kidney transplantation. *Transplant Proc.* 2005;37(8):3542-3.

Gohh RY, Yango AF, Morrissey PE, **Monaco AP**, Gautam A, Sharma M, McCarthy ET, Savin VJ. Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. *Am J Transplant* 2005; (12):2907-12.

Johnson SR, Khwaja K, Pavlakis M, **Monaco AP**, Hanto DW. Older living donors provide excellent quality kidneys: a single center experience (older living donors). *Clin Transplant* 2005; 19(5):600-6.

Johnson SR, Pavlakis M, Khwaja K, Karp SJ, Curry M, Curran CC, **Monaco AP**, Hanto DW. Intensive care unit extubation does not preclude extrarenal organ recovery from donors after cardiac death. *Transplantation* 2005;80(9):1244-50.

**Maki T**, Gottschalk R, Ogawa N, **Monaco AP**. Prevention and cure of autoimmune diabetes in nonobese diabetic mice by continuous administration of FTY720. *Transplantation* 2005;79(9):1051-5.

**Maki T**, Kimura T, Ito A. Subtotal pancreatectomy in mice. *Surg Frontier* 2005;12:79-82.

**Monaco AP**, Morris PJ. Reduction in calcineurin inhibitor exposure and maintenance of effective immunosuppression: clinical experience with everolimus (Certican). *Transplantation* 2005;79(9 Suppl):S67-8.

Morris PJ, **Monaco AP**. Pancreatic islet transplantation: is the glass half-empty or half-full? *Transplantation.* 2005;79(10):1287-8.

Morrissey PE, Dube C, Gohh R, Yango A, Gautam A, **Monaco AP**. Good samaritan kidney donation. *Transplantation* 2005;80(10):1369-73.

Abstracts

Khwaja K, Jonhnsn S, Zaheer A, Pavlakis M, Karp S, **Monaco A**, Bratton C, Hanto D. Donor kidney volume/recipient weight ratio effects renal functin after living donor kidney transplantation. *Am J Transplant* 2005;5(Suppl 11):478.

**Maki T**, Minamimura K, Gao W. Antilymphocyte serum spares and activates regulatory T cells that suppress alloresponse. *Am J Transplant* 2005;5(Suppl 11):818.

Minamimura K, Yagita H, **Monaco AP**, **Maki T**. Tolerance induction in sensitized recipients. *Am J Transplant* 2005;5(Suppl 11):230.



## Leo E. Otterbein, PhD

My work focuses on the potent therapeutic benefit of low concentrations of carbon monoxide (CO) in models of shock, transplantation, and vascular injury. This work stems from the study of heme oxygenase-1, which is also a focus of the laboratory, as an inducible enzyme that generates CO during the catalysis of heme. My research support is to study mechanisms by which CO is protective, which includes identifying novel targets of its action. We are particularly interested in cell signal transduction, and this year we focused on the mitogen activated protein kinases (MAPK), PPAR $\gamma$ , and hypoxia inducible factor (HIF1 $\alpha$ ) in macrophages, as well as the role of RhoA and eNOS and the generation of nitric oxide (NO) in endothelial cells. The genes which encode signaling pathways, with the exception of eNOS, while not containing heme moieties, the otherwise presumed cellular target of CO, are critically involved in allowing CO to exert protective effects.

### Macrophages

Results from a comprehensive gene microarray in CO-exposed macrophages revealed the candidate target gene Egr-1. Egr-1 is a master switch in inflammatory gene regulation. CO abrogated its induction by endotoxin. We confirmed that the ability of CO to block Egr-1 required the upregulation of PPAR $\gamma$  using siRNA and cre-lox technology. In an effort to determine the mechanism by which CO induces PPAR $\gamma$ , we examined the role of mitochondria as being a source of a large pool of heme-containing moieties in the cell. Using confocal microscopy and mito-tracker dyes, we determined that CO increases an oxidative burst in the cell within 15 seconds of exposure. Figure 1 is FACs data showing the increase in fluorescence DCF dye which reacts with oxygen radicals. This mild ROS burst leads to rapid stabilization of hypoxia-inducible factor1- $\alpha$  (HIF1- $\alpha$ ) that significantly precedes expression of PPAR $\gamma$ . The working hypothesis is that CO leads to a mild and transient generation of reactive oxygen species (ROS) that alters the cellular phenotype towards one geared toward cytoprotection involving these two gene products. Our focus this upcoming year will be to confirm these observations and investigate further the mechanisms by which CO and ROS regulate cell signaling. We are currently investigating these events and gene expression patterns and applying them to other systems, such as the endothelial cell, vascular injury and organ rejection following transplantation, where CO exerts salutary effects.

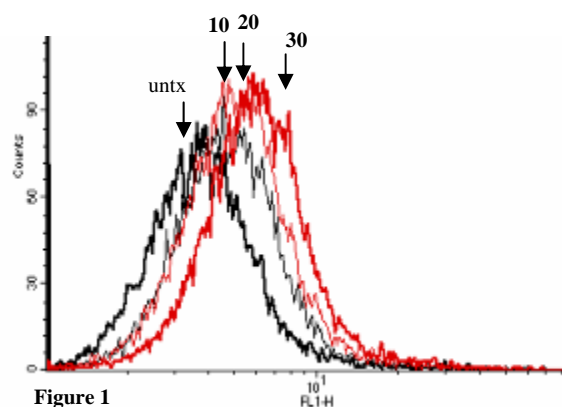


Figure 1

### Endothelial Cells

We are also very interested in the endothelial cell as the principal barrier cell between the vascular lumen and underlying tissue parenchyma. Moreover, the EC is the first target cell (other than the circulating leukocytes) that CO would target. Unlike smooth muscle cells where CO is anti-proliferative, CO augments cellular growth of EC to increase repair of the vessel. Figure 2 depicts CD31 & ICAM staining of rat carotid arteries 5 days post angioplasty.

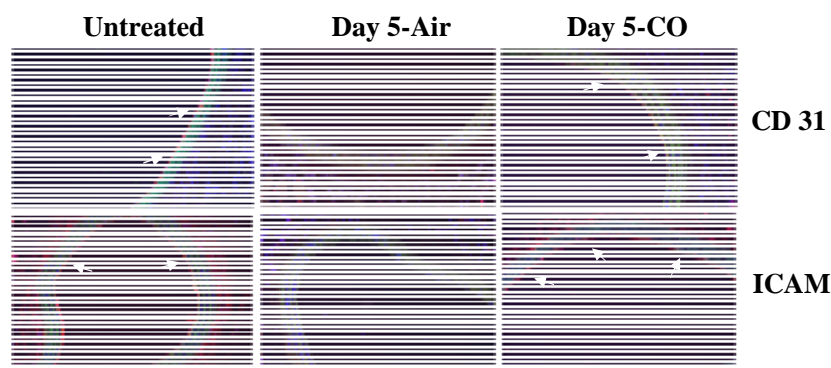


Figure 2

Exposure to CO (250 ppm) for 1 hr leads to more rapid re-endothelialization vs air-treated (arrows depict positively-stained cells) 5 days later. We believe this to be important in limiting intimal hyperplasia and lesion development. The focus of this project is to delineate the mechanism(s) by which this occurs which seems to involve the expression and activation of RhoA and eNOS and NO generation.

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**Current Employees**

Beek Yoke Chin, MD, PhD	Instructor in Surgery
Martin Bilban, PhD	Research Fellow
Kyoichiro Maeshima, MD, PhD	Research Fellow
Jeffery Scott, PhD	Research Fellow
David Gallo	Research Associate
Eva Czismadia	Research Technician

**LIST OF CURRENT FUNDING**

“Carbon Monoxide to Prevent Circulatory Collapse”

National Institutes of Health, NHLBI

Principle Investigator: Leo E. Otterbein, PhD

“Anti-Inflammatory Effects of Carbon Monoxide in the Lung”

National Institutes of Health, NHLBI

Principle Investigator: Leo E. Otterbein, PhD

“Investigations of Mechanisms of Action of Carbon Monoxide as an Anti-Inflammatory and Anti-Proliferative Agent in Vascular Disorders”

Linde Gas Therapeutics, Stockholm Sweden.

Principle Investigator: Leo E. Otterbein, PhD

“Heme oxygenase-1 in Transplantation”

National Institutes of Health, NHLBI

Principle Investigator: Fritz H. Bach, MD, PhD

Co-Investigator: Leo E. Otterbein, PhD

“Heme oxygenase-1 to Prevent Rheumatoid Arthritis”

RIVA Foundation.

Principle Investigator: Fritz H. Bach, MD, PhD

Co-Investigator: Leo E. Otterbein, PhD

“Carbon monoxide to prevent Inflammatory Bowel Disease”

National Institutes of Health

Principle Investigator: Scott Plevy, MD

Subcontract PI: Leo E. Otterbein, PhD

“Carbon Monoxide, Cigarette Smoking and IBD”

Chron's and Colitis Foundation of America

Principle Investigator: Scott Plevy, MD

Subcontract PI: Leo E. Otterbein, PhD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Carbon Monoxide in the Treatment of Pulmonary Hypertension”

Phillip Morris External Research Program

Principle Investigator: Leo E. Otterbein, PhD

“Carbon Monoxide Promotes Vascular Repair”

National Institutes of Health

Principle Investigator: Leo E. Otterbein, PhD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### **Research Accomplishments and Presentations**

As a new faculty member in the division of transplantation I have been involved in getting the laboratory up and functional, integrating new postdocs, and initiating new projects including collaboration with the proteomics core facility at the Broad Institute. I am a part of the training grant that was submitted by the division and am actively collaborating with new colleagues towards integrating my research interests with theirs and have begun sketching out potential program grants.

I lectured at the Gas Enabled Medical Innovations (GEMI) awards foundation ceremony in Stockholm Sweden. I was also a speaker for the Division of Transplantation Seminar series. My lab was an integral part of abstracts presented at the American College of Surgeons, the Society of Thoracic Surgeons, and the American Thoracic Society. These abstracts have been submitted as manuscripts.

### **Patent Disclosures**

I have continuing involvement in the litigation of nine patent applications for the use of carbon monoxide as a therapeutic for organ transplantation. The first patent was awarded this year entitled "Carbon Monoxide Improves Outcomes in Tissue and Organ Transplants and Suppresses Apoptosis."

### **Individual Accomplishments**

I remain a member of the American Heart Association study sections for the Northeast affiliate. This is a four year commitment. I am also a new member of the NIH study section "Special Emphasis Panel/Scientific Review Group for KO2 and KO8 awards. This committee meets triennially for grant review. This is a minimum 4 year commitment.

## **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

### **Original Articles**

Hegazi RA, Rao KN, Mayl A, Sepulveda AR, **Otterbein LE**, Plevy SE. Carbon monoxide ameliorates chronic murine colitis through a heme oxygenase 1-dependent pathway. *J Exp Med* 2005;202:1703-13.

Mazzola S, Forni M, Albertini M, Bacci ML, Zannoni A, Gentilini F, Lavitrano M, Bach FH, **Otterbein LE**, Clement MG. Carbon monoxide pretreatment prevents respiratory derangement and ameliorates hyperacute endotoxic shock in pigs. *FASEB J* 2005;19:2045-7.

Moore BA, Overhaus M, Whitcomb J, Ifedigbo E, Choi AM, **Otterbein LE**, Bauer AJ. Brief inhalation of low-dose carbon monoxide protects rodents and swine from postoperative ileus. *Crit Care Med* 2005;33:1317-26.

Nakao A, Neto JS, Kanno S, Stolz DB, Kimizuka K, Liu F, Bach FH, Billiar TR, Choi AM, **Otterbein LE**, Murase N. Protection against ischemia/reperfusion injury in cardiac and renal transplantation with carbon monoxide, biliverdin and both. *Am J Transplant* 2005;5:282-91.

Ollinger R, Bilban M, Erat A, Froio A, McDaid J, Tyagi S, Csizmadia E, Graca-Souza AV, Liloia A, Soares MP, **Otterbein LE**, Usheva A, Yamashita K, Bach FH. Bilirubin: a natural inhibitor of vascular smooth muscle cell proliferation. *Circulation* 2005;112: 1030-9.

Ott MC, Scott JR, Bihari A, Badhwar A, **Otterbein LE**, Gray DK, Harris KA, Potter RF. Inhalation of carbon monoxide prevents liver injury and inflammation following hind limb ischemia/reperfusion. *FASEB J* 2005;19: 106-8.

**Otterbein LE**, May A, Chin BY. Carbon monoxide increases macrophage bacterial clearance through Toll-like receptor (TLR)4 expression. *Cell Mol Biol* 2005;51:433-40.

**Otterbein LE**, Zuckerbraun BS, Boyle P, Jaffe R, Upperman J, Zamora R, Ford HR. Carbon monoxide protects against the development of experimental necrotizing enterocolitis. *Am J Physiol Gastrointest Liver Physiol*. 2005;289: G607-13.

Sarady-Andrews JK, Liu F, Gallo D, Nakao A, Overhaus M, Ollinger R, Choi AM, **Otterbein LE**. Biliverdin administration protects against endotoxin-induced acute lung injury in rats. *Am J Physiol Lung Cell Mol Physiol* 2005;289:L1131-7.

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Zuckerbraun BS, McCloskey CA, Gallo D, Liu F, Ifedigbo E, Billiar TR, **Otterbein LE**. Carbon monoxide prevents multiple organ injury in a model of hemorrhagic shock and resuscitation. *Shock* 2005;23:527-32.

Books, Monographs, and Textbooks

Otterbein LE, editor. Heme Oxygenase in Biology and Medicine. New York: Nova Science Publishers Inc.; 2005.

# Division of Urology



**William DeWolf, MD**

**Chief, Division of Urology  
Professor of Surgery**

**Division Members**

**Solomon Berg, MD**

**Assistant Clinical Professor of Surgery**

**Paul A. Church, MD**

**Assistant Clinical Professor of Surgery**

**Anurag (Andy) Das, MD**

**Visiting Associate Professor of Surgery**

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Tendai Chizana

Research Student

Ting Ting Fu

Research Student

Jerry Trejo

Research Student

Joanna Jung

Research Student

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**Assistant Clinical Professor of Surgery**

**Michael Kearney, MD**

**Instructor in Surgery**

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**Associate Professor of Surgery**

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Heng Chaay

Research Technician

Anil Purohit

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**Division of Urology**

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MS Biotechnology Student  
MS Biotechnology Student

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**Abraham Morgentaler, MD**

**Associate Clinical Professor of Surgery**

**Aria F. Olumi, MD**

**Assistant Professor of Surgery**

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Xu Huang, PhD  
Liang Zhang, MD, PhD  
Xiaoping Zhang, MD, PhD  
Glen Barrisford, MD  
Benyamin Farahvash

Research Fellow  
Research Fellow  
Research Fellow  
Research Fellow  
Resident (Spring & Summer 2005)  
Undergraduate Student (Summer 2005)

**Brian Saltzman, MD**

**Associate Professor of Surgery**

**Martin Sanda, MD**

**Associate Professor of Surgery**

Joe Castro, RN  
Mariam Eljanne, PhD  
Kyrsten Haram, BA  
Megan Connor, BA  
Renee Gatewood

Clinical and Research Nurse  
Research Associate  
Research Assistant (Basic)  
Research Assistant (Clinical)  
Administrative Assistant



**Anurag K. Das, MD**

Clinical Research

*Fesoterodine research.* A phase 3, parallel group, randomized, double-blind, placebo-controlled multicenter trial to investigate the efficacy, tolerability, and safety of fesoterodine sustained release in subjects with overactive bladder syndrome. Funded by Schwarz Pharma.

*Duloxetine research.* Study of duloxetine in women of different demographic characteristics and co-morbidities with stress urinary incontinence: evaluation of efficacy and safety. Funded by Eli Lilly.



**Dr. Andy Das**

**LIST OF CURRENT FUNDING**

“A Phase 3, Parallel Group, Randomized, Double-blind, Placebo Controlled Multi-center Trial to Investigate the Efficacy and Safety of Fesoterodine in Subjects with Overactive Bladder Syndrome”  
Schwarz Biosciences Inc.  
Principle investigator: Anurag K. Das, MD

“Study of Duloxetine HCI in Women of Different Demographic Characteristics and Co-morbidities with Stress Urinary Incontinence: Evaluation of Efficacy and Safety”  
Eli Lilly and Company  
Principle investigator: Anurag K. Das, MD

**DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

Abstracts Presented at Local, National, and International Meetings

“A Pilot Study to Investigate the Use of Tamsulosin in Women with Lower Urinary Tract Symptoms (Luts)”  
Poster presentation, Western Section, American Urologic Association, August, 2005. Vancouver, BC.

“Frequency of Stress Urinary Incontinence (SUI) Episodes in Women with either Pure SUI or Mixed Urinary Incontinence” Moderated Poster, New England/Northeastern Section, American Urologic Association, Bermuda. November 2005.

Honors and Awards

- I was Vice Chair – Committee on Young Surgeons, American College of Surgeons (ACS)
- I was a member of the Committee on Physician Health and Competency, ACS
- I was a member of the Clinical Cores Service Committee, BIDMC

Invited Presentations (Local, National, and International)

“Advances in the Treatment of Stress Urinary Incontinence”

Indian American Urologic Association Visiting Scholar Lecture, Urological Society of India Congress, Ahmedabad, India. January 2005.

“Current Understanding of Male Lower Urinary Tract Symptoms/benign Prostatic Enlargement”  
Visiting Professor Lecture, Department of Urology, All India Institute of Medical Sciences, New Dehli, India. January 2005.

“Current Advances in the Diagnosis, Pathophysiology, and Treatment of Overactive Bladder”  
Grand Rounds, Division of Urology, SUNY Buffalo, Buffalo, New York. March, 2005.

“Current Concepts in Overactive Bladder”  
Countway Grand Rounds, Brigham and Women’s Hospital, Boston, MA. March, 2005.

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**“Current Understanding of Overactive Bladder Syndrome”**

Neurourology cases with residents, journal club and Grand Rounds lecture. Visiting Professor, Albany Medical College Division of Urology, Albany, New York. March 2005.

**“Pharmacologic Management of Urinary Incontinence”**

IAUA Meeting at the American Urologic Association, San Antonio, TX. May, 2005.

**“Lower urinary tract symptoms in men-diagnosis and treatment options”**

Urology Grand Rounds, Togus V.A. Hospital, Augusta, ME. June, 2005.

**“New Developments in the Diagnosis, Pathophysiology, and Treatment of Overactive Bladder”**

Grand Rounds, Division of Urology, SUNY Syracuse, Syracuse, NY. June 2005.

**REPORT OF TEACHING**

CMR Courses

“Primed updates: Therapeutic Options in the Treatment of Benign Prostatic Hypertrophy (BPH)”. I co-developed content and lectured in Brooklyn, Washington DC, Minneapolis, and Houston.

“New developments in Overactive Bladder.” I lectured at the Maine Urologic Association annual meeting. Sugarloaf, Maine. February, 2005.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Reviews, Chapters, and Editorials (submitted or in press)

**Das AK.** Sacral neuromodulation for overactive bladder. In Goldman H, Vasavada, S. Female Urology and Voiding Dysfunction. Totowa NJ: Humana Press. Accepted and publication pending.

## William C. DeWolf, MD

### Basic Research

The basic component of my own research deals with biochemical characterization of a stem cell antigen called Gp200 that we originally described in 1992. We were the first to sequence the molecule and it was been found to be identical to a protein called podocalyxin (also TRA 1-60, TRA 1-81 and GCTM-2). This molecule is a 528 amino acid membrane protein that is heavily glycosylated and contains a single putative transmembrane protein. Podocalyxin has a large extracellular region containing a mucin and globular domain and a small cytoplasmic domain with a PDZ-binding motif. Podocalyxin was originally identified and cloned from podocytes, the blood-filtering cells of the kidney, where it has been shown to have putative function as a protein anchoring membrane protein that forms complexes with other proteins through its cytoplasmic PDZ-binding motif. This podocalyxin complex is critical for proper podocyte function. We are studying what podocalyxin is interacting with in embryonal carcinoma cells. Protein sequencing data reveal that glucose-3 transporter, the testis and brain-specific glucose transporter, copurifies with podocalyxin in purified protein fractions from embryonal carcinoma stem cells. Immunoprecipitation experiments with antiglucose-3 transporter and podocalyxin antibody confirm a stable complex exists in detergent extracted protein lysates. Podocalyxin may be functioning as an anchoring protein for this plasma membrane glucose transporter in stem cells. Current studies are underway to determine if podocalyxin and the transporter are interacting directly or if other proteins, interacting through the PDZ-binding motif, are tethering podocalyxin to the transporter. We will further explore if there is any critical function for this complex in pluripotent stem cells.

We are also testing this testis cancer model as an example of human pluripotent stem cell differentiation. This is based on the fact that embryonal carcinoma (EC) is a pluripotent stem cell derived from human germ cell tumors. As noted above, all human pluripotent cells share common stem cell defining markers which include TRA 1-60 and TRA 1-81 antigens which disappear from the stem cell surface upon differentiation. We have previously shown that our molecule of interest, podocalyxin, is the molecular carrier of TRA 1-60/TRA 1-81 antigens on EC. Furthermore, podocalyxin has been recently identified as a tumor marker of several distinct human cancers (as well as a marker of undifferentiated human embryonal stem cell lines). We have shown that retinoic acid induced differentiation of EC is associated with a modification of podocalyxin in which the TRA 1-60/TRA 1-81 components are lost. Further studies on these mechanisms are underway.



Dr. W. Michael Schopperle

### Clinical Research

Clinical research within the Division of Urology is very active. It involves not only urologic oncology and associated components but also outcomes analysis and education and teaching aspects, which is noted in the bibliography. Part of this stems from the initiation of our new urologic "Community Clinic" which is being used as a model for urologic care for unrestricted socioeconomic backgrounds and is being developed as a teaching model for medical students and residents learning all new aspects of urologic care including office practice and economics.

### **Current Employee**

W. Michael Schopperle, PhD

Research Fellow

### LIST OF CURRENT FUNDING

Intramural funding, Beth Israel Deaconess Medical Center

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### Research Accomplishments

We completed another phase of work on Gp200, which is a sialomucin expressed on embryonal carcinoma cells. This next installment of work has identified and sequenced the Gp200 protein which has been identified as podocalyxin. To our surprise and delight, we have discovered that glut-3 (which is a glucose transporter isoform found in human testis and brain) copurifies with podocalyxin; thus, podocalyxin and glut-3 transporter form a stable complex in EC cells. The basis for this interaction is not known, however podocalyxin has a PDZ-binding site in its intracellular domain that may play a role in forming protein-protein complexes. Further work is now planned looking at the molecular mechanisms underlying the formation of a podocalyxin and glut-3 complex and provide some insight into why a glucose transporter is interacting with a sialomucin in cancer cells. This work is also being developed to understand the effect of differentiation on the expression on embryonal stem cell marker TRA-1-60 as it is expressed on podocalyxin. Basically upon differentiation of EC stem cells the TRA-1-60 marker is lost. Results now show that antibodies to TRA-1-60 and podocalyxin recognize the 200 kilodalton TRA-1-60 stem cell antigen in protein preps of undifferentiated EC cells. However protein blots of undifferentiated EC cells exposed to retinoic acid reveal that the TRA-1-60 epitope is no longer detectable with TRA-1-60 antibodies. This model is being developed as a previously used EC based differentiation model adapted to stem cell research.

### Individual Accomplishments

- I was a member of the AUA Program Committee for Basic Research: Prostate Cancer.
- I was the AJC Recipient of the National Civic Achievement Award for 2005.
- I was a member of the Medical Advisory Board for the Boston Prostate Cancer Walk.
- I was highlighted in Boston Magazine's List of Best Urologists in Boston, 2005.

### Invited Presentations

I was a speaker at the Plenary Session for the AUA Meeting in 2005.  
"Take Home Message: Localized Prostate Cancer"

## **REPORT OF TEACHING**

### Undergraduate and Medical School Courses:

*Undergraduate Research Opportunities Program.* This is an MIT-based teaching program in which 3-5 undergraduates rotate through our laboratory on 6-12 month basis science projects and gain experience in biological research. This is particularly important because it is the only undergraduate course with opportunity to view surgical operations as part of the curriculum. Additional medical school teaching includes SU518M.1 which is a general course in urologic science for medical students. The course includes a 1 month rotation on the urology service and involves clinical and didactic experience relating to urologic disease.

## **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

### Original articles

Ramsawh H, Morgentaler A, Covino N, Barlow D, **DeWolf WC**. Quality of life following simultaneous placement of penile prosthesis with radical prostatectomy. *J Urol* 2005;174:1395-1398.

### Original Articles (submitted or in press)

Hutchinson LM, Becker CM, Chang EL, Shih M-C, Brice M, **DeWolf WC**, Gaston SM, Zetter BR. Use of thymosin b15 as a urinary biomarker in human prostate cancer. *The Prostate* 2005; in press.

Hutchinson LM, Chang EL, Becker CM, Ushiyama N, Behonick D, Shih M-C, **DeWolf WC**, Gaston SM, Zetter BR. Development of a sensitive and specific enzyme linked immunosorbent assay for thymosin b15, a urinary biomarker of human prostate cancer. *J Clin Biochem* 2005; in press.

Johnson TR, Pedrosa I, Goldsmith J, **Dewolf WC**, Rofsky N. Magnetic resonance imaging findings in solitary fibrous tumor of the kidney. *J Comput Assist Tomogr* 2005; in press.

Kerfoot B.P, Baker H, Jackson TL, Hulbert WC, Federman D, Oats R, **DeWolf WC**. Multi-institutional randomized controlled trial of adjuvant web-based teaching to medical students. *J Academic Med* 2005; in press.

San Francisco I, Dewolf WC, Regan M, Olumi A. Low age adjusted free testosterone levels correlate with poorly differentiated prostate cancer. *J Urol* 2005; in press.

Reviews, Chapters, and Editorials

**DeWolf WC**. (Editorial) Intracapsular clear cell renal carcinoma: ploidy status improves the prognostic value of the 2002 TNM classification. *J Urol* 2005;174:207.

**DeWolf WC**. Take home message: localized prostate cancer. *AUA News* 2005;10:3-4.

Reviews, Chapters, and Editorials (submitted or in press)

**DeWolf WC**. (Editorial) Predicting teratoma in the retroperitoneum for men undergoing post-chemotherapy retroperitoneal node dissection. *J Urol* 2005; in press.

Abstracts

Adey G, Sanda M, Rofsky N, Pedrosa I, **DeWolf WC**. Nodular enhancement of magnetic resonance: imaging of cystic renal lesion predicts malignancy. *J Urol* 2005;173:A380.

Schopperle W, **DeWolf WC**. Differentiated-induced human embryonal carcinoma stem cells express an altered glycoform of the cell adhesion protein podocalyxan. *FASEB J* 2005;19:A8927.





## Sandra M. Gaston, PhD

My laboratory is focused on characterizing the individual biological differences that can influence the clinical behavior of human cancers, with a major emphasis on prostate cancer. We are fortunate to have access to well-documented human clinical samples, and we have developed a number of innovative technologies that allow us to perform detailed molecular analyses of these specimens without compromising patient care. These include a set of tissue print and print-phoresis technologies that allow us to generate spatial-molecular maps of tumor markers in needle biopsies and surgical specimens while preserving the tissue for diagnostic histopathology. Currently, we are utilizing our tissue print technologies to investigate the molecular events that differentiate locally invasive prostate cancer from indolent tumors. We are also using tissue prints to map gene expression profiles that correspond to specific prostate cancer phenotypes that can be imaged in human patients using advanced MRI techniques. These efforts have produced a set of new biomarkers that may ultimately be useful in the management of patients with prostate cancer.



Dr. Sandra Gaston

My laboratory has also developed a set of micro-bioassays that allow us to evaluate bioavailable androgens in complex biological fluids. In an animal model, our bioassays can measure changes in bioavailable serum androgen in response to soy based dietary supplements (in this model, bioavailable serum androgen, as measured by bioassay, is distinct from total and free serum testosterone). We found that our bioassay detected decreases in bioavailable serum androgen that were associated with inhibition of androgen-sensitive prostate cancer by soy dietary supplements; serum total and free testosterone showed no such association. Currently we are investigating the relationship between bioavailable serum androgen (as measured by bioassay) and androgen-dependent gene expression in cell culture models of prostate cancer. We anticipate that that this strategy may have translational applications in the design of pharmacological and dietary interventions for prostate cancer patients who want to incorporate complementary therapies into their cancer care program.

Another focus of my laboratory is to use human semen samples, collected in the Andrology laboratory, to determine individual differences in the susceptibility to mitochondrial toxins, as measured by the effects of these toxins on sperm mitochondrial respiration and motility. Using this approach, we have identified a set of polymorphisms in the mitochondrial ATP synthetase that may be particularly important in determining both therapeutic and toxic responses to specific inhibitors of cell respiration.

### Current Employees

Dang Vu	Research Student
Courtney Klaips	Research Student
Tendai Chizana	Research Student
Ting Ting Fu	Research Student
Jerry Trejo	Research Student
Joanna Jung	Research Student

### LIST OF CURRENT FUNDING

“Tissue Print Micropeels for Molecular Profiling of Cancer”

National Institutes of Health, NCI

Principal Investigator: Sandra M. Gaston, PhD

“New Strategies for Interpreting *in vivo* Prostate MRI/MRS Choline Spectra: Manipulating Gene Expression to Enhance Cancer Specificity”

US Department of Defense Prostate Cancer Research Grant

Principal Investigator: Sandra M. Gaston, PhD

“Prostate MRI and MRS: Correlations with Gene Expression”

National Institutes of Health, NCI

Principal Investigator: Sandra M. Gaston, PhD

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**Division of Urology**

**“3T Magnetic Resonance and Spectroscopy of Prostate Cancer”**

General Electric Industry Sponsored Research

Principal Investigator: Robert Lenkinski, PhD

Co-Investigator: Sandra M. Gaston, PhD

**“Harvard/Michigan Prostate Cancer Biomarker Clinical Center”**

Early Detection Research Network: Clinical Epidemiological and Validation Centers.

National Institutes of Health, NCI

Principal Investigator: Martin Sanda, MD

Collaborator: Sandra M. Gaston, PhD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

**“Tissue Print Micropeels for the Molecular Profiling of Prostate Needle Biopsies”**

National Institutes of Health, NCI

Principal Investigator: Sandra M. Gaston, PhD

**“Choline Metabolism in Prostate Cancers: Response to Dietary Soy Phytochemicals”**

National Institutes of Health, NCI/NCCAM

Principal Investigator: Sandra M. Gaston, PhD

**DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

Research Accomplishments

With NIH and intramural research support, my laboratory has continued to advance the development of a set of novel tissue printing technologies that support the molecular analysis of human tissue specimens. Our tissue print techniques allow us to transfer a microscopic layer of cells and extracellular matrix from the surface of a fresh tissue specimen onto nitrocellulose membranes, creating a “molecular xerox” which preserves the specimen for histopathology. We have combined tissue print techniques with specific protein and RNA/DNA detection methods to generate two-dimensional maps of molecular markers in radical prostatectomy specimens, and these maps have allowed us to identify clusters of molecular markers that co-localize with sites of microscopic invasion of cancer into the prostate capsule. This year, we published some of our major findings on markers of tumor invasion of the prostate capsule and an overview of our tissue printing techniques in *Nature Medicine* (see the Bibliography for reference details).

Because our tissue print techniques do not damage tissue specimens, we have been able to utilize this approach to obtain molecular marker profiles from human prostate needle biopsies. Prostate needle biopsies are key diagnostic specimens that must be submitted in their entirety for surgical pathology and are thus not usually available for molecular marker analysis. In previous studies, we used biopsy cores obtained from radical prostatectomy specimens as model specimens to demonstrate that we could generate both mRNA and protein marker profiles from biopsy tissue prints while preserving the cores for standard H&E and immunohistochemical studies. This last year, we significantly improved the efficiency of our print RNA extraction and have now achieved high quality gene expression profiles on Affymetrix microarrays using RNA obtained from prints from single biopsy cores. These important technical milestones have allowed us to move forward with a pilot translational research protocol for tissue print analysis of diagnostic prostate needle biopsies. This protocol will allow us to capture molecular markers in prostate tissues from a much broader range of patients than can be represented in tissue banks that rely upon radical prostatectomy specimens. Our biopsy print RNAs represent a significant new resource for the biomarker development efforts currently underway in our laboratory and in the larger prostate cancer research community.

With support from General Electric Industry Sponsored Research, we have used tissue prints to produce “molecular whole mounts” of radical prostatectomy specimens that can be mapped point-to-point with structures visualized in vivo by magnetic resonance imaging (MRI) and magnetic resonance spectra (MRS). We have collaborated with Dr. Robert Lenkinski and other investigators in the BIDMC MRI/MRS program to profile the patterns of mRNA expression that underlie the MRI/MRS choline peak that is frequently observed in prostate cancer. The genes that regulate choline metabolism include several that have been identified as

“druggable” targets for new anti-cancer compounds. Recently, we have identified an animal model of prostate cancer that appears to recapitulate some of the tumor-associated changes in choline metabolism that are observed in human patients, and this year we received a DOD prostate cancer research grant to support the development of this animal model for the pre-clinical study of the molecular mechanisms that produce MRI/MRS visible changes in tumor choline metabolism.

Our tissue print “molecular whole mounts” of radical prostatectomy specimens have also allowed us to generate gene expression maps of the angiogenic processes in human prostate cancer that result in MRI visible tumor-associated changes in tissue perfusion, as visualized *in vivo* by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI). Recently, we succeeded in obtaining Affymetrix microarray data that has allowed us to begin to compile a gene expression “signature” of DCE-MRI positive prostate cancers. These studies are an important component of a larger effort to interpret prostate DCE-MRI images in terms of the biological and clinical sub-types of human prostate cancer.

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

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

**Gaston SM**, Goldner DL, Vu D, Chizana TL, Lee JM, Upton MP, Bloch N, Lenkinski RE. “Choline kinase expression patterns in human prostate cancers.” Poster presentation, American Association for Cancer Research Annual Meeting, Anaheim, California. April 16-20, 2005.

#### Individual Accomplishments

For the third consecutive year, I was named to the NIH National Cancer Institute Special Emphasis Panel to review grant applications submitted to the “Innovative Technologies for the Molecular Analysis of Cancer” (IMAT) program.

I was designated a Plenary Presentation Speaker at the National Cancer Institute IMAT Principal Investigator's Meeting in August 2005 (Title of presentation: “Tissue Print Micropeels for Molecular Profiling of Cancer”).

I was named Session Chairperson for the Cambridge Healthtech Institute Conference on Cancer Immunotherapeutics and Targeted Cancer Therapies in September 2005.

I was awarded a DOD Prostate Cancer Research Grant entitled “New Strategies for Interpreting *in vivo* Prostate MRI/MRS Choline Spectra: Manipulating Gene Expression to Enhance Cancer Specificity.” The major goal of this project is to develop an animal model in which we can characterize the molecular and cellular mechanisms that result in MRI/MRS visible changes in choline metabolism in prostate cancer.

I was awarded an NIH grant entitled “Prostate MRI and MRS: Correlations with Gene Expression”. This grant application was given a priority score in the top 0.4 percentile, and represents the first phase of a larger effort to map the changes in gene expression that result in prostate cancer sub-types that can be imaged in human patients by advance MRI techniques.

#### Invited Presentations (Local, National and International)

Gaston SM. “Whole Mount Molecular Maps of Gene Expression Patterns: Correlation with Pathologic Features of Human Prostate Cancers That Can Be Visualized *in vivo* by Advanced MRI” Dvorak Research Group Seminar. May, 2005.

Gaston SM. “Can The Changes In Prostate Cancer That Result From Dietary Interventions Be Visualized *in vivo* By Advanced MRI?” Zhou Research Group Seminar. July, 2005.

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Gaston SM. "Tissue Print Micropeel and Multi-Enzymatic Tissue Liquefaction (MELT)" Seminar, Ambion Inc., Austin, Texas. August, 2005.

Gaston SM. "Tissue Print Micropeels for Molecular Profiling of Cancer" Plenary Presentation, National Cancer Institute IMAT Principal Investigator's Meeting. August, 2005.

Gaston SM. "Mapping Molecular Targets in Human Tissue Biopsies and Surgical Specimens: Tissue Print Micropeel Technologies." Seminar, Cambridge Healthtech Institute Conference on Cancer Immunotherapeutics and Targeted Cancer Therapies, Cambridge, MA. September, 2005.

Gaston SM. "Molecular Maps of Prostate Cancer: Tissue Print Micropeel Profiles of Human Tissue Specimens" Department of Pathology, Boston University School of Medicine (CME Seminar), October, 2005.

Gaston SM. "Profiling Gene Expression Patterns in MRI-Visible Prostate Cancer Phenotypes." BIDMC MRI/MRS Research Seminar. December, 2005.

**REPORT OF TEACHING**

Undergraduate and Medical School Courses

I was a tutor for the HMS course: Principles of Pharmacology (David Golan MD, Director) - Spring 2005

I was a tutor for the HMS course: The Human Body (Kitt Shaffer, MD PhD, Director) - Fall 2005

I was the case editor/author, "The Salesman's Family Plan". This was a new Human Body Block Tutorial Case that was introduced in 2005 and which focused on male genitourinary anatomy and histology.

I was a research mentor for the following undergraduate students:

Courtney Klaips - Wellesley College

Dang Vu, Tendai Chizana, Ting Ting Fu, and Jerry Trejo - MIT

Joanna Jung - Simmons College

Two of my students, Tendai Chizana and Ting Ting Fu, received Howard Hughes summer research fellowships for work in my laboratory. Another of my students, Courtney Klaips, received a Wellesley College Summer Research Fellowship for work in my laboratory.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original Articles

**Gaston SM**, Soares MA, Siddiqui MM, Vu D, Lee JM, Brice MJ, Shih JC, Upton MP, Perides G, Baptista J, Lavin PT, Bloch BN, Genega EM, Rubin MA, Lenkinski RE. Tissue-print and print-phoresis as platform technologies for the molecular analysis of human surgical specimens: mapping tumor invasion of the prostate capsule. *Nat Med* 2005; 11(1): 95-101.

Hutchinson LM, Chang EL, Becker CM, Ushiyama N, Shih M-S, DeWolf WC, **Gaston SM**, Zetter BR. Use of thymosin beta15 as a urinary biomarker in human prostate cancer. *Prostate* 2005; 64(2):116-27.

Hutchinson LM, Chang EL, Becker CM, Ushiyama N, Behonick, D., Shih M-C, DeWolf WC, **Gaston SM**, Zetter BR. Development of a sensitive and specific enzyme-linked immunosorbent assay for thymosin beta15, a urinary biomarker of human prostate cancer. *Clin Biochem* 2005; 38(6):558-71.

Reviews, Chapters, and Editorials (submitted or in press)

**Gaston SM**, Upton MP. Tissue print micropeel: a new technique for mapping tumor invasion in prostate cancer. *Curr Urol Rep* 2005; in press.

Abstracts

**Gaston SM**, Goldner DL, Vu D, Chizana TL, Lee JM, Upton MP, Bloch N, Lenkinski RE. Choline kinase expression patterns in Human Prostate Cancers. *Proc Amer Assoc Cancer Res* 2005; 46;3797A.

**Ann A. Kiessling, PhD**  
**Robert C. Eyre, MD**  
**Paul Church, MD**

#### Basic Research

The long-term goals of our research are to understand tissue specificity and controls on gene and retrovirus expression in genitourinary tract tissues and in embryos. Studies of HIV infection of male GU tract tissues began over 20 years ago with the first measurements of viral burden in seminal plasma from men with AIDS. The immune privilege of male GU tract tissues led to the hypothesis that semen-producing organs could be an isolated sanctuary of HIV disease. Originally controversial, this concept is now broadly accepted.

The work has led to studies of specific immunologic features of prostate, seminal vesicles and epididymis. Results to date suggest that the role of the prostate in immune-protection of spermatozoa may relate to the disease predisposition of the prostate in general, including bacterial infections and cancer. In addition, the unique population of tissue-specific macrophages in seminal vesicles and epididymis that play a role in their normal development and function, may also serve as hosts for HIV infection. If so, they may be important life-long reservoirs of infection, difficult to penetrate by anti-retroviral drugs.



**Dr. Ann Kiessling**

#### Current focus:

(1) *Genetic and phylogenetic analyses of HIV genes cloned from paired specimens of blood and semen contributed by study subjects in a five-year longitudinal study design.* To date, we have sequenced and analyzed approximately 1200 clones of HIV genes, including envelope, protease, and reverse transcriptase genes. The genetic analyses have illustrated unique clustering patterns of HIV quasiespecies isolated from paired blood and semen specimens from long term study subjects. These findings support and extend the concept, proposed by this laboratory over 20 years ago, that semen producing organs are a sequestered focus of HIV infection, separate from blood. Importantly, in the present study, several study subjects have demonstrated the appearance of therapy resistance-conferring mutations in semen before they appear in blood.

More recent analyses of HIV envelope genes have revealed compartmentalization of syncytium-inducing virus species (utilize chemokine receptor CXCR4) and non-syncytium-inducing virus species (utilize chemokine receptor CCR5). This confirms and extends reports from other laboratories that HIV variants which utilize CCR5 receptors to gain access to host cells are the sexually transmitted virus species. Lymphocytes express high levels of CXCR4 receptors, whereas monocytes and macrophages express predominantly CCR5 receptors. As infection progresses, blood HIV variants mutate to express envelopes that preferentially bind to CXCR4 rather than CCR5. This switch in virus tropism is due to point mutations at one or two amino acid residues (S306R or E320K,R) in the V3 loop of HIVenv, and marks a turning point in disease progression due to increased levels of infection and loss of CD4+ lymphocytes incorporated into lymph node syncytia.

The switch in virus tropism has traditionally been attributed to the high error rate inherent in the virus reverse transcriptase, but more recent studies have revealed another possibility. A family of deaminases, CEM15 (APOBEC3G), function as an innate cellular defense mechanism against retroviral infection. CEM15 deaminates cytosine in the nascent DNA strand synthesized by viral reverse transcriptase during the process of infection. The resulting uracil residue triggers destruction of the nascent DNA strand by intracellular DNases. If, however, the nascent DNA is not destroyed, the positive strand has an adenosine substitution for the guanosine residue that formerly paired with the cytosine. To determine if such mutations influence disease progression, we have analyzed two subsets of our HIV sequence data: 53 unique sequences of the V3 loop of Gp120 from a long-term non-progressor and 82 unique sequences of protease from a man who developed therapy resistance at 32 months of treatment.

The logistics of archiving and analyzing a growing data set of gene sequences have necessitated the development of a custom database, which has been recently completed in MySQL. We have begun to use the database as the starting point for sequence analyses.



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### Division of Urology

We have more recently created a public database, <http://www.lrb.med.harvard.edu>, in which we have compiled all of the published HIVenv sequences from semen. We included HIVenv sequences from paired blood specimens when available. This is the first public database of its kind and is providing background for understanding the most significant HIV host cells in semen producing organs, as well as for the design of vaccines targeting semen transmitted disease.

(2) *Immunology of male GU tract tissues with emphasis on the prostate, seminal vesicles and epididymis.* Understanding immune controls in these tissues will provide important insights into not only sexually transmitted diseases, but also specific gland pathologies, such as prostatitis and prostate cancer. Previous studies used mouse model systems to characterize the tissue distribution of leukocyte subsets in testis, epididymis, and seminal vesicles. More recent studies have attempted parallel experiments in human tissues. The figure illustrates immunostaining (red-brown color) of human epididymis and seminal vesicles for the pan-leukocyte marker, CD45, and the tissue-specific macrophage marker, CD97 (Figure 1). These are possible host cells for HIV infection.

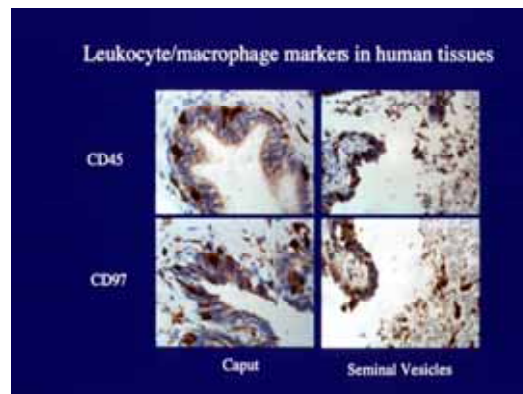


Figure 1

Several lines of evidence, including work from this laboratory, indicate the prostate is immunosuppressed. This characteristic could play an important role in prostate diseases, such as prostatitis and prostate cancer. We have previously reported that prostatitis may drive HIV disease by promoting the development of therapy resistance mutations. For these reasons, we have begun to explore the bacterial species present in prostatic tissues. We have used PCR amplification of bacterial ribosomal gene sequences, followed by sequencing the PCR products and identification through GenBank searches. The work has begun with two cohorts of patients, one group undergoing fertility assessment, and another group undergoing vasectomy. Pre-and post-vasectomy specimens have allowed the comparison of specimens with and without contribution from the epididymis.

We are in the process of compiling the information for publication. We have invested considerable time in developing a reference library of bacterial DNA sequences amplifiable from laboratory reagents, a problem known to haunt this line of investigation. To date, we have amassed a total library of approximately 200 rDNA gene sequences.

(3) *Endogenous retrovirus expression in male urogenital tract tissues.* The human genome contains more retrovirus-related sequences (45%) than the mouse genome (37%). The first human retrovirus identified was an endogenous retrovirus expressed by placental cells – in vivo and in vitro. The physiologic significance of the human endogenous retrovirus repertoire is poorly understood, but there is a growing awareness of the mobility of genomic elements and their role in cancer. A full-length human endogenous retrovirus (HERV-L) appears to be currently active in the human genome. The mouse counterpart, MERV-L, also appears to be active in the mouse genome, and is a likely candidate for the highly epididymal specific retrovirus expression described by his laboratory over a decade ago. For this reason, we have undertaken a preliminary survey of a library of male mouse tissue RNAs for expression of MERV-L. Interestingly, it appears to be expressed in a variety of tissues as both mRNA and cytoplasmic cDNAs. This work is on-going.

(4) *We have established a collaboration with the Southwest Biomedical Research Foundation to examine biopsies of tissues from long-term HIV-infected male chimpanzees.* The goal of this work is to supplement the information we are obtaining in the longitudinal study of paired semen and blood samples from our HIV-infected cohort. The first experiment is planned for September, 2006.

#### Current Employees

Bryan Desmarais  
Heng Chaay  
Anil Purohit  
David Chiavatago  
Joe Loverde

Research Technician  
Research Technician  
Medical Student, HMS  
MS Biotechnology Student  
MS Biotechnology Student



### LIST OF CURRENT FUNDING

"Role of the Male Genital Tract in HIV Disease"  
National Institutes of Health, NIDDK, R01- **DK 52761**  
Principal Investigator: Ann A. Kiessling, Ph.D.

Urologic Research Fund  
(Provides support for the male GU tissue studies not included in the NIH funded project.)

### APPLICATIONS SUBMITTED AND PENDING REVIEW / FUNDING

Competitive renewal of DK 52761, submitted January 1, 2006.

### DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR

#### Research Accomplishments

The longitudinal genetic and phylogenetic analyses of HIV genes are now proceeding rapidly. The results to date indicate that male GU tract organs are a clinically important reservoir of HIV disease in men, including those on therapy. To establish tissue specific reservoirs of disease, we are initiating a collaboration with Southwest Biomedical Research Foundation to analyze tissue biopsies from HIV-infected chimpanzees.

The novel class of macrophages in male mouse and human tissues appear to play a fundamental role in organ function. This could have broad application to understanding the physiology of the prostate, seminal vesicles, and epididymis, as well as their role as reservoirs of HIV infection. The work in the mouse has now been published and the human work is on-going.

We have completed a pilot survey of male mouse genital tract RNAs and DNAs for presence and expression of the endogenous retrovirus, MERV-L. This work formed the basis for the R21 application submitted in Jan., 2005.

We have instituted pilot studies to detect bacteria in semen and prostate tissues using PCR-amplification of bacterial ribosomal RNA gene sequences.

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

Heyd V, Cibelli J, Studer L, **Kiessling AA**. The Reverse Transcriptase Inhibitor, Nevirapine, Promotes Expression of Neuronal Cell Markers in Primate Parthenote Stem Cells. International Stem Cell Society, June, 2005.

Fitzgerald L, **Kiessling AA**. Endogenous Retrovirus Elements are Expressed in Mouse Embryonic Stem Cells and May Have a Functional Role in the Cell Cycle. International Stem Cell Society, June, 2005.

Neville N, Desmarais B, **Kiessling AA**. CEM 15 may promote S1 genotype in HIV-1 species in long-term, non-progressor. International AIDS Society, Rio de Janeiro, Brazil, August, 2005.

#### Individual Accomplishments

##### *Dr. Kiessling*

- Invited to serve on the Research Standards Working Group for the California Institute for Regenerative Medicine, 2005-2011. She was asked to chair the Pre-Clinical Research Standards Subcommittee.

##### *Dr. Church*

- Director of the BIDMC rotation of the Surgical Core Clerkship, Third Year, Lecture Series, Harvard Medical School.

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*Dr. Eyre*

- Member of the American Urologic Association Investment Board.
- Treasurer of the New England Section of the American Urologic Association.
- Listed in "Best Doctors in America, 2005."
- Drs. Eyre and Church also gave multiple lectures to the medical students rotating through the Surgical Core Clerkship, Second Year and Third Year.

Invited Presentations (Local, National, and International)

*Dr. Kiessling*

- "Human Embryonic Stem Cells: the Present and the Future." Invited Faculty, Organon Experts Meeting, Coral Gables, Florida. February, 2005.
- "Human Pluripotent Stem Cells: the Present and the Future." Klewett Annual Lectureship, Annenberg Center for Health Sciences, Eisenhower Medical Center, California. March, 2005.
- "Sexually transmitted HIV has changed the world." Invited Faculty, Annual Symposium, Meharry Medical College, Nashville, Tennessee. April, 2005.
- "Human Pluripotent Stem Cells: the Present and the Future." Keynote Speaker, James Symposium, Meharry Medical College, Nashville, Tennessee. April, 2005.

*Dr. Eyre*

- "Practical management of UTIs." Countway Urology Rounds, Brigham and Women's Hospital. March, 2005.
- "The Specialty of Urology." National Youth Leadership Forum in Medicine, July, 2005.

**REPORT OF TEACHING**

Undergraduate and Medical School Courses:

Dr. Church, Dr. Eyre - Surgical Core Clerkship Lecture Series, Second Year and Third Year.

Dr. Eyre - Director, Senior Surgical Residency Rotation, Faulkner Hospital.

Dr. Kiessling - Lecture on sexually transmitted diseases and human sexuality, Department of Biology, Brandeis University.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original articles

**Kiessling AA.** Eggs alone. *Nature* 2005; 434(7030):145.

**Kiessling AA, Eyre SJ, Desmarais BD.** Detection of drug-resistant HIV-1 strains. *Methods Mol Biol* 2005; 304:287-313.

**Kiessling AA.** Isolation of human immunodeficiency virus type 1 from semen and vaginal fluids. *Methods Mol Biol* 2005; 304:71-86.

Reviews, Chapters, and Editorials (submitted or in press)

Adey GS, **Eyre RC.** Complications of urinary diversions. In: Laughlin K, editor. Complications of urologic surgery and practice: Diagnosis, prevention, and management. 2005; in press.

Nonprint Materials

**Kiessling AA.** NOVA Science Now: Parthenotes for stem cell therapy. March, 2005.

**Eyre RC.** Adult complicated urinary tract infections. A telesymposia series sponsored by Bayer Pharmaceutical for primary care practitioners.

## Aria Olumi, MD

### Basic Research

#### *PROJECT 1: Stromal-Epithelial Interactions Regulate Development of Benign Prostatic Hyperplasia (BPH).*

Development, growth, and tumorigenesis in the prostate are closely regulated by stromal-epithelial interactions. This research project has as its aim to identifying signal transduction pathways that are involved in stromal-epithelial interactions, to enable a better understanding of normal prostate biology and of the pathogenesis of prostatic disease. We hypothesize that the expression of particular stromal genes/proteins is one component that regulates development, growth, and survival of prostatic epithelial cells. It is our goal to determine if BPH results from the altered expression of stromal genes/proteins in adulthood.



Dr. Aria Olumi

Jun-family proteins, which are early transcription factor molecules, have been shown to regulate stromal-epithelial interactions via paracrine modulation of epithelial signaling pathways in other tissues. Jun-family member proteins have also been shown to play an important role in development of the genitourinary organs. Differential expression of Jun-family members in the prostatic stroma may regulate survival or death signals in prostatic epithelial cells. Thus, this project focuses on the way in which Jun-family-mediated paracrine signals from stromal cells regulates proliferation, cell death, and differentiation in prostatic epithelial cells. These studies will improve our understanding of stromal-epithelial interactions that may lead to BPH in adulthood.

#### *PROJECT 2: Molecular Mechanisms of Developing Resistance to Trail-Induced Apoptosis in Prostate Cancer.*

TNF-related Apoptosis Inducing Ligand (TRAIL) has been shown to induce apoptosis in a variety of tumorigenic and transformed cell lines but not in normal cells, hence making TRAIL an ideal cancer therapeutic agent with minimal cytotoxicity. FLICE Inhibitory Protein (c-FLIP) is an important regulator of TRAIL-induced apoptosis. We have demonstrated that persistent expression of c-FLIP(L) is inversely correlated with the ability of TRAIL to induce apoptosis in prostate cancer cells. In a series of correlative and functional studies we have shown that persistent expression of c-FLIP(L) is necessary and sufficient to regulate sensitivity to TRAIL mediated apoptosis in prostate cancer cells. Deciphering the molecular mechanisms of resistance to TRAIL can improve the efficacy of pro-apoptotic agents in treatment of malignancies.

### Clinical Research

#### *PROJECT: Hypogonadism and Association with Diagnosis and Outcome of Patients with Prostate Cancer.*

Androgens regulate normal prostate development and prostate cancer progression. We have previously shown a paradoxical link of serum total and Free-T levels with prostate cancer. The purpose of this project is to evaluate whether hypogonadism is associated with high grade prostate cancer, to examine the relationship between Free-Testosterone, PSA, and age of diagnosis, and to determine whether Free-T levels can be used as predictors for prostate cancer recurrence after surgical therapy for prostate cancer.

### **Current Employees**

Wenhua Li, PhD

Postdoctoral Research Fellow

Xu Huang, PhD

Postdoctoral Research Fellow

Liang Zhang, MD, PhD

Postdoctoral Research Fellow

Xiaoping Zhang, MD, PhD

Postdoctoral Research Fellow

Glen Barrisford, MD

Resident (Spring & Summer 2005)

Benyamin Farahvash

Undergraduate Student (Summer 2005)

### **LIST OF CURRENT FUNDING**

“Role of c-FLIP(L) in Modulating Apoptosis in Prostate Cancer”

Howard Hughes Medical Institute

Principle Investigator: Aria Olumi, MD

**Department of Surgery Annual Research Report 2005**  
**Division of Urology**

“Role of Stromal-Epithelial Interactions in BPH”  
National Institutes of Health NIDDK.  
Principle Investigator: Aria Olumi, MD

“Role of c-FLIP(L) in Apoptosis”  
US Department of Defense-Prostate Cancer Program  
Principle Investigator: Aria Olumi, MD.

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“C-Fos as a Pro-Apoptotic Agent”  
National Institutes of Health NCI  
Principal Investigator: Aria Olumi, MD

“Molecular Mechanisms of c-FLIP(L) Regulation and its Function in TRAIL-induced vs. TNF-induced Apoptosis”  
US Department of Defense.  
Principal Investigator: Xu Huang, PhD

“TRAIL, a Cytokine, Induces Apoptosis in Prostate Cancer Cells”  
Helen Hay Whitney Foundation.  
Principal Investigator: Xu Huang, PhD

“Transcriptional Regulation of c-FLIP(L) and Molecular Mechanism Differentiating TRAIL-induced vs. TNF induced Apoptosis in Prostate Cancer”  
Prostate Cancer Foundation.  
Principal Investigator: Xu Huang, PhD

“Transcriptional Regulation of c-FLIP(L) and Molecular Mechanism Differentiating TRAIL-induced vs. TNF induced Apoptosis in Prostate Cancer”  
American Institute for Cancer Research.  
Principal Investigator: Xu Huang, PhD.

“Upregulation of C-Fos is a Key Step to Promote TRAIL-induced Apoptosis via Suppression of c-FLIP(L) in Prostate Cancer Cells”  
US Department of Defense.  
Principal Investigator: Xiaoping Zhang, MD, PhD.

“In-vivo Study of C-Fos as a Pro-Apoptotic Agent in Human Prostate Cancer”  
American Association for Cancer Research.  
Principal Investigator: Xiaoping Zhang, MD, PhD

“Targeting C-Fos as a Pro-Apoptotic Agent in Human Prostate Cancer”  
Charles A King Trust Fellowship.  
Principal Investigator: Xiaoping Zhang, MD, PhD

“Targeting C-Fos as a Pro-Apoptotic Agent in Human Prostate Cancer”  
Dana Farber Cancer Institute.  
Principal Investigator: Xiaoping Zhang, MD, PhD

**DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

Research Accomplishments

- Young Investigator’s Research Award from Society of Basic Urologic Research, May 2005.
- NIH/NIDDK—K08 grant renewed.
- Department of Defense Grant renewed

Abstracts Presented at Local, National, and International Meetings

Zhang X, Yang H, DeWolf WC, Khosravi-Far R, **Olumi AF**. Increased expression of c-Fos/AP-1 is required for prostate cancer cells to undergo TRAIL mediated apoptosis. American Association Cancer Research, Anaheim, CA.

Zhang L, Zhang X, **Olumi AF**. Differentiating molecular differences between TRAIL-sensitive and TRAIL-resistant renal cell carcinoma cells. American Association Cancer Research, Anaheim, CA.

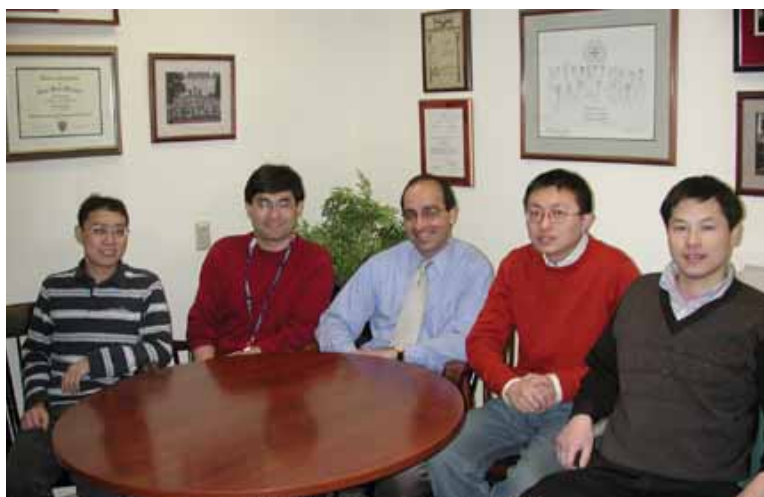
Zhang X, Yang H, DeWolf WC, Khosravi-Far R, **Olumi AF**. c-Fos nuclear translocation represses c-FLIP(L) and enhances TRAIL-induced apoptosis in prostate cancer cells. Cold Spring Harbor – Programmed Cell Death Meeting, Cold Spring Harbor, NY.

Zhang X, Yang H, Zhang L, DeWolf WC, Khosravi-Far R, **Olumi AF**. C-Fos has a pro-apoptotic function and represses c-FLIP(L). Society of Basic Urologic Research. Miami, FL.

Zhang L, Zhang X, **Olumi AF**. HGS-ETR2, a TRAIL-receptor agonist promotes apoptosis by enhancing expression of TRAIL-receptor DR5. Society of Basic Urologic Research. Miami, FL.

Individual Accomplishments

- Invited to be a grant reviewer for Department of Defense Prostate Cancer Program (4<sup>th</sup> year).
- Selected as Editorial Board Member, Journal of Urology – Investigative Urology.



**Olumi Lab: Drs. Wenhua Li, Liang Zhang, Aria Olumi, Xu Huang, and Xiaoping Zhang**

**REPORT OF TEACHING**

Undergraduate

MIT pre-medical advisor for three undergraduate students.

Medical School Courses

Core surgery clerkship lecturer for medical students; topics: BPH and prostate cancer (once every three months).

Resident Teaching: Harvard Program in Urology

- Monthly one-on-one evaluation with interns and residents.
- Weekly faculty representative for the Harvard Urology Program conferences.
- Monthly one-on-one evaluation with interns and residents.

**BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

Original Articles (submitted or in press)

Francisco IF, Regan, MM, DeWolf WC, **Olumi AF**. Low age-adjusted free-testosterone is associated with poorly differentiated prostate cancer. *J Urol* 2005; in press.

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**Division of Urology**

Zhang L, Zhang X, **Olumi AF**. HGS-ETR2, a TRAIL-agonist in renal cell carcinoma. 2005; submitted.

Zhang X, Yang H, DeWolf WC, Khosravi-Far R, **Olumi AF**. c-Fos has a pro-apoptotic function by repressing c-FLIP(L). 2005; submitted.

Reviews, Chapters, and Editorials

Huang X, Farahvash B, **Olumi AF**. Pro-apoptotic therapies for treatment of prostate cancer. *J Urol* 2005;submitted (solicited review article by the journal).

**Olumi AF**, San Francisco I. Editorial letter. *Int J Cancer* 2005; submitted.

**Olumi AF**. Editorial comments. *J Urol* 2005; submitted.



## Martin Sanda, MD

### Basic Research

The principal areas of research in the Sanda laboratory include 1) elucidating mechanisms of T cell tolerance and immune evasion in prostate cancer, and 2) evaluating prostate cancer antigens as targets for immunotherapy and biomarkers for cancer screening and severity assessment. This set of broad research goals provides a unique environment for learning how translational research, utilizing transgenic mice, can concurrently address issues important for developing new therapy while also characterizing fundamental issues of basic tumor immunology. The translational component of this work also focuses on identifying how prostate tumor antigens may be used not only as targets for immunotherapy but also to improve prostate cancer early detection.



Dr. Martin Sanda

### Clinical Research

The clinical research focus in the Sanda laboratory concerns prostate cancer clinical outcomes. These studies include the PROST-QA consortium, a national consortium of prostate cancer referral centers (Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Cleveland Clinic, MD Anderson Cancer Center, MGH, UCLA, University of Michigan, and Washington University) wherein combined evaluation of cancer control, satisfaction with care, and quality of life provides comprehensive characterization of prostate cancer care quality. This study, led by Dr. Sanda, has enrolled over 1800 participants, treated by over 40 physicians nationwide, and is the largest ongoing, NCI-funded prospective study of prostate cancer quality of life. Dr. Sanda also participates in Eastern Cooperative Oncology Group (ECOG), where he is the Urology co-Chair of the GU Early Modalities Subcommittee, which develops multi-center Phase II and Phase III protocols for early stage GU cancers.

### **Current Employees**

Joe Castro, RN	Clinical and Research Nurse
Mariam Eljanne, PhD	Research Associate
Kyrsten Haram, BA	Research Assistant (Basic)
Megan Connor, BA	Research Assistant (Clinical)
Renee Gatewood	Administrative Assistant

### **LIST OF CURRENT FUNDING**

“Harvard/Michigan Prostate Cancer Biomarker Clinical Center” (an EDNRN-CEVC)  
National Institutes of Health, U01 - **CA11391-01**  
Principle Investigator: Martin Sanda, MD

“Survivor HRQOL and Spouse Satisfaction after Prostate Cancer Therapy”  
National Institutes of Health, R01 - **CA95662-01**  
Principle Investigator: Martin Sanda, MD

“Project #3 – Role of Fas in T cell Tolerance in Prostate Cancer.”  
UM-BIDMC O'Brien Center for Urology Research  
National Institutes of Health, P50 - **DK065313-01**  
Project Director: Martin Sanda, MD

“SPOR in Prostate Cancer” (subcontract from University of Michigan)  
National Institutes of Health, P50 - **CA069568-02A1**  
Principle Investigator: Arul Chinnaiyan, MD, PhD; Co-Investigator: Martin Sanda, MD

“Modulating Tolerance for Prostate Cancer Antigen Vaccines”  
National Institutes of Health, R01 - **CA82419-01**  
Principle Investigator: Martin Sanda, MD

## **DIVISIONAL ACCOMPLISHMENTS OVER THE PAST YEAR**

### Research Accomplishments

I participated in two trials this year. The first was the NCI-Radiation Therapy Oncology Group (RTOG) Trial 0232, for which I was the National Protocol co-chair. This was a phase III study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for patients with an intermediate risk for prostate cancer. The second trial was the NCI – Eastern Cooperative Oncology Group (ECOG) Trial E 7805, for which I was the National Protocol Chair. This was a Phase III trial being developed to evaluate 5-alpha reductase inhibitor (dutasteride) versus placebo in preventing progression of histopathologically indolent prostate cancer.

My group gave five presentations at the National American Urological Association (AUA) Annual Meeting in San Antonio, TX. May, 2005.

### Honors and Awards

In 2005, I received the prestigious *Society of Urological Oncology Young Investigator Award* at the American Urological Association Annual Meeting in San Antonio, TX. This award is given annually to the single urologist nationally who is judged to have contributed the most in urological oncology in the first 10 years after completing residency training.

## **REPORT OF TEACHING**

### Undergraduate and medical school courses

I participated in the MIT-Harvard Undergraduate HST Program as a Faculty Supervisor. I mentored C Wang and A Yonekura, who are both undergraduate students.

### Graduate School and graduate medical courses

I participated in the Urology clerkship at HMS.

### CME courses

“Managing Urological Complications” (Course Director), AUA National Meeting. May, 2005.

“Prostate Cancer” (Course Director), Harvard Medical International Course, Lausanne, Switzerland. September, 2005.

## **BIBLIOGRAPHY (JANUARY – DECEMBER 2005)**

### Original Articles

Bradley SV, Oravec-Wilson KJ, Bougeard G, Mizukami I, Li L, Munaco AJ, Sreekumar A, Corradetti MN, Chinnaiyan A, **Sanda MG**, Ross TS. Serum Antibodies to Huntingtin Interacting Protein-1: a new blood test for prostate cancer. *Cancer Res* 2005; 65(10):4126-33.

Miller, D, **Sanda MG**, Dunn RL, Monty JE, Pimentel H, Sandler HM, McLaughlin WP, Wei JT. Long-term outcomes among localized prostate cancer survivors: HRQOL changes 4 to 8 years following radical prostatectomy, external radiation and brachytherapy. *J Clin Oncol* 2005; 23(12):2772-80.

Wang X, Yu J, Sreekumar A, Varambally S, Shen R, Giacherio D, Mehra R, Montie JE, Pienta KJ, **Sanda MG**, Kantoff PW, Rubin MA, Wei JT, Ghosh D, Chinnaiyan AM. Autoantibody signatures in prostate cancer. *N Engl J Med* 2005; 353(12):1224-35.

### Original Articles (submitted or in press)

Miller DC, Wei JT, Dunn RL, Montie JE, Pimentel H, Sandler HM, McLaughlin PW, **Sanda MG**. Utilization of medications or devices for erectile dysfunction among long-term prostate cancer treatment survivors: the potential influence of sexual motivation and/or indifference. *Urology* 2005; in press.

Montgomery JS, Gayed BA, Hollenbeck BK, Daignault S, **Sanda MG**, Montie JE, Wei JT. Obesity adversely affects health related quality of life prior to and following radical retropubic prostatectomy. *J Urol* 2005; in press.

Reviews, Chapters, and Editorials

**Sanda MG**, Rodriguez R. Gene therapy for urologic cancer: basic principles, prospects, and limitations. In: Richie JP, D'Amico AP, editors. Urologic oncology. Philadelphia: Elsevier-Saunders; 2005. p. 18-38.



# Division of Vascular and Endovascular Surgery



**Frank W. LoGerfo, MD**

**Director, Division of Vascular and  
Endovascular Surgery  
William McDermott Professor of Surgery**

## **Division Members**

**Christiane Ferran, MD, PhD**

Soizic Daniel, PhD

Salvatore T. Scali, MD

Mark D. Fisher, MD

Haley Ramsey, MS

Nicholas Ward

Roy Arjoon

Eva Czismadia

**Allen Hamdan, MD**

Despina Hoffman

Jennifer Lambert

## ***Dr. LoGerfo's Laboratory Group***

Mauricio A. Contreras, MD

Leena Pradhan, PhD

Shen-Qian Wu, MD, PhD

Nick Andersen, BS

Sowmya Senani, BS

Monica Jain

Mathew D. Phaneuf, BS

**Associate Professor of Surgery**

Instructor in Surgery

Surgical Resident, Research Fellow and T32  
Trainee

Surgical Resident, Research Fellow and T32  
Trainee

Research Associate I

Undergraduate student, Harvard University

Undergraduate student, Boston University

Research Associate

**Assistant Professor of Surgery**

Research Coordinator

Nurse Practitioner

Instructor in Surgery

Instructor in Surgery

Senior Postdoctoral Fellow

Research Assistant / HMS Student and  
HHMI Fellow

Research Technician

Undergraduate Student, Boston University

Consultant

**Frank Pomposelli, MD**

**Associate Professor of Surgery**

**Sherry Scovell, MD**

**Instructor in Surgery**

**Marc Schermerhorn, MD**

**Visiting Assistant Professor of Surgery  
Section Chief, Endovascular Surgery**



## Divisional Research Report by Frank W. LoGerfo, MD

### Basic Research

#### *Vascular Surgery Research Laboratory – Dr. Frank W. LoGerfo, MD (Laboratory Director)*

The vascular surgery research laboratory has been extensively involved in three main areas of vascular biology research: 1) evaluating mechanisms responsible for prosthetic graft failure, 2) developing novel biomaterial surfaces, and 3) prevention of intimal hyperplasia in vein grafts. 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 cellular proliferation, migration, and extracellular matrix production by smooth muscle cells, leading to AIH. Differential gene expression is assessed using various techniques such as, microarray analysis, qPCR and immunohistochemistry. Laser-Capture Microdissection (LCM), a relatively new technology developed by the National Institutes of Health, which is available at Beth Israel Deaconess Medical Center. We have now established proficiency with LCM, a tool designed to isolate homogeneous populations of cells for genetic analysis. This technique allows direct microscopic visualization and isolation of selected cell populations from frozen tissue sections and permits selection of cells within a chosen area of tissue. The significance and unique aspect of this work is that our group is the first to identify specific genes that are altered following prosthetic arterial grafting and vein grafting in vivo and to examine their role in the cellular environment using various in vitro cell culture assays. This information is now being used to identify targets for RNA silencing. We have established our ability to silence RNA in cell culture and in the vein graft wall. We are working towards systems for RNA silencing that will be practical for intraoperative use.

For biomaterials research, we have designed and patented several novel biomaterial surfaces. An infection-resistant ionic polyurethane was developed in Phase I and II STTR grants in which quinolone antibiotics were incorporated into the polymer using textile dyeing techniques, with this surface demonstrating antimicrobial activity both *in vitro* and *in vivo*. This biomaterial can be used to comprise a wide range of implantable devices such as catheters, wound dressings and vascular grafts, avenues that are currently being explored. A similar ionic polyurethane was then employed to seal FDA-approved knitted Dacron vascular grafts using a patented perfusion technology. As part of a Phase II STTR grant, these sealed vascular grafts were evaluated at various acute and chronic time periods using a canine carotid arterial grafting model. A porcine cardiac surgical model to evaluate a novel infection-resistant Dacron prosthetic valve sewing cuff with optimum antimicrobial properties is currently in the development stages in order to complete the objectives of a Phase II SBIR grant. We have also developed in vitro, as described in our Phase I STTR proposal, a novel small-diameter nanofibrous polyurethane vascular graft via electrospinning technology. Lastly for metallic implants comprised of titanium such as bone joints and dental posts, we have completed early development of a novel titanium surface with mitogenic properties via covalent linkage of bone morphogenic protein-2 (an osteoblast mitogen). Recently we have developed a surface including Activated protein C to prevent thrombosis and to stimulate cellular healing of the Dacron arterial grafts.

This past year two new scientists joined our group. Leena Pradhan, PhD, came from Tulane University with expertise in endothelial cell biology. Her administrative roles include oversight of our research training programs for residents and medical students. In addition, she will spearhead the involvement of our laboratory in translational research related to the pathobiology of ulceration in the Diabetic foot. Our initial focus is on the role of neuropeptides and the relationship between neuropathy and ischemia. This work is in collaboration with Aristidis Veves, M.D., from our division of Podiatry.

The second scientist to join us is Sheng-Quian Wu, PhD, who joined us from Dr. William Aird's laboratory. Dr Wu is developing models of biologically active artificial surfaces to prevent clot formation and to enhance biocompatibility.

#### *Vascular Immunobiology Laboratory – Christiane Ferran, MD, PhD (Laboratory Director)*

Most of my time effort, i.e. eighty five per cent, is devoted to Research. My major research interests are in the field of vascular biology mainly intimal hyperplasia as well as the micro and macrovascular complications of diabetes, transplantation including xenotransplantation and islet transplantation as well as autoimmune diabetes, acute liver failure and liver regeneration. More specifically, the work in my laboratory is focused on the understanding of the function (s) of the anti-apoptotic genes A20, Bcl-2, Bcl-xL and A1 in different cell types, their relationship to the pathophysiology of diseases and their potential therapeutic use in organ transplantation, diabetes, atherosclerosis,



Dr. Christiane Ferran

that A20 based therapies may be highly beneficial for patients presenting with severe liver damage but who still have a fraction of viable hepatocytes. Protecting this reduced functional liver mass in the face of ongoing inflammation would meet metabolic demands and allow enough time for regeneration. Expression of A20 is particularly promising for reducing the donor graft size necessary for living donor liver transplantation, allowing the safe use of steatotic organs, and permitting extensive liver resection for the cure of neoplasia.

diabetic vasculopathy and liver regeneration. This interest is based on our original finding that these genes, mainly A20 serve a broad cytoprotective function in endothelial cells (EC), islets and hepatocytes and an atheroprotective function in smooth muscle cells (SMC). Expression of A20 in endothelial cells, islets and hepatocytes not only protects the cells from apoptosis by interrupting the activation of the caspase cascade but also exerts a broad anti-inflammatory purpose by blocking activation of the transcription factor NF- $\kappa$ B. Uniquely A20 also promotes hepatocyte proliferation hence liver regeneration by down-regulating the cell cycle brake p21<sup>waf1</sup>. In addition, we have recently demonstrated that A20 also increases the expression of peroxisome proliferators associated receptor  $\alpha$  (PPAR $\alpha$ ), which adds to its anti-inflammatory effect in hepatocytes, and unveil its role in regulating lipid metabolism. These novel findings are strong proof

Expression of A20 in SMCs on the other hand inhibits their proliferation and sensitizes neointimal (i.e. the major component of atherosclerotic lesions), but not medial SMC, to apoptosis through a novel NO dependent mechanism. A20 fulfills most of the criteria required for an ideal atheroprotective therapy that confers an athero-resistant phenotype to both EC and SMC. We propose that A20 based therapies hold strong promise for the prevention and

cure of vascular neointimal disease including atherosclerosis, transplant arteriosclerosis, in-stent restenosis and diabetic vasculopathy. This hypothesis is strengthened by our recent demonstration of impaired expression of A20 in failed vein grafts of diabetic patients that could account for their increased susceptibility to atherosclerosis. We have preliminary evidence that expression of the "atheroprotective" protein A20 in the two major target cells of hyperglycemic damage within the vessel wall i.e. Endothelial (EC) and smooth muscle (SMC) cells, is blunted by high glucose (HG) in vitro and uncontrolled hyperglycemia in vivo. Altered A20 expression in face of HG stems from its post-translational modification by O-glycosylation (a newly recognized, key post-translational modification), which marks it for ubiquitination and degradation by the proteasome (Figure 1). Glucose-mediated degradation of A20 in EC/SMC promotes their acquisition of a pro-atherogenic phenotype, contributing to accelerated atherosclerosis in DM.

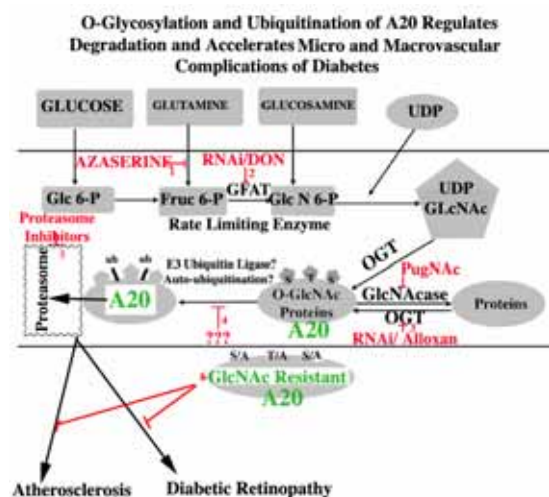


Figure 1

In a similar vein, we have breakthrough evidence that A20 is a negative regulator of angiogenic pathways in EC, both upstream and downstream of VEGF. Expression of A20 in EC inhibits EC tube formation, in vitro, through blockade of PKC $\beta$ II and ERK1/2 activation while enhancing VEGF mediated AKT phosphorylation. As such, its degradation in the face of high glucose, also contributes, through increased angiogenic, to diabetic retinopathy. Restoring adequate levels of the "atheroprotective" and "anti-angiogenesis" protein A20, in the face of high glucose/hyperglycemia, should protect from the macro and microvascular complications of diabetes.

## Clinical Research

### Clinical Research in Vascular Surgery –Allen Hamdan, MD

The clinical research component of the Vascular Division continues to be very vibrant. One of the main problems in the past year was a changing over and updating of our database, which caused some significant delays in entering data as well as computer problems. With hard work by a number of people in the Division, including Lynn Francis and Haig Panossian, we have been able to rectify most of the issues and now can go forward. Another significant

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addition to our Division has been Dr. Marc Schermerhorn who is Section Chief for Endovascular Surgery. He has a strong increase in outcomes and through his efforts has spearheaded our joining the Society of Vascular Surgery registry for carotid stents as well as the Northern New England group that follows all major vascular interventions. This will allow us to be on the forefront of divisions in regards to understanding our own outcomes as well as being able to publish them and to provide patients as well as insurers with that information.

Another significant addition was the hiring of Despina Hoffman as our Research Coordinator. Jennifer Lambert received her Nurse Practitioner's License and has stayed in the Division, but has stepped down as our Research Coordinator. Despina brings an incredible research background, mainly in cancer research, but has significant expertise in running clinical trials.

**Current Members**

*Vascular Surgery Research Laboratory*

Aristidis Veves, MD, DSc	Associate Professor of Surgery (Collaborator)
Mauricio A. Contreras, MD	Instructor in Surgery
Leena Pradhan, PhD	Instructor in Surgery
Shen-Qian Wu, MD, PhD	Senior Postdoctoral Fellow
Nick Andersen, BS	Research Assistant / HMS Student and HHMI Fellow
Sowmya Senani, BS	Research Technician
Monica Jain	Undergraduate Student, Boston University
Mathew D. Phaneuf, BS	Consultant

*Vascular Immunobiology Laboratory*

Soizic Daniel, PhD	Instructor in Surgery
Salvatore T. Scali, MD	Surgical Resident, Research Fellow and T32 Trainee
Mark D. Fisher, MD	Surgical Resident, Research Fellow and T32 Trainee
Haley Ramsey, MS	Research Associate I
Nicholas Ward	Undergraduate student, Harvard University
Roy Arjoon	Undergraduate student, Boston University
Eva Czismadia	Research Associate

*Clinical Research in Vascular Surgery*

Marc Schermerhorn, MD	Visiting Assistant Professor of Surgery
	Section Chief, Endovascular Surgery
Despina Hoffman	Research Coordinator
Jennifer Lambert	Nurse Practitioner

**LIST OF CURRENT FUNDING**

“Mechanisms of Prosthetic Arterial Graft Failure”  
National Institutes of Health NHLBI, RO1- **HL21796-21**  
Principle Investigator: Frank W. LoGerfo, MD

“Harvard-Longwood Research Training in Vascular Surgery”  
National Institutes of Health NHLBI, 5 T32 - **HL007734-12**  
Principle Investigator: Frank W. LoGerfo, MD

“William J. von Liebig Research and Research Training in Vascular Surgery”  
William J. von Liebig Foundation  
Principal Investigator: Frank W. LoGerfo, MD

“Improved Liver Function and Regeneration with A20”  
National Institutes of Health, **DK 063275**  
Principle Investigator: Christiane Ferran, MD, PhD

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“Altered A20 Expression and Diabetic Retinopathy”  
Juvenile Diabetes Research Foundation, **5-2005-1276**  
Principle Investigator: Christiane Ferran, MD, PhD

“Transplant Arteriosclerosis: Role of A20 in Homing of EC and SMC Progenitors”  
Roche Organ Transplant Research Fund  
Principle Investigator: Christiane Ferran, MD, PhD

“Vascular and Metabolic Changes in the Diabetic Foot”  
National Institutes of Health, R01- **HL75678-01**  
Principal Investigator: Aristidis Veves, MD, PhD

“Infection Resistant Prosthetic Valve Sewing Cuffs”  
National Institutes of Health NHLBI, SBIR R44 - **HL065826-02**  
Principle Investigator: Allen Hamdan, MD

“A Nanofibrous Biocomposite Small-Diameter Graft”  
National Institutes of Health NHLBI, SBIR 2 R44 - **HL074771-02**  
Principle Investigator: Mauricio A. Contreras, MD  
Co-Investigator: Frank W. LoGerfo, MD

**APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING**

“Development of Infection-Resistant Suture Materials”  
National Institutes of Health NHLBI  
Principle Investigator: Mauricio A. Contreras, MD  
Co-Investigator: Frank W. LoGerfo, MD

“Glucose Regulation of A20 in Beta-Cells”  
Juvenile Diabetes Research Foundation  
Principle Investigator: Soizic Daniel, PhD  
Co-Principal Investigator: Christiane Ferran MD, PhD

“The Molecular Basis for Increased Atherosclerosis in Diabetes”  
Juvenile Diabetes Research Foundation  
Principle Investigator: Christiane Ferran MD, PhD

“Impaired Atheroprotective Responses in Diabetes”  
Application submitted by Salvatore Scali, MD, surgical resident at the BIDMC to the Loan Repayment Program (LRP), National Institutes of Health.  
Principal Investigator: Christiane Ferran MD, PhD.

**DIVISIONAL ACCOMPLISHMENTS IN THE PAST YEAR**

Research Accomplishments

*Vascular Biology Research Laboratory-Frank W. LoGerfo, MD*

Mechanisms of Prosthetic Arterial Graft Failure: Anastomotic intimal hyperplasia (AIH) remains the most common cause of delayed prosthetic arterial graft failure, a consequence of focal, unregulated gene expression. As graft healing occurs, genes are either up or down-regulated compared to a quiescent arterial wall. Our hypothesis is that altered gene expression results in cellular proliferation, migration, and extracellular matrix production by smooth muscle cells leading to AIH.

Our continued investigation will assess gene expression at different time points (24 and 48 hours; 7, 14, 30, and 60 days) after surgical implantation of ePTFE 6mmID prosthetic grafts in our common carotid artery canine model.



Figure 2



Figure 3

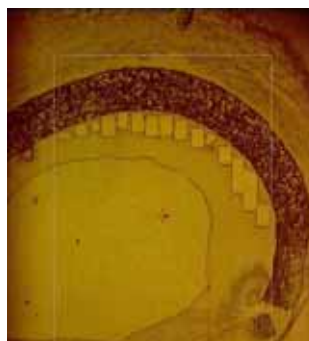


Figure 4

Figure 2: Histological cross section of normal common carotid artery (Control).

Figure 3: Distal anastomosis at 60 days. (H&E / 1X).

Figure 4: Histological cross section of distal anastomosis at 60 days and LCM of neointima (SMC) at the Graft luminal surface. (Unstained / 1X).

To date, we have completed all surgical implantations and have collected specimens for all time intervals (n=3 per time interval). Once specimens were harvested, frozen sections of normal common carotid artery (control, Figure 2) and the distal anastomosis (Figure 3) were generated for Laser Capture Microdissection (LCM). Smooth muscle cells from the neointima and control arterial wall were dissected out through LCM (Figure 4), RNA was extracted and amplified for Affymetrix microarray analysis with qPCR validation on control arterial wall and neointima to facilitate localization of altered gene expression over time (7, 14, 30, and 60 days).

At present we are completing our two remaining time points (24 and 48 hours) for LCM, RNA extraction, amplification and qPCR validation. We plan to have all samples ready for Microarrays by March 2006. Protein expression will be examined using immunohistochemistry and western blot analysis. We believe identifying alterations in gene expression, their time courses, cellular localization and computational analysis will provide a valuable guide to a comprehensive understanding of AIH.

Prevention of Intimal Hyperplasia in Vein Grafts: Intimal hyperplasia in arterialized vein bypass grafts is a significant cause of vein graft stenosis and delayed graft failure. Injury at the time of implantation or as a consequence of transplantation into the high pressure arterial system may contribute to these delayed events. Alterations in gene expression accompany implantation and arterialization injury. These alterations lead to intimal hyperplasia, including transformation of endothelial cells to an inflammatory state and initiating migration and transformation of smooth muscle cells from the contractile to secretory states thus creating the lesion of intimal hyperplasia. It is our hypothesis that silencing of genes upregulated by injury to the vein wall will diminish intimal hyperplasia. Furthermore, gene silencing can be accomplished within the constraints of operating room conditions. We have demonstrated the ability to identify candidate genes associated with intimal hyperplasia and our ability to knockdown gene expression with siRNA. Using LCM we have separated genetic events in the endothelium from those in smooth muscle. Currently we are applying these technologies to (1) systematically identify silencing targets, (2) to silence target genes in vitro, (3) to silence target genes under surgical conditions, (4) to demonstrate inhibition of intimal hyperplasia in vein grafts in vivo. We are performing studies in human tissue and in canine models as well as in vitro using human smooth muscle cells and human coronary artery endothelial cells. In 2005, the work of Dr. Thomas Monahan characterized the contributions of two novel target genes identified by our lab, cadherin 11 (CDH11) and the myristoylated alanine-rich C kinase substrate (MARCKS), to the pathologic in vitro phenotypes associated with intimal hyperplasia and identified both as promising targets for therapeutic gene silencing in vein grafts. These studies resulted in three national presentations, two upcoming journal submissions, and a provisional patent for the use of MARCKS as a target for inhibiting restenosis after vascular interventions. The work of Nicholas Andersen



focused on translating siRNA technology for use in vascular surgical procedures, including the validation of siRNA technology in vascular cells cultured in vitro to the rapid transfection of human vein segments under operating room conditions. Promising results were obtained on both fronts and accepted by two national meetings for presentation in 2006. Continued progress on the inquiry outlined above will greatly strengthen the application of gene silencing to clinical problems in vascular surgery, and broaden our understanding of vascular wall biology.

**Infection Resistant Prosthetic Valve Sewing Cuffs:** Bacterial infection is a major complication associated with implantation of prosthetic valves for cardiac valve replacement. Infections are localized to the biomaterial/tissue interface leading to cuff and annular abscess formation. An infection-resistant knitted polyester (Dacron) cuff material was developed in our laboratory with optimum antimicrobial properties via thermo fixation (pad/heat) dyeing of the antibiotic ciprofloxacin (Cipro). Application of this technology resulted in slow, sustained antibiotic release without the use of exogenous binders. Our hypothesis is that the application of quinolone antibiotics, such as Cipro, to Dacron sewing cuffs using our proprietary dyeing technology will significantly reduce cardiac valve infections when challenged with a significant bacterial inoculum.



Figure 5



Figure 6

Figure 5: Surgical incision and sewing cuff ring implantation into the ascending aorta.

Figure 6: Closure of the ascending aorta with sewing cuff ring in place.

At present, we are conducting our in vivo studies by implanting unmodified (clinical standard/control) and Cipro-dyed sewing cuffs in our porcine ascending aorta infection model (Figure 5 and 6). We will assess control and Cipro-dyed Dacron sewing cuffs via histological/microbiological techniques and determine physical properties of Cipro-dyed sewing cuffs post-explanation.

**A Nanofibrous Biocomposite Small-Diameter Graft:** There is no small-diameter (< 5mm internal diameter) vascular prosthesis approved for clinical use in small vessel reconstruction. Current prostheses are not capable of emulating the biological and physical properties of the normal arterial wall, resulting in high failure rates. Our hypothesis is that the next generation of prosthetic arterial grafts will have to possess multiple structural and biological properties that mimic some of those processes inherent to native arteries in order to prevent complications such as thrombosis from occurring. We have designed a new, nanofibrous biocomposite small-diameter vascular graft comprised of Dacron and Type IV collagen (ESDC). The potent anti-thrombin agent recombinant hirudin (rHir) and endothelial cell-specific mitogen Vascular Endothelial Growth Factor (VEGF) were then covalently bound to the ESDC surface (ESDC-rHir-VEGF). These surface bound agents were biologically active as determined via specific in vitro assays and showed stability under simulated arterial flow conditions. Our goal of this Phase II project is to assess blood permeation and graft patency/healing of the ESDC-rHir-VEGF graft using a canine arterial grafting model (femoral artery interposition).

**Development of a Biologically-Active Prosthetic Graft:** Surface thrombosis and lack of cell in growth lead to prosthetic vascular graft implantation failure. Biological modification of existing materials remains one of the promising approaches to overcome the problems. Activated protein C (APC) is a potent anticoagulant and the ligand for endothelial cell protein C receptor (EPCR), which is primarily expressed on endothelial cells and on some hematopoietic stem cells. This project sets out to test the feasibility of immobilizing APC to Dacron and to evaluate the biocompatibility of APC bound Dacron. When modified with the crosslinker sulfo-SMCC, APC covalently bound to Dacron underwent multi-step modification. Surface bound APC has promising physical and

functional stability as tested using a static system and a simulated arterial flow system. The APC bond Dacron surface demonstrated good anti-coagulant activity as indicated by chromogenic assay and clotting assay. An abstract based on our preliminary study has been accepted by the Society for Biomaterials for presentation. A research grant application will be submitted to CIMIT for the fiscal year of 2006.

Role of neuropeptides in diabetic foot ulcerations: Abnormal wound healing is a major complication of both type I and type II diabetes and is the most frequent cause of non-traumatic lower limb amputation. Wound healing requires the orchestrated integration of complex biological and molecular events. Inflammation, proliferation, and migration of cells followed by angiogenesis and re-epithelization are essential phases of wound healing. Recently, dysregulation of neuropeptides, such as Substance P (SP) and Neuropeptide Y (NPY), secreted from peripheral nerves have been implicated in abnormal wound healing. The link between wound healing and the nervous system is clinically apparent as peripheral neuropathy is reported in 30-50% of diabetic patients and is the most common and sensitive predictor of foot ulceration. Furthermore, molecular studies have shown SP and NPY levels are reduced in diabetic patients. Receptors for SP are found on relevant wound healing cells including monocytes, mast cells, endothelial cells (ECs) and keratinocytes. SP is known to evoke an acute inflammatory response, consistent with the inflammatory phase of wound healing. It also has a proliferative effect on ECs, an important step in angiogenesis. Thus, SP affects numerous phases of wound healing and any dysfunction in the production, release or signaling of SP could impair wound healing. NPY has a similar proliferative effect on ECs, and NPY receptor null mice demonstrate impaired wound healing. Although SP and NPY production and metabolism appear to play a role in diabetic wound healing, the exact molecular and cellular mechanisms underlying these complex interactions remain elusive.

Our hypothesis is that inadequate levels of neuropeptides such as SP and NPY and/or dysregulation in their signaling pathways leads to abnormal wound healing in diabetes. We are planning on testing this hypothesis in vitro, in vivo, and in human samples obtained from diabetic patients with clinical neuropathy and chronic foot ulcerations. Molecular in vitro studies will be conducted in Human Dermal Microvascular Endothelial Cells (DMVECs) and U-937 monocytes to delineate neuropeptide signaling mechanisms in the setting of high glucose. In vivo studies will be performed in alloxan induced diabetic rabbits in which wounds will be created in the ear and wound closure monitored in the presence or absence of exogenous SP and/or NPY. Our novel approach includes rendering the ear neuroischemic prior to wounding and studying the individual and combined contributions of neuropathy and ischemia to diabetic wound healing. In human samples, we will analyze the relationship of plasma and skin neuropeptides with markers of angiogenesis. This study will be critical in determining the role of neuropeptides in clinical human disease.

Based on this hypothesis, a grant proposal was submitted by Leena Pradhan to the Juvenile Diabetes Foundation for the Advanced Postdoctoral Fellowship award for the year 2006.

*Immunobiology Research Center-Christiane Ferran, MD, PhD*

The past year, we have mainly extended our program to studying the impact of A20 upon diabetic vasculopathy and diabetic retinopathy. Our preliminary results resulted in the discovery that diabetes mellitus impairs the expression of atheroprotective genes such as A20. A20 is blunted in diabetic patients due to metabolic disturbances aggravated by genetically determined factors specific to patients with type I DM. This work has set the basis for a Juvenile Diabetes Research Foundation grant aimed at evaluating the role of A20 upon diabetic retinopathy that has already been funded. This work was also the subject of a proposal to the NIH loan repayment program (LRP) submitted by Salvatore Scali MD that is currently under review. Our groundbreaking data on the role of A20 in DV has also set the basis for an NIH grant proposal that has just been submitted aimed at evaluating the role of A20 glycosylation upon the development of DV and of complementary grant proposal submitted to the Juvenile Diabetes Research Foundation on January 16<sup>th</sup> 2006. The work on the role of A20 in the development of DV was also the subject of a proposal to the NIH loan repayment program (LRP) that was successfully awarded last year to Gautam Shrikhande MD.

We have also been successful in expanding our work demonstrating the beneficial effect of A20 expression in medial smooth muscle in preventing intimal hyperplasia to studying its impact on already established disease. Our data demonstrate that expression of A20 in neointimal smooth muscle cells induces the regression of established lesions via its unique capacity to sensitize neointimal SMC to apoptosis via a NO dependent mechanism. These provocative and exciting results have been finalized in a manuscript now under revision for



publication to FASEB journal. This work was the subject of a proposal to the NIH LRP that was successfully awarded to Virendra Patel MD last year. In addition, it has served as a basis to 2 grant proposals. The first one was successfully submitted to the Roche Organ Transplant Research Foundation and funding will begin on January 1<sup>st</sup> 2006. The second was submitted as an RO1 application to the NIH. It previously received a priority score of 170 (14.7 percentile) and is currently pending a funding decision. This later work was also submitted in a proposal to the NIH loan repayment program (LRP) that was successfully awarded to Mark D. M. Fisher MD.

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 p21<sup>waf1</sup>. This data has been published in *Hepatology*. New stimulating data generated, implicating an effect of A20 on the cyclin dependent kinase p21<sup>waf1</sup> and PPAR $\alpha$ , are solid leads for the competitive renewal of this grant by the end of next year.

We have also been successful in expanding our work demonstrating the beneficial effect of A20 expression in medial smooth muscle in preventing intimal hyperplasia to studying its impact on already established disease. Our data demonstrate that expression of A20 in neointimal smooth muscle cells induces the regression of established lesions via its unique capacity to sensitize neointimal SMC to apoptosis via a NO dependent mechanism. These provocative and exciting results have been finalized in two manuscripts submitted for publication to the *Journal of Experimental Medicine*. This work was also the subject of a proposal to the NIH LRP that was successfully awarded to Virendra Patel, M.D.

We 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 p21<sup>waf1</sup>. Data were presented at the annual BIDMC competition for surgical residents by Christopher Longo, MD and received an award. Results were also finalized in a manuscript submitted for publication in *Hepatology*.

#### *Vascular Surgery Clinical Research-Allen Hamdan, MD*

Inflammatory marker trial: This is a prospective trial looking at about 300 patients in concert with the Brigham and Women's Hospital under the direction of Dr. Mike Conte. Patients are prospectively followed who undergo vein bypass grafts. A number of inflammatory markers including C reactive protein are evaluated pre- and post-operatively to see if there is any impact on progression of vascular disease. There was a recent acceptance of an abstract on the relation of C reactive protein to perioperative events that we presented at the Society of Vascular Surgery national meeting, which I suspect will be published in the *Journal of Vascular Surgery* six months later. We continue to actively enroll patients.

Crest trial: Dr. Schermerhorn is now the site PI for this trial. It is a randomized trial looking at carotid stent vs. carotid endarterectomy. All of the surgeons are eligible to perform carotid endarterectomy in the trial. Dr. Schermerhorn is eligible to perform endarterectomy as well as carotid stenting. He is one of the few surgeons in the country who has this dual nomination. We will be actively enrolling patients in this very important trial.

Capture registry: This is a post-marked release registry to evaluate a carotid stent and embolic protection system. In addition, this allows for us to treat patients with stents and have their procedures covered through the trial, which is a welcome addition to the proper patient.

Pivotal trial: We are awaiting final IRB approval of this trial, but basically it will evaluate patients with 4.0 to 5.0 cm. abdominal aortic aneurysms. They will be randomized into an early treatment arm using endovascular stent graft vs. ultrasound and CT surveillance. The intent of this study is to identify patients who are better treated early for aneurysm disease as opposed to standard, which is watchful waiting. We are a number of approximately 70 centers across the country evaluating this issue.



Dr. Allen Hamdan

Abstract Presentations at Local, National, and International Meetings

Andersen ND, Monahan TS, Jain M, Daniel S, **Ferran C, LoGerfo FW**. "An *ex vivo* Human Vein Knockdown Model Using Silencing RNA". Poster presentation at the National Heart Lung and Blood Institute's PGA Symposium, Bethesda, MD. July, 2005.

Daniel S, Patel VI, Shrikhande GV, Scali ST, Arvelo MB, **Ferran C**. "A20 Differentially Affects Apoptosis in Endothelial Cells and Smooth Muscle Cells". 13th European Conference on Apoptosis, Budapest Hungary. October 1-4, 2005.

Monahan TS, Andersen ND, Panossian H, Kalish JA, **Contreras MA**, Phaneuf MD, **Ferran C, LoGerfo FW**. "The Role of OB-Cadherin in Vascular Smooth Muscle Cell Migration and Proliferation". Oral presentation at the New England Society for Vascular Surgery, Stowe, VT. September, 2005.

Monahan TS, Andersen ND, **Contreras MA**, Phaneuf MD, **Ferran C, LoGerfo FW**. "Effects on Cellular Migration and Proliferation after siRNA-mediated Knockdown of PKC Substrates in Human Vascular Smooth Muscle and Endothelial Cells". Poster presentation at the North American Vascular Biology Organization, Chicago IL. June, 2005.

Monahan TS, Andersen ND, Popescu-Vladimir A, Kalish JA, Contreras MA, Phaneuf MD, Daniel S, Shrikhande GV, **Ferran C, LoGerfo FW**. "RNA Interference Targeting MARCKS Arrests Human Vascular Smooth Muscle Cell Proliferation *in vitro* and *ex vivo*". Oral presentation at the Society of University Surgeons, Nashville, TN. February, 2005.

Patel VI, Daniel S, Longo CR, Shrikhande G, Scali ST, Czismadia E, Groft C, Shukri T, Grey ST, Arvelo MB, **Ferran C**. A20 promotes regression of neointimal hyperplasia via a novel NO-dependent pro-apoptotic function in neointimal smooth muscle cells. Presented and awarded at the annual surgical research competition at the Beth Israel Deaconess Medical Center. June, 2005.

Scali ST, Shrikhande GV, Bolash R, Fisher MD, Daniel S, **Ferran C**. A novel anti-angiogenic function of A20: Implications in diabetic retinopathy. Annual surgical research competition, Beth Israel Deaconess Medical Center, June 2005; and Research Day, Beth Israel Deaconess Medical Center. October, 2005.

Shrikhande GV, Scali ST, Daniel S, Patel VI, Arjoon R, Smith J, Csizmadia E, Dore C, Monahan T, Fisher MD, Veves A, Ushveva A, **Ferran C**. Altered A20 expression in diabetes mellitus contributes to increased risk of atherosclerosis. Annual surgical research competition, Beth Israel Deaconess Medical Center, June 2005; and Research Day, Beth Israel Deaconess Medical Center. October, 2005.

Patents

- Christiane Ferran, inventor; Beth Israel Deaconess Medical Center assignee. Use of pro-apoptotic factors in treatment of atherosclerosis. U.S. Serial No: 10/461,200. Publication number: US-2003-0207838-A1.
- Christiane Ferran, co-inventor. Measurement of protective genes in allograft rejection. US patent 6,900,015 B2. 2005 May 31.

Patent Disclosures

- Application of Antibiotics to Polyurethane Biomaterials Using Textile Dyeing Technology (09/834,978).
- Development of a Dacron Vascular Graft with an Ionic Polyurethane Sealant with Protein Binding Capabilities (60/186,154).
- Method for Making Infection-Resistant Fabricated Textile Articles for Biomedical Applications (09,876,604).
- Methods for Making Infection-Resistant Fabricated Textile Articles and Devices Suitable for Non-Implantable Biomedical, Environmental, Safety and Other Protective Applications (Full Patent Submitted).
- Bioactive Surface for Titanium Implants (Full Patent Submitted).
- Development of a Bifunctionalized Dacron Surface (Full Patent Submitted).
- Monahan TS, Andersen ND, and LoGerfo FW. Methods of Inhibiting Vascular Smooth Muscle Cell Migration and Proliferation. U.S. Patent Application Number 1440.2045-000.

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- Ferran, C, inventor; No assignee. Use of Pro-apoptotic factors in treatment of atherosclerosis. US serial no 09/765,519. 2001, January 19.
- Ferran C: Inventor. Anti-angiogenic effects of A20 in diabetes and cancer. 2005; in progress.

#### Individual Accomplishments

*Christiane Ferran, MD, PhD*

- Reviewer for the NIH/NIDDK Special emphasis panel: ZDK1 GRB-G. Ancillary studies to Adult Liver Transplantation Clinical Research (July 22<sup>nd</sup> 2005).
- Reviewer for Several peer review highly ranked journals including: Blood, Journal of Clinical Investigation, Circulation, Atherosclerosis Thrombosis and Vascular Biology, Transplantation, American Journal of Transplantation, American Journal of Kidney Diseases, Nephrology Dialysis and Transplantation, Kidney International, Oncogene, American Journal of Rheumatology
- Invited lecture at the Beaune Seminar in Transplant Research. Endothelial Cell in Organ Transplantation: Friend or Foe. Beaune, France (June 2<sup>nd</sup>-3<sup>rd</sup> 2005).
- Invited lecture at IX Brazilian Congress of Organ Transplantation Atheroprotective genes and chronic rejection. Salvador Bahia Brazil: (July 2<sup>n</sup> -6<sup>th</sup> 2005).
- Invited lecture at the American Society of Transplant Surgeons (ASTS). Winter Symposium , Basic Science. Scottsdale, Arizona, January 19<sup>th</sup>-22<sup>nd</sup> 2006.
- Member of the Scientific Advisory Committee for the Roche Organ Transplant Research Foundation (ROTRF).
- Reviewer for the American College of Cardiology 2006.
- Reviewer for the Wiener Wissenschafts Forschungs und Technologiefonds, Vienna Austria.

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### REPORT OF TEACHING

#### Undergraduate and Medical School 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 atherogenesis, intimal hyperplasia, prosthetic/host interactions and thrombosis. Trainees pursue a program of intense research activity. Students carry out their research projects under the guidance of a faculty advisor, selected from renowned vascular researchers based at Harvard Medical School hospitals (Beth Israel Deaconess Medical Center and Brigham and Women's Hospital).

For summer of 2005 seven students were enrolled in the program.

#### Mentors

**Frank W. LoGerfo, MD**

#### Students

Ian Driscoll  
University of Florida College of Medicine  
"Delivery of siRNA to human vein segments"

Monica Jain  
Boston University  
"Gene silencing in vascular tissue"

Lena Caron  
Guilford College  
"In vitro mechanisms of non-distending pressure transfection"

**Christiane Ferran, MD, PhD**

Robert Bolash  
 University of Miami School of Medicine  
 “Protective effects of A20 in diabetic retinopathy”

**Bruce Furie, MD**

Department of Medicine  
 Beth Israel Deaconess Medical Center  
 Professor of Medicine, Harvard Medical School

Justin Gainor  
 Harvard Medical School  
 “Real-time imaging of platelets and von Willebrand factor in arterial thrombus formation”

**Richard N. Mitchell, MD, PhD**

Department of Pathology  
 Brigham and Women’s Hospital  
 Associate Professor of Pathology,  
 Harvard Medical School

Andrew Gulbis  
 University of Arizona Medical School  
 “Development of in vitro model of graft arterial disease”

**Michael S. Conte, MD**

Division of Vascular Surgery  
 Brigham and Women’s Hospital  
 Associate Professor of Surgery,  
 Harvard Medical School

Min Jung Park  
 Brown Medical School  
 “Mineralocorticoid receptor (MR) expression in rabbit vein graft”

**Michael Klagsbrun, MD**

Department of Surgery  
 Children’s Hospital  
 Patricia A. Donahoe Professor of Surgery (Pathology),  
 Harvard Medical School

Sang Kim  
 Harvard Medical School  
 “Role of abelson tyrosine kinase and ephrin in semaphorin- neuropilin mediated repulsive endothelial migration”

**Vascular Surgery Research Laboratory Students**

**Mentor: Frank W. LoGerfo, MD**

Nicholas Andersen, from Harvard Medical School, an HHMI fellow and graduate of our 2004 William J. von Liebig Summer Research Fellowship is currently working full time in my laboratory. Project: “Prevention of Intimal Hyperplasia in Vein Grafts” *Award - Young Investigator Award: International Society for Applied Cardiovascular Biology (ISACB) (ISACB) 10th Biennial Meeting; 2006; La Jolla, CA; 2006.*

Monica Jain, an undergraduate student at Boston University. William J. von Liebig Summer Research Fellow for 2005. Project: “Gene silencing in vascular tissues”. Under the guidance of Nicholas Andersen, Monica has continued to work part-time in the lab on this project.

**Immunobiology Research Center**

**Mentor: Dr. Christiane Ferran, MD, PhD**

There are 3 students who spend between 10 and 20 hours/ week of work in the laboratory. All have benefited from bench top teaching as well as didactic teaching sessions.

Nicholas Ward, undergraduate student. Harvard University.

Roy Arjoon, undergraduate student. Boston University.

Robert Bolash, Medical student and scholar of the Von Liebig Foundation for Vascular Biology. University of Miami, Miami, FL (11 weeks summer training).

Graduate school and graduate medical courses:

**T-32 Training Program: Harvard-Longwood Research Training Program in Vascular Surgery (T32)**

**Principal Investigator: 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 addresses the absence of adequate research training for vascular surgeons as it applies to specific areas of clinical disease. This program is in its twelfth year. Trainees pursue a program of research activity supplemented with course work in research design, ethics, statistics and evaluation

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of published research in the areas of molecular and cell biology, biomechanics, coagulation and thrombosis and angiogenesis. Clinically relevant problems such as atherogenesis, intimal hyperplasia, prosthetic/host interactions and thrombosis will be the main focus of these research projects. Trainees carry out their research projects under the guidance of a faculty advisor selected from 20 renowned vascular researchers based at four Harvard Medical School hospitals (Beth Israel Deaconess Medical Center, Brigham and Women's, Children's Hospital (Boston) and Joslin Diabetes Institute) and the Massachusetts Institute of Technology. Upon completion of the program, trainees are capable of independent research and possess the scientific and research background needed to obtain peer-reviewed grants. Selection of trainees is based on candidate's demonstrated ability and career choice of academic practice. Applicants are resident physicians who have completed either 2/3 years of clinical post-doctoral experience (surgical residency) or 5 years of clinical training (i.e. are board eligible). Only those applicants with career goals in academic surgery, with a keen interest in basic research in vascular surgery are compatible. Trainees in the program are not involved in any clinical activities unless research related.

*Trainee*

Richard Bafford, MD  
 Thomas S. Monahan, MD  
 Salvatore Scali, MD  
 Gautam Shrikhande, MD  
 Grace J. Wang, MD  
 Mark Fisher, MD  
 Karen Ho, MD

*General Surgery Training Program*

Brigham and Women's Hospital  
 Beth Israel Deaconess Medical Center  
 Beth Israel Deaconess Medical Center  
 Beth Israel Deaconess Medical Center  
 Massachusetts General Hospital  
 Beth Israel Deaconess Medical Center  
 Brigham and Women's Hospital

\* Graduated 2005  
 \* Graduated 2005  
 \* Graduated 2005  
 \* Recruited 2005  
 \* Recruited 2005

**Vascular Surgery Research Laboratory Students**

**Mentor: Frank W. LoGerfo, MD**

Thomas Monahan, MD was a T32 Fellow who graduated from the program and is now back in his residency program. Upon completion of his General Surgery Residency, Thomas has a keen interest in pursuing a fellowship in Vascular and Endovascular Surgery.

Shen-Qian Wu, MD is working on development of Biologically Active Surfaces. He will be submitting a proposal to CIMIT in the near future.

**Immunobiology Research Center**

**Mentor: Dr. Christiane Ferran, MD, PhD**

There are weekly teaching sessions for the 2 surgical residents and a Master of Science that are working in the laboratory, in addition to informal bench based teaching.

Salvatore T. Scali, MD. Surgical Resident, BIDMC.

Mark D. Fisher, MD. Surgical Resident, BIDMC.

Haley Ramsey, MS. Research Associate.

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**Clinical Fellows and Residents**

**Mentor: Dr. Allen Hamdan, MD**

One of our most important functions is to teach fellows as well as the surgical residents how to do clinical research, present at meetings, and write abstracts and papers. Dr. V. Patel presented a paper on "lower extremity arterial revascularization in obese patients" and Dr. K. Hughes presented a paper on "upper extremity bypass graft procedures" both at the New England Society of Vascular Surgery. Both of those papers are currently at the Journal of Vascular Surgery being reviewed. Shashir Maithel presented a paper at the American College of Surgery, working with our division, entitled "Creatinine Clearance, but not serum Creatinine alone that predicts long-term post-operative survival after lower extremity revascularization", which is current in review at the Journal of American College of Surgery.

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**Monahan TS, Phaneuf MD, Contreras MA**, Andersen ND, **Popescu-Vladimir A**, Bide MJ, Dempsey DJ, Mitchell RN, **Hamdan AD, LoGerfo FW**: In vivo testing of an infection-resistant annuloplasty ring. *J Surg Res* 2005; 130:140-5.

**Monahan TS, Shrikhande GV, Pomposelli FB**, Skillman JJ, **Campbell DR, Scovell SD, LoGerfo FW, Hamdan AD**. Preoperative cardiac evaluation does not improve or predict perioperative or late survival in asymptomatic diabetic patients undergoing elective infrainguinal arterial reconstruction. *J Vasc Surg* 2005; 41:38-45.

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