

From the Chairman



Research within the Department of Surgery at the Beth Israel Deaconess Medical Center continues to do extremely well. This year's Annual Research Report, describing activities from January-December 2009, attests to the outstanding research presence and activity in the Department.

The growth of research and funding in the Department that has occurred during the past five years, from 2005 through 2009, reflects both the success of our recruiting efforts and the productivity of existing research programs in Surgery. Since 2007, when we were greatly affected by the NIH down-turn, external funding for research has rebounded and the number of R01 grants and other federal and

non-federal funds awarded to faculty in the Department increased significantly. This occurred in concert with an equally dramatic increase in the clinical programs within the Department and with the strategic recruitment of a number of outstanding basic scientists with strong research programs in Surgical Research. Departmental research has also been strengthened considerably by the interaction between clinically active academic surgeons and basic investigators in numerous areas of surgical specialty.

In addition to the clinical and research activities, our educational programs continue to be an important mission. One substantial benefit of our outstanding basic and clinical research programs is the opportunity provided to our residents for research training. In 2009, we were fortunate to have two strong NIH funded training grants (Cardiovascular Surgery and Vascular Surgery) and departmental faculty also participate in GI Surgery, Transplant Immunology, and Cardiovascular Research training grants together with colleagues at the Brigham and Women's Hospital and at the Massachusetts General Hospital. These resources have supported our residents in research laboratories and have added considerably to our research mission.

This year's Annual Research Report highlights our research effort. For this, I wish to thank all Division Chiefs and members of the Department, faculty and staff alike, for their continued outstanding efforts in making our Department a competitive and world-renowned academic program. I am grateful to Drs. Per-Olof Hasselgren and Susan Hagen for putting this report together and for their continued efforts in building and promoting a strong academic program in Surgery.

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DIVISION OF SURGICAL RESEARCH

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

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INTRODUCTION

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

The Division of Surgical Research has the following responsibilities: 1) Pre-award review and approval of all grant submissions in the Department of Surgery. This includes assisting in the

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process of submission of grant applications and interaction with the BIDMC Office of Sponsored Programs; 2) Management of research space, including laboratory and office space, and shared research equipment. For this, the allocation of research space within the Department is overseen, shared tissue culture facilities are maintained, and the Department is represented at various institutional committees and subcommittees dealing with research space at the BIDMC; 3) Organizing monthly Surgical Research Seminars, open for both clinical and research faculty in the Department as well as other members of the BIDMC community; 4) Preparing the Department of Surgery Annual Research Report; 5) Organizing laboratory and shared equipment maintenance and telecommunications; 6) Supporting and mentoring junior faculty in the establishment of research laboratories; 7) Interacting with and providing information to Surgical Residents who plan to spend time in the research laboratory; 8) Obtaining visas for foreign scholars in Research and in preparing applications for Harvard Medical School appointments for Research Fellows and Instructors in Surgery Research; 9) Making recommendations concerning research faculty appointments and reappointments in Surgery (working together with the Department of Surgery Appointment, Reappointment, and Promotion Committee); and 10) Assisting the Chairman with the development of existing and new research areas within the Department of Surgery, including both short- and long-term strategic planning and recruitment.

RESEARCH FACULTY

The number of individuals involved in research (basic and clinical research) in the Department of Surgery has varied between 120 and 160 over the last 5 years. This year, research in the Department was conducted by 127 individuals, including 65 faculty, 38 postdoctoral research fellows, 13 surgical residents, numerous research associates and assistants, 3 nurse educators/practitioners, 3 dieticians, and many undergraduate, graduate, or medical students. Numerous research coordinators, administrative assistants, and administrative coordinators provide important administrative support for research efforts in the Department.

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

In 2009, most Research Faculty in Surgery were invited speakers around the world. Faculty members were invited speakers in interesting locations that varied from Mexico (DeCamp), Germany (Ernst), Japan (Levitsky), Italy (Zhou), Greece (Callery and Koulmanda), Belgium (Gaston), Spain (Hasselgren and Hanto), and Maui (Lee). Surgery investigators also received prestigious awards in 2009 including the Mickey Stunkard Lifetime Achievement Award (Blackburn), the Rachmiel Levine Scientific Achievement Award (Wang), and The Eleanor and Miles Shore Scholars in Medicine Award from HMS (Arredouani). Drs. Wang and Arredouani, recipients of the later awards, are junior faculty in the Department.

Research Faculty in the Department of Surgery also participate in teaching endeavors. These include acting as mentors in the NIH in-service teacher program, MIT Bioengineering Undergraduate Research Program, Biomedical Science Careers Program, Project Success, Undergraduate Research Opportunities Program, and Research Scholars Institute Summer Program. The Vascular and Endovascular Surgery Division remains actively involved in the William J von Leibig research training program for both medical and postdoctoral students. Several of the Surgical Research Faculty teach at Harvard Medical School in the Body, Cell Biology, Pharmacology, and GI Pathophysiology courses and most of the surgeons in the Department participate in the surgical clerkships. In 2009, there were also two active research training grants (NIH, T32's) in the Department headed by Drs. Sellke (cardiovascular surgery research) and LoGerfo (vascular surgery research), and faculty and residents participated in two additional T32 programs directed by Drs. Soybel (GI surgery) and Iacomini (transplantation surgery).

RESEARCH ACTIVITIES AND FUNDING

Research activities within the Department of Surgery at the Beth Israel Deaconess Medical Center are strong and have shown considerable growth in the past few years, especially in 2009 (Figure 1). Research and development constitute one of the cornerstones and missions of the Department, in addition to patient care and teaching. Both basic and clinical research programs are active in the Department. From a thematic standpoint, research programs in Surgery include Cancer Biology, Inflammation, Development, Vascular Biology, Cardiothoracic

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research, Transplantation-Immunology, Obesity-Nutrition-Metabolism, Wound Healing, Epithelial and Endothelial Biology, and Clinical Outcomes.

All research, both basic and clinical, in the Department of Surgery is supported by external funding and more than 2/3 of this funding is in the form of NIH grants. Most Divisions within the Department of Surgery presently conduct NIH-funded research. In 2009, Surgery held 100 NIH grants (R01, R21, K08, U19, U01, R03, R41, and R42) ; 2 T32 training grants, 2 K08 grants, 181 non-federal grants, 8 Department of Defense grants, and 1 F32 training grant for a total of **296 total grant awards**. **It should be noted that, in 2009, Surgery exceeded funding levels for the past 4 years despite considerable budget restrains imposed on the NIH.** This level of continued funding, which was a 29% increase in funding from 2008 levels, is due to the persistence and acclaim of our research programs. The level of funding is also remarkable considering that a number of those faculty members who contribute substantial grant funds to the research effort are also clinically very active. The federal (almost exclusively NIH), non-federal, and total external funding during the 5-year period, 2005-2009, is illustrated below in Figure 1.

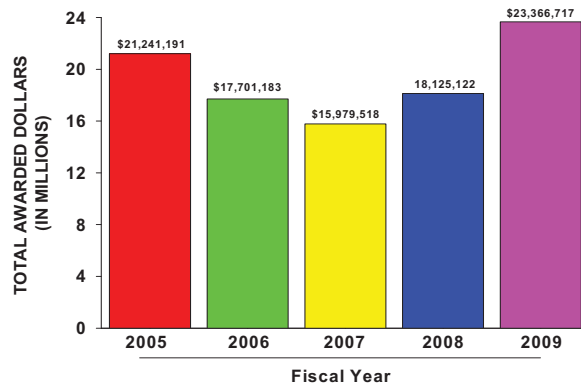


Figure 1 Total (direct and indirect, federal and non-federal) awarded funds during the 5-year period 2005-2009.

The current distribution of external funding between the different Divisions in the Department of Surgery is illustrated by the diagram in Figure 2. The Transplant Surgery and General Surgery Divisions have the largest external funds constituting approximately 30-40% each of the total departmental funding. To account for the large rise in funding in 2009, Neurosurgery and Transplantation Surgery both showed a 7% increase and Urology a 2.5% increase in funding from levels in 2008.

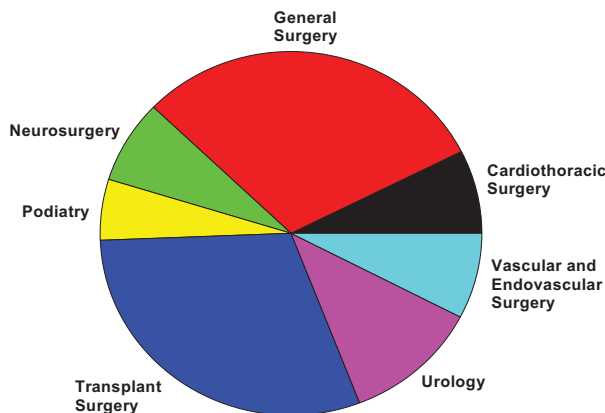


Figure 2 Total (federal and non-federal) funding in 2008 by Division.

Training Grants

In 2009, the Department held two active active NIH training grants, one in Vascular Surgery Research (PI, Dr Frank LoGerfo) and the other in Cardiovascular Surgery Research (PI, Dr. Frank Sellke). Investigators in Surgery also actively participate in a GI Surgery Research Training Grant, which is a joint training grant between the three HMS teaching hospitals led by Dr. Richard Hodin (PI) at the Massachusetts General Hospital, with co-

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investigators Dr. Soybel at the Brigham and Women's Hospital and Dr. Per-Olof Hasselgren at BIDMC. An additional NIH training grant for Transplant Immunology Research is based at the Brigham and Women's Hospital and is led by Dr. John Iacomini.

Surgical Residents and Research

Over the past few years, approximately 10 residents per year elected to spend time in a basic or clinical research laboratory as part of their surgical training. In 2009, however, 17 residents elected to do research (**Figure 3**). Most of the residents performed research in a basic science laboratory doing bench research. Although not obligatory, the present policy is to have residents dedicate time to research between their second and third clinical years. This extends the surgical residency from 5 years to 7-8 years, but learning to do bench research is an important and worthwhile experience.

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

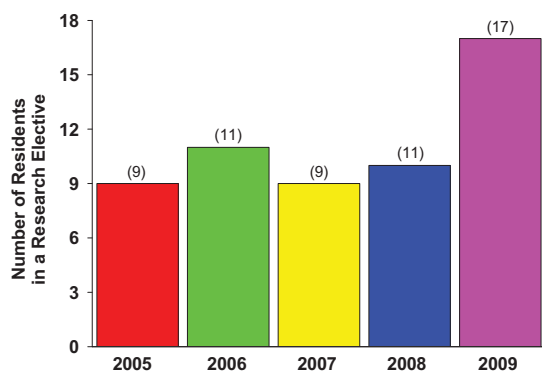


Figure 3 Number of surgical residents per year spending time (2-3 years) in a research elective.

An important aspect of a Residents' research training is obtaining funding. The process that has been adopted in the Department in past years is for the resident who plans to go into the laboratory to write and submit at

least two credible grant/fellowship applications (typically applying at sources such as various National Surgical Societies, NIH, and the American College of Surgeons) – those applications are usually written together with and supported by the research mentor with whom the resident will work. If the applications are not funded, training grants in the Department or other funds within the individual laboratories can frequently provide support and it is only exceptionally that the resident has to rely on Departmental financial support for the time in the laboratory. To assist residents in obtaining funding, the Division of Surgical Research has made available a 50 page booklet entitled "Funding Sources for Surgical Residents" (right), which describes various funding sources, deadlines, financial support available, and application forms. This booklet is updated annually. It is also available electronically at:



www.bidmc.org/~media/Files/CentersandDepartments/Surgery/Residents%20Funding%20Sources_2009.ashx

The **Annual Residents' Research Competition** was done again this year and attracted outstanding abstracts. This competition is open for all residents who are or have recently been in a research laboratory or who are involved in a clinical research project. Ten abstracts were submitted this year and they were scored by a committee consisting of Faculty in the Department. Four finalists presented their papers at a Surgical Grand Rounds in June and the winner was selected among the 4 finalists. The presentations at Grand Rounds were evaluated based on both scientific content and delivery. The 4 finalists in the 6th Annual Residents' Research Competition (2009) were:

Zhen Huang, MD

"Differential temporal gene expression of selectively isolated vein graft endothelial and smooth muscle cells by

laser capture microdissection”.

Mentor: Dr. Frank LoGerfo, Division of Vascular and Endovascular Surgery, BIDMC.

Onkar Khullar, MD

“Nanoparticle-based drug delivery of chemotherapy via lymphatic migration in a large animal model”.

Mentor: Dr. Yolonda Colson, Division of Thoracic Surgery, BWH.

Jonathan Meisel, MD

“Down-regulation of bone morphogenic protein-4 is an important mediator of mus muscularis hepatocyte proliferation”.

Mentor: Dr. Mark Puder, Division of Pediatric Surgery, CH.

Michael Robich, MD

“The effects of the red wine derived resveratrol on swine with hypercholesterolemia and chronic myocardial ischemia”.

Mentor: Dr. Frank Sellke, Division of Cardiothoracic Surgery, BIDMC.

This year’s first place prize was awarded to Dr. Michael Robich.

ANNUAL RESEARCH REPORTS

The Division of Surgical Research continues to highlight progress in research by producing an Annual Research Report. The report is made available to all faculty members of the Department, senior leadership of the Hospital including the Chairs of all departments. It is also sent to most Surgical Chairs at major Academic Centers in the country. In addition, the Annual Research Report is an important source of information for Resident Candidates and Postdoctoral Fellows when interviewing for a position in the Residency Program at the BIDMC or in one of the research laboratories.

The Annual Research Report for 2008 (featured right), can be found along with previous yearly reports at:



<http://www.bidmc.org/Research/Departments/Surgery/DepartmentofSurgeryAnnualReports.aspx>

APPOINTMENTS, REAPPOINTMENTS, AND PROMOTION COMMITTEE

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

RESEARCH FACILITIES AND SPACE

The Department of Surgery occupies approximately 22,819 square feet of laboratory space including wet labs, special purpose rooms (cold rooms, tissue culture rooms, and shared equipment rooms), and office space. Although the greatest number of research faculty and staff in Surgery are located on the 8th floor of the Dana/Research West building on the East Campus, Surgery has research space in several different locations.

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These spaces include (in square feet) 3,773 in CLS (Center for Life Sciences), 13,369 in Dana/Research West, 431 in Slosberg-Landy, and 2,833 at Research North. Clinical research space includes 443 (in square feet) in Palmer and 1,501 in Feldberg. The overall dollar density in 2009 for research space in the Department of Surgery was approximately \$169/sq foot.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

In addition to external funding, the number of publications is an important measure of the success of the research effort conducted in the Department. Over the past few years, the number of publications from the Department increased significantly. In 2009, 112 original articles were published by members of Surgery (this is a 12% increase from 2008) and numerous publications were submitted or were in press. Additionally, numerous review articles, editorials, book chapters, and books were published by Department faculty. Of note, an obesity surgery book was edited by Dr. Jones and Dr. Ernst edited 2 books in 2009.

Bold represents Research Faculty, Fellows, and Staff in Surgery at BIDMC.

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Educational Materials

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Yao D, **DeWolf WC**, **Sanda M**, Bloch N, Genega E, Barry A, Ngo L, Rofsky N. Increased positive yield of clinically significant prostate cancer with MRI prompted biopsies. J Urol 2009;181:782A.

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DIVISION OF CARDIOTHORACIC SURGERY AND INTERVENTIONAL PULMONOLOGY

2009 has been a very productive year and represents the second year of a combined report for this new research unit. Members of the Division are active in sponsored and investigator initiated trials. Activities include basic science research, clinical outcomes research, as well as pre-clinical development in a dedicated animal laboratory. Members of the Division also serve as mentors to students, residents and fellows in their pursuit of an academic career. Close working relationships exist with other investigators within our institution, Harvard Medical School, and with established academic hospitals across the country and internationally.

Sidhu P. Gangadharan, MD
Acting Chief, Division of Cardiothoracic Surgery
Instructor in Surgery, HMS



Malcolm M. DeCamp Jr., MD
Chief,
Division of Cardiothoracic Surgery (through November, 2009)
Lecturer in Surgery



CARDIOTHORACIC DIVISION MEMBERS

Section of General Thoracic Surgery and Interventional Pulmonology

Sidhu P. Gangadharan, MD

Acting Section Chief

Instructor in Surgery

Malcolm M. DeCamp Jr., MD
Armin Ernst, MD

Former Section Chief

Chief, Interventional Pulmonology

Associate Professor of Medicine and Surgery

Michael Kent, MD

Instructor in Surgery

Adnan Majid, MD

Instructor in Medicine

Gaetane Michaud, MD

Instructor in Medicine

Arthur Dea, CCRP

Administrative Research Director

Robert Garland, RRT

Technical Director/Interventional Pulmonology

Hisashi Tsukada, MD

Research Associate

Deirdre Keogh, NP

Clinical Nurse Practitioner

Paula Mulkern, RN

Research Coordinator

Charles Bakhos, MD

Cardiothoracic Surgery Fellow

Walter Lech, MD

Cardiothoracic Surgery Fellow

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Division of Cardiothoracic Surgery

Cardiothoracic Division Members Cont'd

Samaan Rafeq, MD
David Odell, MD
Saleh Alazemi, MD
Chakravarthy Reddy, MD
Archan Shah, MD
Andres Sosa, MD

Interventional Pulmonology Fellow
Clinical Investigator Training Program Fellow
Research Fellow
Research Fellow
Research Fellow
Research Fellow

Robert Berger, MD

Director for Clinical Research

F. Henry Ellis Jr., MD, PhD

Clinical Professor of Surgery, Emeritus

Section of Cardiac Surgery
Kamal Khabbaz, MD

Section Chief
Assistant Professor of Surgery

Robert C. Hagberg, MD

Assistant Professor of Surgery

Sidney Levitsky, MD

Cheever Professor of Surgery

James D. McCully, PhD

Associate Professor of Surgery

Frank W. Sellke, MA, MD

Johnson & Johnson Professor of Surgery

Cesario F. Bianchi, MD, PhD
Jun Feng, MD, PhD
Richard Clements, PhD
Yuhong Liu, MD
Robert Osipov, MD
Shizu Oyamada, MD
Michael Robich, MD
Shu Hua Xu, PhD
Edo Bedzra, BS
Hilary Glazer, BS

Assistant Professor of Surgery
Instructor in Surgery
Instructor in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Research Fellow, Surgical Resident
Research Associate
Med Student, HMS
Med Student, Wash U

RESEARCH SUMMARY

BASIC AND CLINICAL RESEARCH

We are pleased to present the research activities of the Chest Disease Center at BIDMC. 2009 has been a productive and successful year for the combined efforts of the members of the Division. Our report shows the extraordinary breadth and depth of our work, as well as our continued collaboration with members of other Divisions and Departments throughout the hospital.

Traditional strengths have been high quality outcomes research and participation as a lead center in industry sponsored trials. Our clinical database for diagnostic and therapeutic interventions in tracheomalacia is now the largest in the world. We are participating in trials evaluating novel therapies such as endobronchial lung volume reduction and diagnostics such as molecular markers for early diagnosis of lung cancer.

We have been successful in establishing additional facets to our research. In the Animal Research Facility at BIDMC, we are working on establishing animal models for tracheomalacia and improving technologies for medical device companies. In collaboration with the Division of Matrix Biology, we are researching the biology of central airway obstruction and collapse.

The Office of Clinical, Sponsored, and Translational Research continues to grow as we move into the next academic year. We are proud to say that our activities are recognized nationally and internationally as evident by the numerous abstracts, oral presentations, and scientific posters accepted at professional conferences and meetings.



Malcolm M. DeCamp Jr., MD (upper left)
Sidhu P. Gangadharan, MD (upper right)

Armin Ernst, MD (lower right)

LIST OF CURRENT EMPLOYEES

Michael Kent, MD	Instructor in Surgery
Adnan Majid, MD	Instructor in Medicine
Gaetane Michaud, MD	Instructor in Medicine
Robert Berger, MD	Dir., Clinical Research
Arthur Dea, CCRP	Admin Director
Robert Garland, RRT	Tech. Director
Hisashi Tsukada, MD	Res. Associate
Deirdre Keogh, NP	Clin. Nurse Practitioner
Paula Mulkern, RN	Res. Coordinator
Charles Bakhos, MD	CT Surgery Fellow
Walter Lech, MD	CT Surgery Fellow
Dilip Nataraj, MD	Interv. Pulm Fellow
Samaan Rafeq, MD	Interv. Pulm Fellow
David Odell, MD	CITP Res. Fellow
Saleh Alazemi, MD	Research Fellow
Chakravarthy Reddy, MD	Research Fellow
Archan Shah, MD	Research Fellow
Andres Sosa, MD	Research Fellow

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LIST OF CURRENT FUNDING

"National emphysema treatment trial"
NIH/NHLBI: 5 N01 HR76105-007
Project period: 1998-present
PI: Malcolm DeCamp, Jr.

"Tracheal transplantation or replacement"
BIDMC Department of Surgery
Project period: 2006-present
Co-PI: Malcolm DeCamp, Jr.

"Evaluation of pulmonary nodules using 3T MRI"
NIH
Project period: 2006-2011
Co-Investigator: Malcolm DeCamp, Jr.

"EASE trial: Exhale® airway stents for emphysema"
Broncus Technologies
Project period: 2006-present
PI: Armin Ernst

"T1 size descriptor should be subdivided for stage IA (T1N0) non-small cell lung cancer (NSCLC) for better prognostic value"
Kopelman Fund
Project period: 2008-2012
Co-Investigators: Malcolm DeCamp, Jr. and Armin Ernst

"Computed tomography diagnosis of tracheomalacia in patients with chronic Obstructive Pulmonary Disease"
NIH: RO1 HL084331
Project Period: 2007-present
Co-Investigator: Armin Ernst

"Large animal model of tracheobronchomalacia"
BIDMC Department of Surgery Foundation
Project period: 2008-present
PI: Malcolm DeCamp, Jr.

"Matrix biology of structural airway disorders"
BIDMC Department of Medicine Foundation
Project period: 2008-present
PI: Armin Ernst

"Airway gene expression in the diagnosis of lung cancer"
Allegro Diagnostics
Project period: 2008-present
PI: Armin Ernst

"The use of a new endoscope compared to standard endoscopes"
Boston Scientific
Project period: 2009-present
PI: Armin Ernst



Michael Kent



Gaetane Michaud



Adnan Majid

“Transbronchial tissue sampling in sheep”

Broncus Technologies

Project period: 2009-present

PI: Armin Ernst

“A prospective, randomized, open label, multicenter, pilot study to evaluate the ROX Anastomotic Coupler System (ACS) in patients with Chronic Obstructive Pulmonary Disease”

ROX Medical

Project period: 2009-present

PI: Armin Ernst

“Bronchio-adventitial drug delivery: Paclitaxel for Bronchial Carcinoma”

NIH/STTR: R41 CA141907-01

Project period: 2009- present

Site PI: Armin Ernst

“Impact of aggressive versus standard drainage regimen using a long term indwelling pleural catheter on the incidence of Auto Pleurodesis in patients with Malignant Pleural Effusions (The ASAP Study)”

Duke University Medical Center/ Cardinal Health

Project period: 2009- present

PI: Gaetane Michaud

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Open and Ongoing Clinical Trials:

- Registry of treatment outcomes in patients with tracheomalacia
- Outcomes databases after interventional endoscopic procedures
- The role of GERD in structural airway disorders
- EASE Trial: Exhale® airway stents for emphysema
- Matrix biology of structural airway disorders
- Airway gene expression in the diagnosis of lung cancer
- CT diagnosis of tracheomalacia in patients with COPD
- Gas embolism with use of argon plasma coagulation
- Relapsing polychondritis and airway involvement
- Endoscopic alveolar imaging using fibered confocal fluorescence microscopy
- WALK Study: ROX ACS in patients with COPD
- ASAP Study: Aggressive vs. standard drainage regimen in patients with malignant pleural effusions

Animal Laboratory:

- a. Bioabsorbable stents in the management of tracheomalacia
- b. Creation of a large animal model of tracheomalacia
- c. Aortic allografts for tracheal replacement/transplantation
- d. Bronchio-adventitial drug delivery

Abstracts Presented at Local, National and International Meetings

Okereke I, **Ganagadharan S, Kent M**, Nicotera S, **DeCamp MM**. SUV predicts sSurvival in non-small cell lung cancer. Presented at the 2009 Annual Meeting of the Society of Thoracic Surgeons, San Francisco, CA; January 2009.

Rafeq S, Majid A, Michaud G, Reddy C, Herth F, **Ernst A**. Bronchoscopic imaging using fibered confocal fluorescence microscopy. Presented at the 2009 American Thoracic Society Annual Conference, San Diego, CA; May 2009.

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Abstracts Presented at Local, National and International Meetings Contd.

Tsukada H, DeCamp MM, O'Donnell C, Garland R, Ernst A. A sheep model for Hyperdynamic Central Airway Collapse. Presented at the 2009 American Thoracic Society Annual Conference, San Diego, CA; May 2009.

Nataraj D, Majid A, DeCamp MM, Kent M, Gangadharan G, Michaud G, Lembo A, Chuttani R, Herth F, Ernst A. Tracheobronchomalacia & gastroesophageal reflux disease. Presented at the 2009 American Thoracic Society Annual Conference, San Diego, CA; May 2009.

Majid A, Sosa A, Ganagadharan S, Shah A, Michaud G, Herth F, Ernst A. The effect of tracheobronchoplasty on lung hyperinflation a prospective descriptive analysis. Presented at the 2009 European Respiratory Society Annual Congress, Vienna, Austria; September 2009.

Nataraj D, Majid A, Mahmood F, Michaud G, Herth F, Ernst A. Gas embolism with the use of bronchoscopic argon plasma coagulation. Presented at the 2009 European Respiratory Society Annual Congress, Vienna, Austria; September 2009.

Nataraj D, Kent M, Gangadharan S, DeCamp MM, Majid A, Michaud G, Herth F, Lembo A, Ernst A. Gastroesophageal reflux disease and subglottic stenosis. Presented at the 2009 European Respiratory Society Annual Congress, Vienna, Austria; September 2009.

Ernst A, Nataraj D, Majid A, DeCamp MM, Chuttani R, Lembo A, Herth F, Kent M, Gangadharan S. Prevalence of gastroesophageal reflux in patients with tracheobronchomalacia. Presented at the 2009 European Respiratory Society Annual Congress, Vienna, Austria; September 2009.

Tsukada H, O'Donnell C, Litmanovich D, Garland R, DeCamp MM, Ernst A. A sheep model for hyperdynamic tracheal collapse. Presented at the 2009 European Respiratory Society Annual Congress, Vienna, Austria; September 2009.

Alazemi S, Majid A, Berkowitz D, Michaud G, Lunn W, Ernst A. Healthcare resources utilization and costs of endoscopic removal of metallic airway stents. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Reddy C, Majid A, Michaud G, Ernst A. Stent placement for tracheobronchomalacia: is it possible to predict who would benefit from the procedure? Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Tsukada H, Ernst A, Gangadharan S, Garland R, DeCamp MM. Experimental tracheal replacement with a bioabsorbable scaffold. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Nataraj D, Majid A, Mahmood F, Alazemi S, Berkowitz D, Michaud G, Herth F, Ernst A. Gas Embolism with the Use of Bronchoscopic Argon Plasma Coagulation. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Sosa A, Majid A, O'Donnell C, Gangadharan S, Shah A, Michaud G, Ernst A. Pulmonary function tests and the flow volume loops in patients with severe tracheobronchomalacia. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Ost D, Simoff M, Feller-Kopman D, Kovitz K, Eapen G, Greenhill S, Michaud G, Majid A, HeyM J, Jimenez C, Herth F, Ernst A. Risk adjusted diagnostic yield and outcomes for endobronchial ultrasound guided TBNA: results of the ACCP ACQUIRE registry. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Nataraj D, Majid A, Chuttani R, DeCamp MM, Kent M, Gangadharan S, Lembo A, Herth F, Ernst A.

Prevalence of gastroesophageal reflux in patients with tracheobronchomalacia. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Nataraj D, Sugimoto H, Mariappan R, Ernst A, Majid A, DeCamp MM, Gangadharan G, Kent M, Herth F, Kalluri R. Histopathology of tracheobronchomalacia. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Shah A, Majid A, Gangadharan S, Alazemi S, Berkowitz D, Michaud G, Ernst A. Central airway stabilization for patients with Mounier- Kuhn Syndrome. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Odell D, Michaud G, Alazemi S, DeCamp MM. Acromegaly: an unusual presentation of bronchial carcinoid. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Bakhos C, Alazemi S, Michaud G, DeCamp MM. Staged repair of benign tracheo-neo-esophageal fistula 12 years after esophagectomy for esophageal cancer. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Reddy C, Majid A, Michaud G, Ernst A. Airway stabilization in tracheobronchomalacia: correlation between subjective improvement and objective measures. Presented at CHEST 2009 Annual Meeting of the American College of Chest Physicians, San Diego, CA; November 2009.

Gilmore D, Kent M, DeCamp MM, Gangadharan S. Minimally-invasive Resection of Foregut Duplication Cysts and Pericardial Cysts in Adults. Presented at 57th Annual Meeting of the Massachusetts Chapter of the American College of Surgeons, Boston, MA; December 2009.

Invited Presentations

Malcolm DeCamp, Jr

Invited Speaker:

“A stage-based approach to esophageal cancer”. Northeast Thoracic Summit (NETS). Mashantucket, CT. 2009.

“Pulmonary Update: 2009; LVRS: Where is the Evidence”. New England Chapter American College of Chest Physicians. Boston, MA. 2009.

“Lung volume reduction surgery: What happened?” Society of Thoracic Surgeons Annual Meeting. San Francisco, CA. 2009.

“Stage IIIA Lung Cancer: Who is a surgical candidate?”

“Tracheomalacia: The Emperor’s New Clothes?”

Multidisciplinary Management of Lung Cancer, Emphysema and Benign Airway Disease, Penn Medicine CME. Philadelphia, PA. 2009.

“Lung Transplantation:Results from the USA”

“New Techniques of Pulmonary Parenchymal Preservation (VATS, RFA, SRS)”

“Complex Surgery of the Airways”

“NETT: What Happened?”

Mexican Society of Pulmonary Medicine and Thoracic Surgery Annual Meeting. Veracruz, Mexico. 2009.

Course Director/Lead Faculty:

“Flexible and rigid bronchoscopy and mediastinoscopy”. Thoracic Surgery Director’s Association “Boot Camp”. Chapel Hill, NC. 2009.

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Armin Ernst

Chair:

“New Techniques in Bronchoscopy” and “Upper Airway Disorders”. German Society of Pulmonary Medicine (DGP). Mannheim, Germany. 2009.

“Obstructive Lung Diseases- Treatment beyond Inhalers”. European Respiratory Society. Vienna, Austria. 2009.

Invited Speaker:

“Confocal microscopy and Tracheomalacia - basic principles and endoscopic management”. German Society of Pulmonary Medicine (DGP). Mannheim, Germany. 2009.

“Endoscopic Staging of Lung Cancer”. Heart and Lung Institute. Sao Paulo, Brazil. 2009.

“Update in Interventional Pulmonology”, “Lung Cancer Staging”, “Treatment of Lung Transplant Complications”, and “Complications of Endoscopy”. Mexican Society of Pulmonary Medicine and Thoracic Surgery Annual Meeting. Veracruz, Mexico. 2009.

“Interventional Pulmonary Grand Rounds” and “Radiofrequency Ablation in Thoracic Oncology”. European Respiratory Society. Vienna, Austria. 2009.

“Endobronchial Ultrasound”, “Stenting- State of the Art”, and “The State of Endobronchial Lung Volume Reduction for Emphysema”. Papworth Hospital. Cambridge, Great Britain. 2009.

“Endobronchial management of central airway obstruction”. Cedars Sinai Med. Center. Los Angeles, CA. 2009.

“Endoscopic Mediastinal Staging in Lung Cancer”. Fox Chase Cancer Center. Philadelphia, PA. 2009.

“Mediastinal Staging”. Perspectives in Lung Cancer Symposium. Charleston, South Carolina. 2009.

“Endoscopic Lung Cancer Staging”. Grand Rounds at St. Luke’s Hospital. St. Louis, MI. 2009.

“Complex Airway Disorders”. St. Luke’s Hospital. New Bedford, MA. 2009.

“EBUS in Lung Cancer Staging”. Harvard Fellowship Rounds. Boston, MA. 2009.

“Building your research dream house”. BIDMC Research Rounds, Boston, MA. 2009.

“Endoscopic treatment of asthma and emphysema- is it possible?” Medical Grand Rounds at Tufts Medical Center. Boston, MA. 2009.

Sidhu Gangadharan

Invited Speaker:

“Management of Metastatic Disease to the Thorax”. Grand Rounds, St. Luke’s Hospital, New Bedford, MA. 2009.

“Complex Airway Obstruction: Stents Versus Surgery”. Thoracic Surgery Symposium, Society of Thoracic Surgeons Annual Meeting. San Francisco, CA. 2009.

Gaetane Michaud

Invited Speaker:

“Introduction to interventional pulmonology”. BIDMC Anesthesia Grand Rounds. Boston, MA. 2009.

“Approach to Pleural Effusions”. Tufts Pulmonary Critical Care Introductory Course. Boston, MA. 2009.

“Bronchoscopy Simulation Course”. American College of Chest Physicians, Chicago, IL. 2009.

Adnan Majid

Invited Speaker/Hands-On :

“Central Airway Obstruction”. Southcoast Hospitals Group Annual Spring Conference. Dartmouth, MA. 2009.

“Tracheostomy Related Complications” and “Introduction to Rigid Bronchoscopy”. Therapeutic Bronchoscopy Course at New York Methodist Hospital. Bronx, NY. 2009.

“Endobronchial Ultrasound” and “Advanced Bronchoscopic Procedures”. General Hospital. Mexico City, Mexico. 2009.

Invited Speaker:

“Endoscopic diagnosis of early-stage lung cancer”. State of the Art of Lung Cancer Management, STS/ACCP Session at CHEST 2009. San Diego, CA. 2009.

Moderator:

“Interventional pulmonary procedures”. Poster Session at CHEST 2009. San Diego, CA. 2009.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Anantham D, Herth F, **Majid A, Michaud G, Ernst A**. Vibration response imaging in the detection of pleural effusions: a feasibility study. *Respiration* 2009; 77:166-72.

Boiselle P, O'Donnell C, Bankier A, **Ernst A**, Millet M, Potemkin A, Loring S. Tracheal collapsibility in healthy volunteers during forced expiration: assessment with multi-detector CT. *Radiology* 2009; 252:255-62.

Eberhardt R, **Ernst A**, Herth F. Ultrasound guided transbronchial biopsy of solitary pulmonary nodules less than 20 mm. *Eur Resp J* 2009; 34:1284-7.

Ernst A, Rafeq S, Boiselle P, Sung A, **Reddy C, Michaud G**, Herth F, Trentham D. Relapsing polychondritis and airway involvement. *Chest* 2009;135:1024-30.

Ernst A, Eberhardt R, Krasnik M, Herth F. Efficacy of endobronchial ultrasound-guided, transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. *J Thoracic Oncol* 4(8):947-50.

Herth F, Anantham D, **Ernst A**. Narrow-band imaging bronchoscopy increases the specificity of bronchoscopic early lung cancer detection. *J Thoracic Oncol* 4(9):1060-5.

Mantri S, Macaraeg C, Shetty S, Aljuri N, Freitag L, Herth F, Eberhardt R, **Ernst A**. Measurement of collateral flow in the lung with a dedicated endobronchial catheter system. *J Bronchol Intervent Pulmol* 2009;16:141-4.

Martin J, **Kent M**, Fabian T. Prevention of delayed gastric emptying following esophagectomy: a single centre's experience with botulinum toxin. *Ann Thorac Surg* 2009; 87: 1708-13

Okereke I, **Gangadharan S, Kent M**, Nicotera S, **DeCamp MM**, Shen C. Standard uptake value predicts survival in non-small-cell lung cancer. *Annals of Thoracic Surgery* 2009; 88(3):911-5; discussion 915-6.

Reddy C, Michaud G, Majid A. Herth F, **Ernst A**. Photodynamic therapy in the management of endobronchial metastatic lesions from renal cell carcinoma. *J Bronchol Intervent Pulmonol* 2009;16:245-9.

Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, **DeCamp MM**. Factors associated with local and distant recurrence and survival in patients with resected nonsmall cell lung cancer. *Cancer* 2009; 115(5):1059-69.

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Division of Cardiothoracic Surgery

Varlotto JM, Recht A, Nikolov M, Flickinger JC, **DeCamp MM**. Extent of lymphadenectomy and outcome for patients with stage I non-small cell lung cancer. *Cancer* 2009; 115(4): 851-8.

Ye C, Masterman JR, Huberman MS, **Gangadharan S**, McDonald D, **Kent M**, **DeCamp MM**. Subdivision of the T1 size descriptor for stage I non-small cell lung cancer has prognostic value: a single institution experience. *Chest* 2009; 136(3): 710-5.

Original Articles (submitted or in press)

Washko GR, Martinez FJ, Hoffman EA, Loring SH, Estepar RS, Diaz A, Sciurba FC, Silverman EK, Han M, **DeCamp MM**, Reilly JJ, Research Group N. Physiologic and computed tomographic predictors of outcome from lung volume reduction surgery. *Am J Respir Crit Care Med* 2009; submitted.

Reviews, Chapters, and Editorials

Anantham D, Siyue MK, **Ernst A**. Endobronchial ultrasound. *respiratory medicine* 2009; 103(10):1406-14.

Bechara R, **Ernst A**. Medical management of non-malignant pleural effusions. In: Sugarbaker D, editor. *Adult chest surgery*. New York: McGraw Hill Publishing; 2009. p. 912-6.

Ernst A. Ablative endoscopic therapy for endobronchial lesions. In: Sugarbaker D, editor. *Adult chest surgery*. New York: McGraw Hill Publishing; 2009. p. 498-506.

Ernst A. Bronchoscopy: a need for standards, quality improvement, and databases. *Chest Physician* 2009; 4(4):10.

Ernst A, Simoff M, Ost D, Herth F. Response to letter to the editor. *Chest* 2009; 135:1402-3.

Gangadharan S. Benign pleural diseases. In: Sugarbaker D, editor. *Adult chest surgery: concepts and procedures*. New York: McGraw-Hill; 2009. p. 902-11.

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RESEARCH SUMMARY

BASIC RESEARCH

The primary focus of the laboratory is to elucidate the mechanisms and subcellular localization of biochemical and molecular events contributing to myocardial cell death. In particular, we are interested in the discriminant and/or coordinate contribution of necrosis and apoptosis to myocardial cell death in the mature and aged male and female with particular emphasis on the development of novel and specific cardioprotective protocols. 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 male and female cardiac surgical patient. The laboratory is also involved in the analysis of the role of collagen type XI alpha-1 in human aortic aneurysm formation. Study methodologies incorporate surgical procedures, global and regional functional analysis, biochemical and immunohistochemical analysis, molecular biological analysis, and integrated transcriptomic and proteomic analysis using an in house derived non-redundant cDNA library consisting of > 3000 non redundant cDNAs with an average insert size of >1.6 kb.



Sidney Levitsky, MD
James D. McCully, PhD

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Integrated Transcriptomic/Proteomic Analysis of Cardioprotection: Large scale data base studies have demonstrated that aged women undergoing coronary artery bypass grafting (CABG) have a significantly higher operative mortality (4.5%) compared with that of men (2.6%; $P < 0.0001$) and have a significant increase in the incidence of perioperative myocardial infarction as compared to men (4.5% vs. 3.1%; $p < 0.05$). In the analysis of co-morbidities and anatomy relating to early mortality, it has been noted that preoperative risk factors are more prevalent among women than men. These factors include age above 70, angina class 3 or 4, urgent operation, preoperative intraaortic balloon pump usage, congestive heart failure, previous percutaneous transluminal coronary angioplasty, diabetes, hypertension, peripheral vascular disease and smaller coronary artery size and smaller mean body surface area as compared to men. After adjusting for all co-morbidities including body surface area, female gender is an independent predictor of increased mortality following coronary artery bypass surgery, with a risk adjusted operative mortality of 3.81% for women as compared to 2.43% for men.

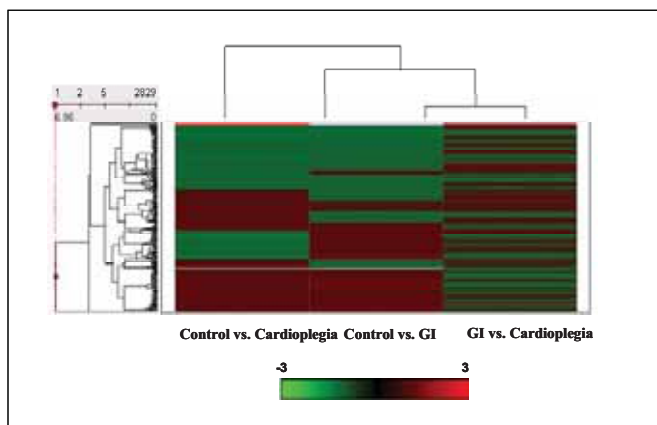
The present paradigm to alleviate surgically induced ischemia/reperfusion injury requires the use of cardioplegia. However, in recent studies we have shown that the cardioprotection afforded by cardioplegia is significantly decreased and left ventricular end diastolic pressure (LVEDP) and infarct size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

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

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

We have constructed rabbit heart cDNA libraries and have isolated and 5' sequenced 8647 rabbit heart cDNAs and have identified and stored 3000 non-redundant cDNAs with a mean insert size of 1.67 kb. These non-redundant cDNAs have been used to construct rabbit heart microarrays to allow for the parallel determination of relative abundance levels of the multiple transcriptomic/proteomic products associated with global ischemia and with the cardioprotection afforded by cardioplegia.

Our published results (Physiol Genomics. 2009, 38:125-137. PMID: 19454556) demonstrate that cardioplegia partially ameliorates the effects of global ischemia and that cardioprotection is modulated by RNA and protein dependent mechanisms. Transcriptomic and proteomic enrichment analysis indicated that global ischemia down-regulates genes/proteins associated with the mitochondrion function and energy production and cofactor catabolism, generation of precursor metabolites of energy. In contrast, cardioplegia significantly increases differentially expressed genes/proteins associated with the mitochondrion and mitochondrial function and significantly up-regulates the biological processes of muscle contraction, involuntary muscle contraction, carboxylic acid and fatty acid catabolic processes, fatty acid beta-oxidation and fatty acid metabolic processes.



These preliminary studies provide the basis for the integration of the genomics and proteomics data to enhance biochemical understanding in terms of signaling pathways, biological processes, and compartmentalization and

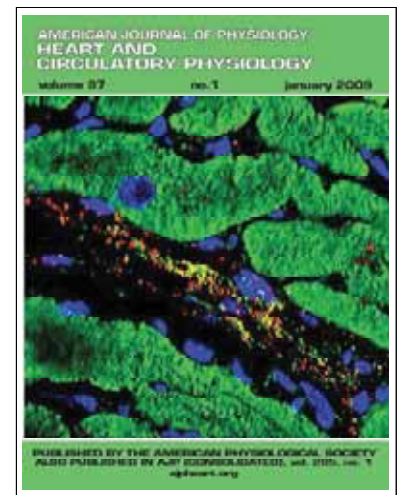
allow for the development of protocols leading to enhanced cardioprotection in the aged female through directed modulation of cardioprotection.

The laboratory focus in this area is to:

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

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

Recently, we demonstrated (Cover article, right: Am J Physiol Heart Circ Physiol 2009; 296: 94-105) that autogeneic mitochondria isolated from the patient's own body, from remote skeletal tissue unaffected by ischemia, and then directly injected into the ischemic zone of the myocardium during early reperfusion, significantly decreases myonecrosis (necrosis and apoptosis) and significantly enhanced post-ischemic functional recovery. Our studies also demonstrated that transplanted mitochondria are viable, respiration competent, maintain membrane potential, are present in the myocardium for at least 21 days after injection and were distributed from the epi- to the sub-endocardium at significant distance from the site of injection.



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

The laboratory focus in this area is to:

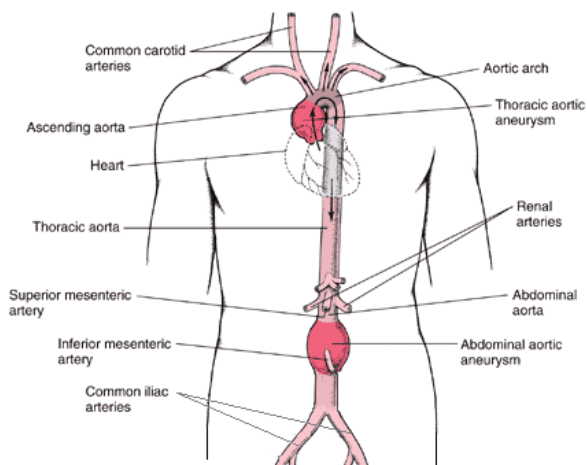
- Demonstrate that autogeneic mitochondrial transplantation enhances myocardial protection in the blood perfused CABG and PCI-STEMI in-situ heart model.
- Optimize mitochondrial storage time in syringe, storage temperature, needle bore size, rate of ejection, mitochondrial sub fraction, the concentration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

The Role of Collagen Type XI Alpha-1 on Aortic Aneurysm Formation: The major disease processes affecting the aorta are aortic aneurysms and dissections and these diseases represent a leading cause of morbidity and mortality worldwide, especially in ages above 65. Aortic aneurysms tend to expand asymptotically until a catastrophic event occurs such as aortic rupture or dissection.

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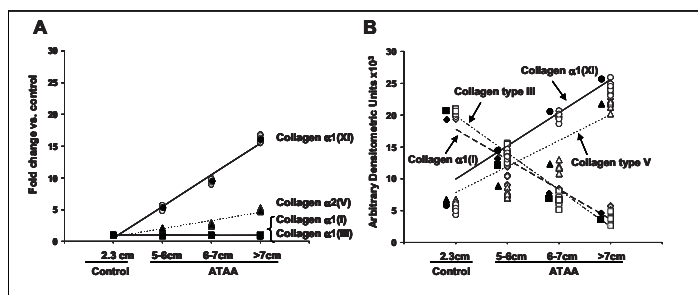
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The most common location for aneurysms is the infrarenal abdominal aorta, followed by the ascending thoracic aorta. The formation of thoracic aortic aneurysms (TAAs) and abdominal aortic aneurysms (AAAs) is a complex and chronic process that results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



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

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



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The laboratory focus in this area is to:

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

LIST OF CURRENT FUNDING

“Myocardial protection: reperfusion injury amelioration “

National Institutes of Health, RO1 HL 29077

Project period: 2004-2011

CO-PI: Sidney Levitsky, MD

CO-PI: James D. McCully, PhD

The goals of this application are to determine the effects of RNA and protein synthesis on the cardioprotection afforded by cardioplegia in the aged female.

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

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

“Autogeneic mitochondria: surgical cardioprotection”

National Institutes of Health, 1R01HL103642-01

Project Period: 2010-2014

PI: James D. McCully, PhD

The primary goals of this application are to demonstrate that autogeneic mitochondrial transplantation ameliorates myonecrosis and enhances myocardial function in the clinically relevant in situ CABG and PCI-STEMI model; to optimize the clinical efficacy of autogeneic mitochondrial transplantation for use in CABG and PCI-STEMI; and to identify the specific mechanism(s) through which autogeneic mitochondrial transplantation significantly enhances post-ischemic functional recovery and significantly decreases myonecrosis using biochemical/immunohistochemical, NMR and integrated transcriptomic and proteomic analysis.

“Mechanical stabilization of the heart with cellularized fibrin sealant”

Harvard Medical School, Children’s Hospital Boston (D.B. Cowan, PD), Harvard Catalyst Grant

Project Period: 2009-2011

Co- PI: James D. McCully, PhD

The primary goal of this pilot grant project is to demonstrate that myocardial structural enhancement in a rabbit model of reversible acute myocardial infarction using a FDA-approved fibrin sealant infiltrated with dermal fibroblasts can significantly reduce morbidity and mortality.

“Cardiovascular surgery research training grant”

National Institutes of Health, National Heart Lung and Blood Institutes, T32

Project Period: 2010-2015

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

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 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 β -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.

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.

Plans for the coming academic year include the addition of new surgical fellow and technician a continuation of age and gender microarray and proteomic studies.

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Invited Presentations

Sidney Levitsky, MD

"Myocardial Protection: 2009". Japanese Association of Thoracic Surgery, Red Cross Hospital & Kobe University School of Medicine. Yokohama, Japan. October 12, 2009.

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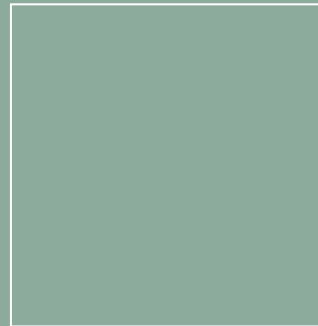
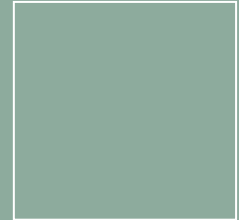
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RESEARCH SUMMARY

BASIC RESEARCH

Drs. Sellke and Bianchi investigate changes in vascular function and signal transduction during cardiac surgery and myocardial ischemia, and therapeutic angiogenesis using protein growth factors in the setting of hypercholesterolemia, diabetes mellitus, metabolic syndrome, and increased oxidative stress. The laboratory was active at BIDMC until November of 2009, when it relocated to Brown University in Providence RI.



Frank W. Sellke, MD, FAHA, MA (upper left)
Cesario Bianchi, MD, PhD (lower right)

LIST OF CURRENT EMPLOYEES

Currently all staff are at Brown University

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Chief, Division of General Surgery
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Carl J. Hauser, MD, FACS, FCCM

Kiyoshi Itagaki, PhD
Qin Zhang, MD
Tolga Sursal, BS

Visiting Professor of Surgery

Instructor in Surgery and Laboratory Manager
Research Associate
Research Student

Mary Jane Houlihan, MD

Assistant Professor of Surgery

James M. Hurst, MD

Acting Chairman, Department of Surgery

Visiting Professor of Surgery

Daniel B. Jones, MD

Professor of Surgery

Director, Center for Minimally Invasive Surgery

Bariatric Program
Benjamin E. Schneider, MD
Maritza Avendaño

Surgeon
Administrator

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Sue Walker, LICSW, MSW
Kelly Moore, RD, LDN
June Skoropowski, RD, LDN
Amanda Bryant
Yulissa Sepulveda
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Simulation and Skills Center

David Fobert
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Robert Andrews, MD

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Yu Chen, MD
Abdala Elkhail, PhD
Yuka Sumi, MD, PhD
Tobias Woehrle, MD
Yongli Yao, MD
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Ariana Brooks-James
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Tara Kent, MD

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Guoqi Zhang, MD, PhD
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Susan L. Troyan, MD

Charles M. Vollmer, MD

Medical Director
Nurse Educator
Social Worker
Dietician
Dietician
Program Admin. Assist
Program Admin. Assist
Administrative Assistant
Platinum Service, General Surgery NP

Administrator, Simulation and Skills Center
Research Assistant, Simulation and Skills Center
Coordinator, Simulation and Skills Center
Volunteer, Simulation and Skills Center

Surgeon
Surgeon
Surgeon
Surgeon
Surgeon
Surgeon

Instructor in Surgery
Instructor in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Research fellow in Surgery
Student
Student
Project Success Student

Instructor in Surgery

Clinical Instructor in Surgery

Assistant Clinical Professor of Surgery

Assistant Professor of Surgery

Assistant Professor of Surgery

Research Assistant
Research Fellow in Surgery
Research Fellow in Surgery

Instructor in Surgery

Instructor in Surgery

Assistant Professor of Surgery

Department of Surgery Annual Research Report 2009
Division of General Surgery

Jin-Rong Zhou, PhD

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Mohamad-Reza Eskandari, MD
Yi Gong, PhD
Yanli Li, PhD
Linglin Li, MS
Jian Qin, MS

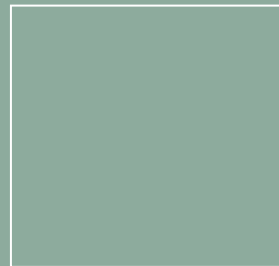
Assistant Professor of Surgery

Clinical Research Fellow in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Research Fellow in Surgery
Research Associate
Research Assistant

RESEARCH SUMMARY

BASIC RESEARCH

Surgical nutrition traces its root to the Cocoanut Grove Fire of 1942 and the study of the metabolic response to burns, trauma, infection and cancer cachexia. Surgical nutrition plays a life-saving role in intensive care units (ICUs) worldwide, preventing protein-energy malnutrition and facilitating recovery in critically ill patients suffering from burns, trauma, infections, and cancer cachexia. Introduced into surgical ICUs in the late 1960s, it pioneered the development of parenteral and total parenteral nutrition support, providing essential nutrients to the most vulnerable patients. Obesity, undernutrition, cancer, and metabolic complications associated with surgical trauma continue to drive advances in nutrition science and patient care. This report describes novel work and notable accomplishments achieved in these areas by the Center for the Study of Nutrition Medicine (CSNM) and the Nutrition Metabolism Laboratory (NML) in 2009.



George L. Blackburn, MD, PhD (upper left)
Jin-Rong Zhou, PhD (lower right)

LIST OF CURRENT EMPLOYEES

Center for the Study of Nutrition Medicine (CSNM)

Anne McNamara RN	Research Associate
Kristina Day Spellman, RD, LD	Research Dietician
Samuel Wollner, BS	Research Assistant
Kathleen Fitzgerald	CME Coordinator
Barbara M. Ainsley, DTR	Administrative Assoc

Nutrition Metabolism Laboratory (NML)

Weijun Pan, MD, PhD	Clinical Fellow
Hamid Abdolmaleky, MD	Research Fellow
Mohamad-Reza Eskandari, MD	Research Fellow
Yi Gong, PhD	Research Fellow
LianUy Guo, PhD	Research Fellow
Yanli Li, PhD	Research Fellow
Linglin Li, MS	Research Associate
Jian Qin, MS	Research Assistant

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BASIC RESEARCH CONT'D



Center for the Study of Nutrition Medicine and the Nutrition Metabolism Laboratory

Back (from left): Linglin Lee, Kathleen Fitzgerald, Samuel Wollner, Hamid Abdalmaleky, George Blackburn, Jin-Rong Zhou, Mohamad-Reza Eskandari.

Front (From left): Yanli Li, Lian Yu Gao, Kristina Spellman, Yi Gong, Barbara Ainsley.

The long-term focus of research in the Nutrition Metabolism Laboratory is to study the role of diet and nutrition in the prevention/treatment of cancer. In particular, our focus has been in breast, prostate, pancreatic, and bladder cancers. Furthermore, we aim to elucidate the mechanisms by which active dietary and nutritional components protect against cancer development. Several research projects are aimed to investigate the potential effects of certain dietary bioactive components on the prevention and treatment of cancer. Over many years, our important research strategy has been to integrate several research components that are essential for effective identification, efficacy evaluation, and mechanism elucidation of nutritional and natural active compounds in a synergistic manner. This integrated system, as outlined in

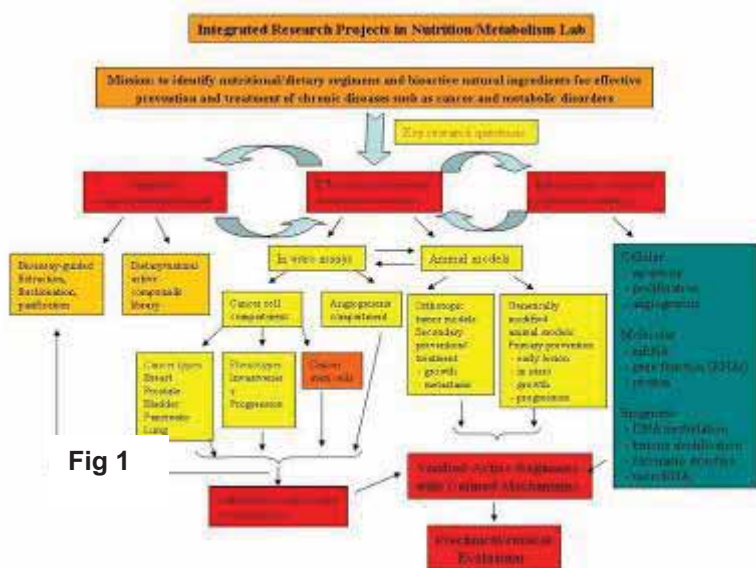


Fig 1, includes application of clinically relevant tumor animal models to evaluate the efficacies of a given dietary or nutritional regimen and to elucidate the underlying cellular, molecular, and epigenetic mechanisms of active components actions, the use of bioactivity-guided fractionation, and purification approaches to further identify anticancer active natural components. We also search for potentially novel risk factors of cancer development and progression, aiming at designing novel nutritional regimens.

CLINICAL RESEARCH

The obesity epidemic could result in an erosion of public health gains observed since early in the 20th century. Disturbingly, rates of extreme obesity (BMI >40 kg/m²) are increasing faster than any other weight class subgroup in the United States. In response to this body of evidence, the Center for the Study for Nutrition Medicine (CSNM) has reaffirmed its mandate to develop best practices for surgical and non-surgical treatments of obesity, especially extreme obesity.

Building off last year's initiative, the CSNM worked with the Weight Loss Surgery Center at BIDMC and the Nutrition and Weight Management Center at Boston University Medical School to implement a progressive resistance training (PRT) protocol as a practical and effective form of exercise for weight loss surgery candidates. The protocol promises to improve strength, fitness, and health in patients preparing for bariatric surgery. To facilitate further investigation into novel and practical approaches to exercise medicine in obesity, the CSNM has organized a research symposium at Experimental Biology 2010 entitled "The Science of Exercise for Obesity".

Recently, the CSNM teamed up with the Berenson-Allen Center for Noninvasive Brain Stimulation to pioneer investigations into the neurocognitive correlates of healthy eating behavior. This research is the first to demonstrate a link between variability in healthy eating and brain and cognitive measures. Our findings suggest that specific neurocognitive resources may be needed to translate nutrition advice into healthy dietary behaviors at the individual level.

The CSNM continues to give health care providers and the public clear, actionable information about achieving healthy body weight, eating nutritious foods, being physically active, getting enough sleep, managing stress, and enjoying life. In cooperation with our world class faculty, the CSNM offers the latest in best practices for obesity medicine at our annual Harvard CME ("International Conference on Practical Approaches to the Treatment of Obesity"). In an effort to extend our bench-to-bedside reach, we are working to create an internet platform for dynamic, on-demand patient-provider interactions. Initial efforts were focused within the BIDMC community as CSNM dietitian, Kristina Spellman, led a 10-week online class through the bidmc.org. Ongoing initiatives will focus on postoperative bariatric surgery patients. These patients represent a target population in need of customized behavioral counseling to help optimize the benefits of weight loss surgery.

CLINICAL RESEARCH COLLABORATORS

Daniel B. Jones, MD, MS and Ben Schneider, MD (Surgery, Section of MIS, BIDMC); Christina C. Wee, MD, MPH and Christos Mantzoros, MD (Medicine, BIDMC); Lee Kaplan, MD, PhD (Weight Loss Center, MGH); Caroline Apovian, MD and Lalita Khadthiar, MD (Medicine, BUMC); Robert Lim, MD (Surgery, MIS Clinical Fellow); James Adair, MD (Surgery, MIS Clinical Fellow); Alvaro Pascual-Leone, MD, PhD (Neurology, BIDMC); Miguel Alonso-Alonso, MD, MSc (Neurology, BIDMC); Jorge Serrador, PhD (Neurology)

LIST OF CURRENT FUNDING

George L. Blackburn

"Look AHEAD Action for Health in Diabetes"

NIDDK 5 U01 DK057154-09

Project Period: 08/01/09-07/31/10

PI: David Nathan

Co-Investigator: George Blackburn

"Boston Obesity Nutrition Research Center (BONRC) –Administrative Core"

NIH/NIDDK, 2 P30DK46200

Project Period: 4/01/08-03/31/13

PI: Barbara Corkey

Associate Director: George Blackburn

"Understanding How Patients Value Bariatric Surgery"

NIH/NIDDK, R01 DK073302-01A1

Project Period: 7/1/2007-6/30/2011

PI: Christina Wee

Co-investigator: George Blackburn

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“Oldenlandia diffusa for prostate cancer treatment”

NIH/NCI, R21 CA 133865-01A2

Project Period: 9/14/2007-8/31/2009

PI: Jinrong Zhou

Co-Investigator: George Blackburn

“LISA (Lifestyle Intervention Study in Adjuvant Treatment of Early Breast Cancer)”

Novartis Pharmaceuticals

Project Period: 2008-2016

PI: Ontario Clinical Oncology Group (OCOG) Pamela Goodwin

Co-Investigator: George Blackburn

Jin-Rong Zhou

“Soy and black tea combinations for prevention of prostate cancer”

Prevent Cancer Foundation

Project Period: 01/15/2007-01/14/2010

PI: Jin-Rong Zhou

“Oldenlandia diffusa for prostate cancer treatment”

National Institutes of Health, R21 CA133865

Project Period: 09/14/2007-08/31/2010

PI: Jin-Rong Zhou

“Parental metabolic status and offspring cancer risks”

National Institutes of Health, RO3 CA130131

Project Period: 09/01/2007-08/31/2010

PI: Jin-Rong Zhou

“Synergy between phytochemicals for prostate cancer prevention”

National Institutes of Health, RO3 CA130133

Project Period: 09/01/2007-02/28/2010

PI: Jin-Rong Zhou

“Metabolic syndrome as pancreatic cancer etiology”

National Institutes of Health, R21 CA127794

Project Period: 04/08/2008-03/31/2010

PI: Jin-Rong Zhou

“Tanshinones as effective therapeutic agents for prostate cancer”

Department of Defense, PC073988

Project Period: 06/01/2008-05/31/2011

PI: Jin-Rong Zhou

“Induction of huntingtin protein as a novel strategy for prevention and treatment of breast cancer”

Department of Defense, BC076551

Project Period: 09/01/2008-02/28/2010

PI: Jin-Rong Zhou

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

Nichimo Company, Japan

Project Period: 03/01/2001-02/28/2010

PI: Jin-Rong Zhou

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

George L. Blackburn

“The Role of right prefrontal cortex in obesity: a multidisciplinary research study using fMRI”

National Institutes of Health,

Project Period: 12/1/09-11/30/2014

PI: Miguel Alonso-Alonso

Co-Investigator: George Blackburn

Jin-Rong Zhou

“Tanshinones from Salvia Miltiorrhiza for pancreatic cancer treatment”

National Institutes of Health, R21 AT005272-01A1

Project Period: 07/01/2010-06/30/2012

PI: Jin-Rong Zhou

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

National Institutes of Health, R21 CA153355-01

Project Period: 07/01/2010-06/30/2012

PI: Jin-Rong Zhou

“Synergistic combination of active components in a Chinese herb Danshen for effective breast cancer therapy”

Susan G. Komen Breast Cancer Research Foundation, KG100239

Project Period: 03/01/2010-02/28/2013

PI: Jin-Rong Zhou

“Targeting epigenetic regulation of reelin as a novel strategy for prevention of breast cancer progression”

Department of Defense, BC095083P1

Project Period: 07/01/2010-06/30/2012

Co-PI: Jin-Rong Zhou

“Tanshinones in Salvia Miltiorrhiza for effective prevention and therapy of lung cancer”

Department of Defense, LC090314

Project Period: 04/01/2010-03/31/2011

PI: Jin-Rong Zhou

“Huntingtin as a novel target for prevention and treatment of lung cancer”

Department of Defense, LC090308

Project Period: 04/01/2010-03/31/2011

PI: Jin-Rong Zhou

“Active dietary and natural components for effective therapy of lung cancer by targeting lung cancer stem cells”

Department of Defense, LC090307

Project Period: 04/01/2010-03/31/2011

PI: Jin-Rong Zhou

“The role of inflammation in breast cancer stem cells”

Department of Defense, BC097669

Project Period: 07/01/2010-06/30/2011

PI: Jin-Rong Zhou

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“Active components in Salvia Miltiorrhiza for breast cancer therapy by targeting breast cancer stem cells”

Department of Defense, BC097292

Project Period: 07/01/2010-06/30/2011

PI: Jin-Rong Zhou

“Huntingtin-associated protein 1 as a novel target for breast cancer therapy”

Department of Defense, BC097290

Project Period: 07/01/2010-06/30/2011

PI: Jin-Rong Zhou

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

Center for the Study of Nutrition Medicine

Look AHEAD (Action for Health in Diabetes)

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

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

Look AHEAD is designed to determine the long-term impact of weight loss on cardiovascular morbidity and mortality in a sample of over 5000 overweight individuals with diabetes. Participants in Look AHEAD were randomly assigned to an intensive lifestyle intervention group or to diabetes support and education (control group). The one year results, published in Diabetes Care (2007) showed that the lifestyle group had reduced their body weight by 8% compared to 1% in the control group. In addition, the lifestyle group had significantly greater improvements in systolic and diastolic blood pressure, HbA1c and glucose, HDL-cholesterol, and triglycerides. Four year results of Look AHEAD will be presented in June at the American Diabetes Association meeting.

Diabetes Support and Education (DSE)

- Two DSE classes were offered in 2009 that covered nutrition and Tai Chi. Another class covering core strengthening and organic and sustainable food was also offered and well attended. Lunch was also provided at that meeting.
- Thank you gifts -first aid kits- were given to all DSE participants as they came in for annual visits as well as a visit from the Interventionist taking over the DSE arm of the study.
- A survey/update letter was sent to all DSE participants requesting feedback for convenient meeting times and ideas for future topics as a way to help re-engage those participants who have not been coming to the group classes.

Lifestyle Intervention

- In January '09 we continued with the Holiday Challenge started in 2008.
- A regular monthly support group was held in February.
- In March we hosted two Zumba/Belly Dancing classes to encourage more aerobic exercise and suggest adding variety to the exercise routine.
- April through June we offered the Lessons Learned national campaign, which ran for 8 weeks.
- May through September we held two monthly support groups each month addressing different topics.
- The Going Green refresher was held for four weeks in October with two additional weeks added on for those needing extra time to reach their weight loss goals.
- This led into The Holiday Challenge, which began in Early November and continues into next year.

Retention

- Retention remains high (> 95%) as the cohorts begin completing their Year Eight annual visits.
- We hosted a luncheon in May, which included both study arms, DSE and Lifestyle Intervention. It was well attended, and we received very positive feedback from the participants.
- We held two information sessions in October, one for each study arm, regarding the Two Year Extension. Both Principal Investigators, Drs. Horton and Blackburn, addressed the groups and supper was served. Staff was available following the event to provide consent forms and to answer additional questions. Everyone in attendance consented to extend their participation and we are continuing to consent participants as they come in for Look Ahead visits.

Look Ahead Training

- Central training for Study Coordinators and Outcomes Staff was held in Winston-Salem, NC in July. Study Coordinator Sharon Jackson, and Outcomes Staff Nurses, Melissa Williams and Anne McNamara attended. Study procedures, physical measurements and outcomes adjudication were reviewed.
- Interventionist training was conducted in Nashville, TN in September for interventionist. Barbara Fagnoli and Jeanne Spellman attended.

Outcomes

- All participants are interviewed for Study Outcomes twice a year. Annual visits additionally include body measurements, vital signs, laboratory and EKG assessments and health questionnaires.

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

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

As of December 2009 the LISA study had enrolled their 313th patient overall. The patient count at BIDMC is currently 24. The funding for this study has been reduced and this study was closed for enrollment as of December 15, 2009.

Progressive resistance training to improve strength, fitness and metabolic health in weight loss surgery patients

Severe obesity is associated with sedentary behavior, low fitness, and metabolic dysmetabolism. Exercise can improve strength, fitness, and metabolic health independent of weight loss in obese patients. Progressive Resistance Training (PRT) is particularly beneficial in modifying body composition, developing musculoskeletal strength, and improving metabolic health.

The goal of this project is to measure strength, fitness, and physical performance outcomes following a 12-week PRT exercise protocol in Class III obese candidates undergoing surgical treatment. We hypothesize that Progressive Resistance Training represents a new evidence-based approach to improve strength, fitness, and metabolic health in Class III obese, weight loss surgery patients.

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As of December 2009, the PRT study had enrolled 8 patients between the two investigation sites (BIDMC and Boston Medical Center). Study results will be presented at the 12th Annual World Conference of Endoscopic Surgeons in April 2010.

Abstracts presented at Local, National and International Meetings

Abstract Presentations

Lim R, Barrios L, Jones DB, Rooks D, Lin H, Schneider B, Dushay J, Corsuro C, **Blackburn GL**. Can healthcare providers increase perioperative exercise behavior in bariatric patients? Presented at the American Society for Metabolic and Bariatric Society 2009 Annual Scientific Meeting, Grapevine, TX; June 21, 2009.

Nutrition Metabolism Laboratory Progress Report

In the past year, we continued to investigate the effects of dietary/nutritional components and ingredients from natural resources, alone and in their combinations on the prevention and treatment of cancer. The purpose is to identify potential synergistic combinations of active components to target on different important cellular pathways as effective candidates of preventive regimens. We identified several synergistic combination regimens of dietary active components and natural components that significantly inhibited the growth of pancreatic cancer, breast cancer, prostate cancer and lung cancer cells and angiogenesis in vitro. We are evaluating the effects of these candidate combination regimens on the growth/progression of tumors in the clinically relevant orthotopic animal models. We identified certain active anti-cancer components with less cytotoxicity to normal cells from Baihuashishicao and Danshen, and are verifying their efficacies in animal models. Several proposals have been submitted for funding support.

We continue research on elucidating how epigenetic modification may play in understanding the mechanisms by which nutritional/natural active components and their combinations may prevent the development and progression of cancer. In addition to studying DNA methylation as an important epigenetic modification event, we investigate how our effective treatment regimens may modulate histone modification and microRNA expression as other possible epigenetic mechanisms. We expand our gene function evaluation by establishing stably transfected cell lines with specific genes (such as Huntingtin, Huntingtin associated protein-1 and reelin). We also investigated the effects of nutritional and natural active compounds on targeting cancer stem cells and identified several potent candidate components. We believe that expansion to these research areas will facilitate us to achieve our research goals to identify the effective nutritional regimens for the prevention and treatment of cancer and to elucidate the underlying mechanisms of actions of these active regimens.

Abstract Presentations

Abdolmaleky SH, Eskandari MR, Li L, Zhou J-R. Epigenetic modifications of huntingtin-related genes by nutritional manipulations for prevention and treatment of breast cancer. *Frontiers in Cancer Research*, Abst. #368, Houston, TX, Dec. 2009.

Gong Y, Li Y, Zhou J-R. Bioactive tanshinones in *Salvia Miltiorrhiza* for prostate cancer chemoprevention. *Frontiers in Cancer Research*, Abst. #394, Houston, TX, Dec. 2009.

Administrative Accomplishments

George L. Blackburn

- Formation of Obesity Research Interest Section (RIS) for American Society for Nutrition (ASN)
- Physician Credentialing Steering Committee Obesity Medicine Certification for Physicians (14 Professional Societies Involved)
- MIS_WLS Research Group (Monthly meetings with staff and fellows focused on research projects)
- Steering Committee of Stop Obesity Alliance
- Glucose Control Protocol to BIDMC Executive Committee

Individual Accomplishments

George L. Blackburn

- Recipient of the Mickey Stunkard Lifetime Achievement Award, The Obesity Society
- American Society for Nutrition, Member and Co-Chair
- Obesity Research Interest Section (RIS)
- American Society for Nutrition, Member Sub-committee for Continuing Medical Education (CME)
- Food Research and Action Center, Washington, D.C. Board of Directors
- Obesity Specialist Credentialing Committee, ASN Representative
- Co-Chair, Reality Coalition
- Stop Obesity Alliance, Steering Committee Member
- Editorial Board, Obesity Management
- Nominated to Editorial Board of Diabetes Care
- Invited Grant Reviewer:
 - NIH Loan Repayment Grants
 - PSI Foundation Grant
 - Canadian Cancer Society Research Institute
- Journal Reviewer:
 - American Journal of Clinical Nutrition
 - American Journal of Lifestyle Medicine
 - American Journal of Preventative Medicine
 - Archives of Internal Medicine
 - Cell Metabolism
 - Circulation
 - Diabetes Care (Nominated to Editorial Board)
 - Journal of Clinical Oncology
 - New England Journal of Medicine
 - Obesity
- One of Top 30% of all Reviews for Annals of Internal Medicine

Jin-Rong Zhou

- Scientific Advisor of Cancer Hospital of Jiangsu Province, Jiangsu, China
- Editorial Board
 - Chinese Journal of Surgical Oncology
 - Nutrition and Metabolic Insights
 - Clinical Medicine: Endocrinology and Diabetes
- Grant Reviewer:
 - Special Emphasis Panel of Cancer/Dietary Prevention (ZRG1 ONC-P 03M), NIH
 - Challenge Grants Panel 10 (ZRG1 OTC-K(58)R), NIH
 - Special Emphasis Panel of Cancer Biology and Therapy Pilot Studies, NIH
 - Israel Science Foundation
 - Center for Scientific Review SEP (ZRG1 OTCW02)
 - NCI Cancer Prevention Research II (ZCA1 SRLB-F J2R), NCI/NIH
 - USDA Agriculture and Food Research Initiative (AFRI) Competitive Grants Program
- Journal Reviewer:
 - British Journal of Nutrition
 - Cancer Letter
 - Molecular Cancer Therapy
 - Journal of Agriculture and Food Chemistry

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Invited Presentations

George Blackburn

"Medical nutrition therapy" Boston Dietetic Interns Obesity Day. Boston, MA. January 26, 2009.

"Achieving best practices in obesity surgery: Betsy Lehman Center for Patient Safety" Boston Surgical Society, Boston, MA. February 2, 2009.

"Nutritional aspects in bariatric patient".

"Obesity: A state or a disease".

Cleveland Clinic Forgut Symposium. Coral Gables, FL February 17, 2009

"Metabolic syndrome: A new challenge to treating malnutrition in the hospitalized patient" Dudrick Symposium, Yale Medical Center. New Haven, CT. March 28, 2009.

"Energetic implications of dietary patterns and body composition differences". Experimental Biology, American Society for Nutrition. New Orleans, LA. April 18, 2009.

"Nutrition support and tight glucose control in the surgical ICU". Beth Israel Deaconess Medical Center Surgical Grand Rounds. Boston, MA. April 22, 2009.

"High risk weight loss surgery and best practices". Beth Israel Deaconess Medical Center, Anesthesia Grand Rounds. Boston, MA. August 26, 2009.

"LookAHEAD year 4 results". Joslin Diabetes Center, Presentation to DSE Study Group. Boston, MA. October 7, 2009.

"2009 Mickey Stunkard lifetime achievement award lecture—then & now: physical activity and human obesity". The Obesity Society Annual Meeting. Washington DC. October 25, 2009.

"Exercise & overweight/obesity". Active Doctors Active Patients HMS CME Program. Boston, MA. November 13, 2009.

"High risk weight loss surgery and best practices". Surgical Grand Rounds St. Vincent Hospital. Worcester, MA. November 18, 2009.

"Medical nutrition therapy for obesity treatment". Obesity Day for Boston Area Dietetic Interns. Boston, MA. December 7, 2009.

Jin-Rong Zhou

"Soy, isoflavones, and mammary cancer: Overview of results from animal studies". Invited Speaker, The Symposium on Evaluating the Efficacy and Safety of Isoflavones for Postmenopausal Women. Milan, Italy. May 2009.

"Basic and clinical research in targeted therapy of lung cancer". Invited Speaker, The 1st Jinling Cancer Forum. Nanjing, China. June 2009.

"Combination of active components in danshen for prostate cancer treatment by acting on multiple targets". Invited Speaker, Bio-Pearl River Forum and the 14th Annual Conference of Chinese Niopharmaceutical Association. Guangzhou, China. July 2009.

REPORT OF TEACHING

George L. Blackburn

Graduate School and Graduate Medical Courses

Tutor for the HMS course, "Fundamentals of Medicine YII Nutrition"

HMS PD II OSCE 80

Mentor for: Belinda Waltman, HMS III Guide her on defining her research focus and applying for funded research programs.

Robert Lim, MD MIS Fellow, Research focus and grant application submission

Jorge Serrordor, PhD, Neurology

Miguel Alonso-Alonso, MD, Neurology

CME Courses

HMS, Department of Continuing Medical Education, "Practical Approaches to the Treatment of Obesity" Cambridge, MA. June 18-20, 2009, Course Director.

Other Teaching Contributions:

- Nutrition Curriculum Sub Committee at Harvard Medical School.
- Harvard Fundamentals of Medicine YII Nutrition Sub Committee.
- E-Learning Committee, Division of Nutrition, Harvard Medical School.

Jin-Rong Zhou, Ph.D.

Other Teaching Contributions

- Mentoring Post-Doc and Research Fellows in the Nutrition Metabolism Lab.
- Nutrition Curriculum Sub Committee member at Harvard Medical School.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Hagen SJ, Ohtani M, **Zhou JR**, Taylor NS, Rickman BH, **Blackburn GL**, Fox JG. Inflammation and faveolar hyperplasia are reduced by supplemental dietary glutamine during *Helicobacter pylori* infection in mice. J Nutr 2009;139:912-8.

Hoy MK, Winters BL, Chlebowski RT, Papoutsakis C, Shapiro A, Lubin MP, Thomson CA, Grosvenor MB, Copeland T, Falk E, Day K, **Blackburn GL**. Implementing a low-fat eating plan in the Women's Intervention Nutrition Study. J Am Diet Assoc 2009;109:688-96.

Feng JF, Wu JZ, Hu SN, Gao CM, Shi MQ, Lu ZH, Sun XC, **Zhou JR**, Chen BA. Polymorphisms of the ribonucleotide reductase M1 gene and sensitivity to platin-based chemotherapy in non-small cell lung cancer. Lung Cancer 2009; 66:344-9.

Wadden TA, West DS, Neiberg RH, Wing RR, Ryan DH, Johnson KC, Foreyt JP, Hill JO, Trence DL, Vitolins MZ; **Look AHEAD Research Group**. One-year Weight losses in the Look AHEAD Study: factors associated with success. Obesity 2009;17:713-22.

Original Articles (submitted or in press)

Alonso-Alonso M, **Blackburn GL**, Radziejowska J, Pascual-Leone A. Neurocognitive correlates of healthy eating in lean female subjects. Am J Clin Nutr 2009; submitted.

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Gong Y, Li Y, Li L, Abdolmaleky H, **Zhou JR**. Bioactive tanshinones in *Salvia miltiorrhiza* inhibit prostate cancer cells *in vitro* and in mice. *Cancer Res* 2009; submitted.

Li M, Jiang RW, Hon PM, Cheng L, Li LL, **Zhou JR**, Shaw PC, But PPH. Authentication of the anti-tumor herb Baihuasheshecao with bioactive marker compounds and molecular sequences. *Food Chem* 2009; in press.

Papageorgis P, Cheng K, Lambert AW, Ozturk S, Abdolmaleky HM, **Zhou J-R**, Thiagalingam S. Smad4 inactivation promotes malignancy and drug resistance of colon cancer. *Cancer Res* 2009; in press.

Reviews, Chapters, and Editorials

Blackburn GL. Counteracting the effects of chemosensory dysfunction. *J Support Oncol* 2009;7:66-7.

Blackburn GL. The ROI on weight loss at work. *Harvard Business Review*. December 2009.

Blackburn GL, Hu FB, Hutter M. Updated evidence-based recommendations for best practices in weight loss surgery. *Obesity* 2009;17:839-841.

Blackburn GL, Hutter MM, Harvey AM, Apovian CM et al. Expert panel on weight loss surgery: executive report update. *Obesity* 2009;17: 842-62.

Blackburn GL, Wang KA, Day K. Dietary guidelines. In: Jones SB, Jones DB, editors. *Obesity surgery: patient safety and best practices*. Woodbury: Cine-Med, Inc; 2009. p. 39-46, 61-68.

Kelly JJ, Shikora S, Jones DB, Hutter M, Robinson MK, Romanelli J, Buckley F, Lederman A, **Blackburn GL**, Lautz D. Best practice updates for surgical care in weight loss surgery. *Obesity* 2009;17: 863-70.

Shikora SA, Kruger RS, **Blackburn GL**, Fallon J, et al. Best practices in policy and access for weight loss surgery. *Obesity* 2009;17:918-23.

Reviews, Chapters and Editorials (submitted or in press)

Abdolmaleky HM, **Zhou J-R**. Dietary and environmental influences on the genomic and epigenomic code in cancer. In: *Systems biology of cancer*. Thiagalingam S, editor. Cambridge University Press 2009; in press.

Blackburn GL. From bench to bedside: novel mechanisms and therapeutic advances through the development of selective PPAR γ modulators. *Am J Clin Nutr* 2009; in press.

Blackburn GL, Spellman K, Wollner S. Overweight, obesity, and cardiovascular risk. In: Blumenthal RS, Foody JM, Wong ND, editors. *Prevention of cardiovascular disease companion to Braunwald's heart disease*. Elsevier 2009, in press.

Blackburn GL, Wollner S, Heymsfield SB. Lifestyle interventions for the treatment of class III obesity: a primary target for nutrition medicine in the obesity epidemic. *Am J Clin Nutr* 2009; in press.

RESEARCH SUMMARY

CLINICAL RESEARCH

Our work focuses on outcomes research in high-acuity pancreaticobiliary surgery. Fueled by a robust clinical practice which focuses on treatment of pancreatic malignancies, cystic lesions, pancreatitis, and complex biliary conditions in a multidisciplinary setting, we perform over 200 major pancreaticobiliary operations per annum. A prospective database of over 4000 operations and 600 pancreatic resections has been developed and maintained from this practice, and provides the substrate for our investigations. Areas of emphasis have been the development and critical analysis of clinical pathways and other systems initiatives for optimal patient care. Separate investigations are centered on technical and perioperative management aspects of surgical care for diseases of the pancreas and biliary tree. Also explored has been the impact of surgical complications associated with these operations. We are now also embarking on Quality of Life analyses for these disease processes.



Mark P. Callery, MD, FACS (upper left)
Charles M. Vollmer, Jr. MD, FACS (lower left)
Tara S. Kent, MD (right)

LIST OF CURRENT EMPLOYEES

Jennifer Erdrich, MD	Surgical Resident, Stanford
Satish Nadig, MD	Surgical Resident
Wande Pratt, MD	Surgical Resident, Wash U
Teviah Sachs, MD	Surgical Resident
Norberto Sanchez, MD	Clinical Research Fellow

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RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

One of our primary endeavors has been in caring for patients with incidentally identified, asymptomatic pancreatic lesions. This clinical focus by our group has led to a landmark publication which describes the predominance of malignant and premalignant pathologies encountered in this scenario. Other work has contributed to a better understanding of managing cystic lesions of the pancreas – particularly Intraductal Papillary Mucinous Neoplasm (IPMN). We continue to establish parameters of recovery following pancreatic resections. We have defined benchmark outcomes for pancreatic resections in the elderly cohort (> 75 y.o.) featuring our interdisciplinary collaboration with gerontology consultation. We have also described the importance of optimal operative performance, including minimizing blood loss, as well as the negative influence of preoperative hospitalization for patients requiring pancreatic resection. We are also very interested in the emerging concept of “borderline resectable” pancreatic tumors, and have illustrated the predictive capacity of CT Angiograms for this problem. In addition, through collaboration with our radiology and oncology consultants, we defined the value of Cyberknife Radiotherapy for pancreatic cancer, both on locally advanced disease, as well as the situation of positive margins following resection. Other investigations have focused on technical approaches to pancreatic surgery, and we have contributed to two Consensus Conference monographs on pancreatic cancer surgery. Future endeavors will be aimed at biospecimen acquisition for gene discovery projects spearheaded by the Dana Farber Cancer Center.

Abstracts Presented at Local, National, and International Meetings

Kent TS, Pedrosa I, Brown A, **Callery MP**, and **Vollmer CM**. Clinical utility of secretin MRCP for pancreatic diseases. Presented (as a poster) at the American Pancreatic Association 39th Annual Meeting, Chicago, IL; November 7, 2008. Oral Presentation at The Pancreas Club – 43rd Annual Meeting. Chicago, IL; May 31, 2009.

Kent TS, **Callery MP**, Brown A, Raptopoulos V, **Vollmer CM**. Escalating Computed Tomography Angiogram (CTA) grade predicts unresectability and positive margins for pancreaticobiliary neoplasms. Oral Presentation at the American Hepato-Pancreato-Biliary Annual Congress, Miami, FL; March 14th, 2009.

Newman L, Brodsky D, **Vollmer CM**, Roberts D, Johansson A, Atkins KM, Schwartzstein R. Determining precise expert rating standards for peer observation of medical lectures. Presented (as a poster) at HMS Medical Education Day, Boston, MA; 2009.

Individual Accomplishments

Mark P. Callery

- Served as Past-President of the AHPBA for 2009-2010
- Served as Program Committee Chairman, and on Board of Trustees, Society for Surgery of the Alimentary Tract (SSAT), 2006-present
- Served on Board of Governors, SAGES, 2006-present
- Served on Executive Council for the IHPBA (International Hepato-Pancreato-Biliary Association)
- Served as Associate Editor for *HPB*
- Editorial Board for the following Journals:
 - Journal of Gastrointestinal Surgery
 - Surgical Endoscopy
 - Journal of Laparoendoscopic & Advanced Surgical Techniques
- Reviewer for the following Journals:
 - Annals of Surgery
 - Journal of the American College of Surgeons (JACS)
 - Journal of Gastrointestinal Surgery (JOGS)
 - Surgery
 - Annals of Surgical Oncology
 - HPB
 - New England Journal of Medicine
- External Advisory Board – NCI Grant “Genetics and Biology of Pancreatic Ductal Adenocarcinoma”

Charles M. Vollmer

- Served as Chairman of the Membership Committee and member of the Executive Council for the AHPBA
- Served on Program Committee (Pancreatic Subcommittee) for the SSAT
- Elected as new member of the Society of University Surgeons
- Visiting Professor: National Congress of Gastroenterology: Mexican Gastroenterologic Association
- Reviewer for the following Journals:
 - Journal of the American College of Surgeons (JACS)
 - Journal of Gastrointestinal Surgery (JOGS)
 - Cancer
 - Annals of Surgery
 - Journal of Surgical Oncology
 - Digestive Diseases and Sciences
 - Surgery
 - Annals of Surgical Oncology
 - CA: A Cancer Journal for Clinicians
 - HPB Surgery
 - Southern Medical Journal
 - HPB

Tara S. Kent, MD, FACS

- Reviewer for the following Journals:
 - Journal of the Pancreas (JOP)
 - Annals of Surgery

Invited Presentations

Mark Callery

"Quality assessment in high - acuity surgery". Long Island Jewish Medical Center, Philip Lear Memorial Lecturer. Great Neck, NY. 2009.

"Managing complications of acute pancreatitis: introduction". SSAT/AHPBA Joint Symposium, SSAT Annual Meeting, Chicago, IL. June 2, 2009.

"Pancreatic cancer". Beverly Hospital, Tumor Board Meeting. Beverly, MA. June 9, 2009.

"Preoperative staging of pancreatic neoplasms". Creighton University, 4th Annual Fall Midwest GI Conference. Omaha, NB. September 29, 2009.

"Prevention and management of hemorrhage and delayed gastric emptying after pancreatic cancer surgery". EHPBA Meeting, Breakfast with the Professors IV. Athens, Greece. June 19, 2009.

Invited Session Moderator

"Pancreatic and digestive surgery". American College of Surgeons Annual Meeting. Chicago IL. Oct 13, 2009.

Symposium Coordinator

"Managing complications of acute pancreatitis". SSAT Annual Meeting, SSAT/AHPBA Joint Symposium. Chicago, IL. June 2, 2009.

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Charles Vollmer, Jr.

"The surgeon's perspective on pancreatic cancer for oncologists". Beth Israel Deaconess Medical Center – Harvard University, Hematology/Oncology Fellows Conference. Boston, MA. January 12, 2009.

"What is this thing IPMN?" Saint Vincent's Hospital, Department of Surgery Grand Rounds. Worcester, MA. February 18, 2009.

"Zen of consults". Beth Israel Deaconess Medical Center, Center for Faculty Development. Boston, MA. 2009.

"Pancreatic cystic neoplasms". Beth Israel Deaconess Medical Center – Harvard University, GI Fellows Conference. Boston, MA. April 22, 2009.

"Pancreatic cancer". Beverly Hospital, Tumor Board Meeting. Beverly, MA. June 9, 2009.

"Survey of surgical faculty on best operating room teaching practices". Harvard Medical School Inter-Hospital Educational Collaborative, BIDMC's Hospital-based Academy Report on Current Educational Initiatives. Boston, MA. Dec 16, 2009.

"Teaching in the operating room".

"Panel discussion on teaching".

Principles of Medical Education: Maximizing Your Teaching Skills. Cambridge, MA. March 21, 2009.

"Surgical management of pancreatic cancer". National Pancreas Foundation (NPF), NPF Fellow's Symposium. Chicago, IL. April 17-19, 2009.

"High acuity surgery in the elderly – The pancreas". SSAT/AGA Combined Clinical Symposium – Digestive Disease Week, Gastrointestinal Surgery in the Elderly. Chicago, IL. June 2, 2009.

"Acute pancreatitis: when to operate".

"Choledocholithiasis: surgeon or endoscopist".

"The significance of incidental pancreatic lesions".

"Infected pancreatic necrosis and abscess".

National Congress of Gastroenterology: Mexican Gastroenterologic Association. Guadalajara, Mexico. December 9 - 11, 2009.

Invited Session Moderator

"Resources at BIDMC and HMS".

"Designing and Conducting Clinical Trials".

Beth Israel Deaconess Medical Center – Harvard University Center for Faculty Development, Distinguishing Yourself as an Independent Clinical Investigator. Boston, MA. May 8, 2009.

Beth Israel Deaconess Medical Center – Harvard University Center for Medical Education. Oral Presentation Judge, Hospital-wide Resident/Fellows Research Day. Boston, MA. May 12, 2009.

Americas Hepato-Pancreato-Biliary (AHPBA) Annual Congress. Pancreas Competitive Video Session. Miami, FL. March 15, 2009.

The Pancreas Club 43rd Annual Meeting. Poster-side Professor Rounds. Chicago, IL. May 30, 2009.

Tara S. Kent, MD

"Today's approach to pancreatic cystic neoplasms". Montefiore Medical Center, Department of Surgery Grand Rounds. Bronx, NY. March 30, 2009.

REPORT OF TEACHING

Undergraduate Teaching

Jennifer Erdrich, MSIV has worked with us throughout the FY09 academic year investigating clinical predictor of malignancy in Intraductal Papillary Mucinous Neoplasia (IPMN).

Undergraduate Courses

Mark Callery

Introduction to the Abdominal Exam (Patient-Doctor II) – Physical Exam Instructor

Charles Vollmer, Jr.

- Principle Clinical Experience (PCE) Faculty (BIDMC) – Part of a core faculty who provide the longitudinal education curriculum to HMS III students.
BaSIC Conference facilitator:
“Pancreatitis”.
“Pancreatic Malignancy”.
Lecturer “Abdominal Radiology Clinical Correlation” .
Comprehensive OSCE Examiner (2nd and 4th year exams)
- Introduction to the Abdominal Exam (Patient-Doctor II) – Physical Exam Instructor

Other Teaching Contributions

- John Warren Surgical Society (HMS Surgery Interest Group) – Founding Faculty Advisor
Provided leadership for a student-led Surgical Society designed to expose junior medical students to the field and to prepare senior students for a career in surgery. Developed a topical curriculum and faculty mentorship program.
- Resource Faculty (BIDMC Educational Task Force) - Department Representative
Purpose is to promote development of faculty teaching in our department, as well as the institution as a whole, with the overarching goal of improving the quality of education of medical students and residents. Participation in Teaching Consult Service.

Tara Kent

- Introduction to the Abdominal Exam (Patient-Doctor II) – Physical Exam Instructor
- Associate Clerkship Director - 3rd year medical student clerkship in surgery

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Callery MP, Chang KJ, Fishman EK, Talamonti MS, Traverso LW, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009; 15 (5): 235-42.

Demirjian AN, **Vollmer CM**, McDermott DF, Atkins MB, **Callery MP**. Refining indications for contemporary surgical treatment of renal cell carcinoma metastatic to the pancreas. *HPB (Oxford)* 2009; 11(2):150-3.

Evans DB, Farnell MB, Lillemoe KD, **Vollmer C Jr**, Strasberg SM, Schulick RD. Surgical treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Ann Surg Oncol* 2009;16(7):1736-44.

Pratt WB, **Callery MP**, **Vollmer CM**. The latent presentation of pancreatic fistulae. *Br J Surg* 2009; 96(6):641-9.

Pratt WB, Gangavati A, Agarwal K, Schreiber R, Lipsitz LA, **Callery MP**, **Vollmer CM**. Establishing standards of quality for outcomes of elderly patients undergoing pancreatic resection. *Arch Surg* 2009;144(10): 950-6.

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Pratt WB, **Vollmer CM, Callery MP**. Outcomes in pancreatic resection are negatively influenced by preoperative hospitalization. *HPB (Oxford)* 2009; 11(1):57-65.

Powers K, Rehrig ST, Schwaitzberg SD, **Callery MP**, Jones DB. Seasoned surgeons assessed in a laparoscopic surgical crisis. *J Gastrointest Surg* 2009; 13 (5): 994-1003.

Sachs T, Pratt WB, **Callery MP, Vollmer CM**. The incidental asymptomatic pancreatic lesion: nuisance or threat? *J Gastrointest Surg* 2009;13(3):405-15.

Sawhney MS, Al-Bashir S, Cury MS, Brown A, Chuttani R, Pleskow DK, **Callery MP, Vollmer CM**, International consensus guidelines for surgical resection of mucinous neoplasms cannot be applied to all cystic lesions of the pancreas. *Clin Gastroenterol Hepatol* 2009; 7:1373-6.

Sawhney MS, Devarajan S, O'Farrel P, Cury MS, Kundu R, **Vollmer CM**, Brown A, Chuttani R, Pleskow DK. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc* 2009; 69(6):1106-10.

Original Articles (submitted or in press)

Dubay DA, Kachura JR, Ho CS, Beecroft JR, Cheow PC, **Vollmer CM**, Ghanekar A, Guba M, Nanji S, Cattral MS, McGilvray ID, Kashfi A, Qiu K, Smith RJ, Sherman M, Levy GA, Grant DR, and Greig PD. Radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation prolongs wait list eligibility. *Transplantation* 2009; submitted.

Kent TS, Raptopoulos V, Gatum S, **Callery MP, Vollmer CM**. Escalating computed tomography angiogram (CTA) grade predicts unresectability, margin status, and survival for pancreaticobiliary neoplasms. *HPB* 2009; in press.

Mahadevan A, Jain S, Goldstein M, Miksad R, Pleskow DK, Sawhney MS, Brennan D, **Callery MP, Vollmer CM**. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiation Oncology, Biol Phys* 2009; in press.

McMahon C, **Vollmer CM**, Goldsmith J, Brown A, Pleskow D, Pedrosa I. An unusual variant of anomalous pancreaticobiliary junction in a patient with pancreas divisum diagnosed with secretin-magnetic resonance cholangiopancreatography. *Pancreas* 2009; in press.

Reviews, Chapters, and Editorials

Callery MP, Pratt WB, **Vollmer CM**. Prevention and management of pancreatic fistula. *J Gastrointest Surg* 2009; 13 (1):163-73.

Cannon JW, **Callery MP, Vollmer CM**. Diagnosis and management of pancreatic pseudocysts: what is the evidence? *J Am Coll Surg* 2009; 209(3): 385-93.

Hueman MT, **Vollmer CM**, Pawlik TM. Evolving treatment strategies for gallbladder cancer. *Ann Surg Oncol* 2009; 16(8): 2101-15.

Kakoza RM, **Vollmer CM**, Stuart KE, Takoudes T, and Hanto DW. Pancreatic adenocarcinoma in the pregnant patient: A case report and literature review. *J Gastrointest Surg* 2009;13(3):535-41.

Maithel S, **Vollmer CM**. How do I evaluate for and treat patients with autoimmune pancreatitis? In: Tenner S, Brown A, Gress F, editors. *Curbside consultation for the pancreas: 49 clinical questions*. Thorofare: Slack Incorporated; 2009. Chapter 49.

Maithel S, **Vollmer CM**. What is the best approach to nutrition for acute pancreatitis? In: Tenner S, Brown A, Gress F, editors. *Curbside consultation for the pancreas: 49 clinical questions*. Thorofare: Slack Incorporated; 2009. Chapter 6.

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

Callery MP. Cholecystolithiasis and stones in the bile duct: which approach and when? In: Jarnigan W, editor. Blumgart's surgery of the liver, biliary tract, and pancreas, 5th Edition. 2009; in press.

Nadig SN, **Vollmer CM.** Post-cholecystectomy problems. In: Jarnigan W, editor. Blumgart's surgery of the liver, biliary tract, and pancreas, 5th edition. 2009; in press.

Vollmer CM. Unusual pancreatic tumors. In: Cameron JL, editor. Current surgical therapy, 10th edition. St. Louis: Mosby. 2009; in press.

Vollmer CM, Callery MP. Open surgical approaches to pancreatic pseudocyst drainage. In: Adams RB, editor. Atlas of hepatobiliary and pancreatic surgery. 1st edition. 2009; in press.

Clinical Communications

Afdhal NF, **Vollmer CM.** Complications of laparoscopic cholecystectomy. In: Rose BD, editor, UpToDate. Waltham, MA, 2009.

Vollmer CM. Unexpected identification of gallbladder carcinoma during cholecystectomy. J Gastrointest Surg 2009; 13 (11): 2034-6.

RESEARCH SUMMARY

BASIC RESEARCH

Our primary basic research project concerns the identification of a marker for breast cancer detection and involves collecting blood samples from women with a diagnosis of breast cancer. Samples are analyzed for a nuclear matrix protein that may be linked with early detection of breast cancer.

CLINICAL RESEARCH

Women's Health Study in Accra, Ghana

This study is an assessment of the burden of communicable and non-communicable disease in a cohort of 3200 adult women who reside in Accra.

Assessing the ideal body image for Ghanaian women and men

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

EDUCATIONAL RESEARCH

Assessment of the impact of leadership courses for academic medical faculty

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

Assessment of career goals, mentorship and other factors for new full time faculty.

The history of women at BIH and NEDH and BIDMC.



Rosemary B. Duda, MD, MPH

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LIST OF CURRENT FUNDING

“Health, poverty and place: modeling inequities in Accra, Ghana using RS and GIS”

NIH, 5R01-HD054906-03

9/2007-6/2012

PI: John R. Weeks (San Diego State University)

Co-Investigator: Rosemary B. Duda

“Reproductive health and overall health outcomes and their economic consequences for households in Accra, Ghana.”

Hewlett Packard/Global Teams of Research

Project Period: 2008-2009

Consultant: Rosemary B. Duda

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Individual Accomplishments

- Professional and Educational Leadership Role
- Commission on Cancer, American College of Surgeons
- Conference Planning Committee
- Genetics Subcommittee
- Society of Surgical Oncology
- Chair, Clinical Affairs Committee
- Volunteer medical service in Nicaragua
- Co-investigator on an NIH funded study to assess the burden of disease in Accra, Ghana.
- Development of a breast cancer program at the regional hospital in Matagalpa, Nicaragua.

RESEARCH SUMMARY

BASIC RESEARCH

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



Sandra M. Gaston, PhD

LIST OF CURRENT EMPLOYEES

Andrew Guerra, BS	Research Technician
Julie Meadows, BS	Research Technician
Rajiv Nadadur	Research Student
Ashley Hlastava	Research Student
Maria Pellon Consunji	Research Student
Maria Bonatsakis	Research Student

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BASIC RESEARCH CONT'D

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

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

LIST OF CURRENT FUNDING

"Prostate MRI and MRS: correlations with gene expression"

NCI: R21 CA116866

Project Period: 2006-2009

PI: Sandra M. Gaston

"Improving patient care for prostate cancer"

Ellison Foundation Research Grant

Project Period: 2007-2010

Co-PI: Sandra M. Gaston

"Multi-analyte assessment of PrCa Chr21 rearrangements in diagnostic biopsies"

National Institutes of Health, Early Detection Research Network

Project Period: 2006-2009

PI: Sandra M. Gaston

"MicroRNAs as potential biomarkers for specific subtypes of TMPRSS2-ERG positive prostate cancer"

NIH, Early Detection Research Network

Project Period: 2007-2009

PI: Sandra M. Gaston

"Magnetic resonance imaging as a genomic/proteomic expression correlate to characterize renal cell carcinoma"

Pilot Project: DF/HCC Renal Cancer SPORE

Project Period: 2008-2009

Co-PI: Sandra M. Gaston

"Choline metabolism in prostate cancers: response to dietary soy phytochemicals"

National Institutes of Health, R21 CA130013

Project Period: 2007-2010

PI: Sandra M. Gaston

“MicroRNA blood tests for high risk prostate cancers”
Agilent Technologies Foundation University Research Project: 09US-668
Project Period: 2008-2009
PI: Sandra M. Gaston

“DNA Methylation Markers in High Risk Prostate Cancer Biopsies”
Oncomethylome Sciences Industry Sponsored Research Project
Project Period: 2009-2010
PI: Sandra M. Gaston

“Tissue Print Analysis of Prostate Needle Biopsies: Evaluation of Molecular Markers in the Clinical Stratification of Patients with ‘Suspicious’ and ‘Premalignant’ Cores”
National Institutes of Health, NCI EDNR Program for Rapid Independent Diagnostic Evaluation
Project Period 2009-2011
PI: Sandra M. Gaston

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

PENDING FUNDING – APPROVED AWARDS

“Biomarkers in the Detection of Prostate Cancer in African Americans”
Department of Defense Prostate Cancer Research Program
Project Period: 2009-2013
PI: Sandra M. Gaston

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Accomplishments

With NIH and intramural research support, my laboratory has continued to advance the development of a set of novel tissue printing technologies that support the molecular analysis of human tissue specimens. Our tissue print techniques allow us to transfer a microscopic layer of cells and extracellular matrix from the surface of a fresh tissue specimen onto nitrocellulose membranes, creating a “molecular xerox” which preserves the specimen for histopathology. We have combined tissue print techniques with specific protein and RNA/DNA detection methods to generate two-dimensional maps of molecular markers in radical prostatectomy specimens, and these maps have allowed us to identify clusters of molecular markers that co-localize with sites of microscopic invasion of cancer into the prostate capsule. This year, with support from the BIDMC Renal Cancer SPORE and the Harvard Catalyst Program, we have applied this novel approach to map gene expression patterns associated with DCE-MRI visible features in renal cancers. These studies have identified candidate genes that may be important determinants of the type of tumor vasculature found in renal cancers.

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

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grants entitled “Multi-Analyte Assessment of PrCa Chr21 Rearrangements in Diagnostic Biopsies” and “MicroRNAs as Potential Biomarkers for Specific Subtypes of TMPRSS3-ERG Positive Prostate Cancer.” We have also received industry support for this project from the Agilent Technologies Foundation with an award entitled “MicroRNA Blood Tests for High Risk Prostate Cancers.”

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



Andrew Guerra (left) and Julie Meadows (right) in the laboratory.

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

New Research Initiatives

- This year we will begin a new DOD prostate cancer research grant entitled “Biomarkers in the Detection of Prostate Cancer in African Americans.” The goal of this project is to evaluate a series of prostate cancer biomarkers in biopsy tissues from African and European American patients. This study will be one of the first to incorporate ancestry admixture markers into an analysis of prostate cancer biomarkers in these two populations.
- We are continuing the second year of our NIH grant “Tissue Print Analysis of Prostate Needle Biopsies: Evaluation of Molecular Markers in the Clinical Stratification of Patients with ‘Suspicious’ and ‘Premalignant’ Cores”. The primary goal of this effort is to identify biomarkers that can be used to guide the management of patients with suspicious but not definitive findings on prostate biopsy.
- We will expand our efforts to develop tissue print biomarker protocols to support reliable, efficient detection of cancer-associated mitochondrial deletions in biopsy tissues and in micro-metastases.
- We will expand a collaborative study with Dr. Ivan Pedrosa (BIDMC Radiology) to use tissue prints to map gene expression patterns associated with DCE-MRI visible features in renal cancers, with a focus on genes involved in pharmacologically important kinase pathways.
- We look forward this year to several important new and/or expanded research collaborations. These include:
 - William Grizzle, MD PhD, University of Alabama, Birmingham, is a major collaborator in our studies of gene expression patterns in prostate needle biopsies. This collaboration has allowed us to more fully incorporate high risk minority patients into our study population.

- We will expand our collaborations with Joseph Bigley and his colleagues at Oncomethylome Sciences to translate DNA hypermethylation patterns as tumor markers that can be used to evaluate prostate needle biopsies.

Abstracts Presented at Local, National, and International Meetings

Gaston SM, Kishawi I, **Guerra AL**, **Nadadur RD**, **Kearney MC**, Cheng Y, Meltzer SJ, Kearney GP. The metastatic prostate cancer biomarker miR-141: expression in prostate biopsy tissues. AACR Special Conference on Advances in Prostate Cancer Research. San Diego, CA; January 21, 2009.

Gaston SM, **Guerra AL**, **Meadows J**, **Nadadur RC**, **Kearney MC**, Kearney GP. Molecular biomarker analysis of diagnostic prostate biopsies using tissue print micropeel samples. NIH 2nd Annual Biospecimen Research Network (BRN) Symposium. Bethesda, MA; March 16, 2009.

Gaston SM, Kishawi I, Guerra AL, Cheng Y, Nadadur RC, Kearney MC, Meltzer SJ, Pinsky P, Sorbara L, Srivastava S, Kearney GP. Expression of the metastatic prostate cancer biomarker miR-141 in prostate biopsy tissues. Presented at the annual meeting of the American Assoc for Cancer Research, Denver, CO; April 2009.

Sorbara LR, Kishawi I, Pinsky P, Meltzer S, Franklin W, Bemis L, **Gaston SM**, Rom W, Srivastava S. MicroRNA microarrays for biomarker discovery: Joint EDRN-Agilent project. Presented at the annual meeting of the American Assoc for Cancer Research, Denver, CO; April, 2009.

Gaston SM, Kishawi I, **Guerra AL**, Cheng Y, **Nadadur R**, **Kearney MC**, Pinsky P, D'Andrade P, Sorbara L, Srivastava S, Meltzer SJ and Kearney GP. miRNA profiling in prostate biopsy tissues: Overexpression of the metastatic PrCa biomarker miR-141 in patients with newly diagnosed prostate cancer. NCI 6th Early Detection Research Network (EDRN) Scientific Workshop. Bethesda, MA; September 1, 2009.

Gaston SM, **Guerra AL**, **Meadows J**, Bigley J, Renard I, Louwagie J, Bierau K. Molecular biomarker analysis of clinical prostate biopsy specimens: Tissue print techniques simplify development of DNA methylation marker tests while preserving the FFPE specimen for histology. EORTC-NCI-ASCO Annual Meeting on Molecular Markers in Cancer, Brussels, Belgium; October 16, 2010.

Individual Accomplishments

Sandra M. Gaston

- For the seventh 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.
- For the third consecutive year, I served as the chairperson for grant application review meetings of the NIH National Cancer Institute Special Emphasis Panel "Innovative Technologies for the Molecular Analysis of Cancer" (IMAT) program.
- I was named to three Special Emphasis Panels to review grant applications submitted to RFAs under the Trans-NIH Recovery Act Research Support Program.
- I continued to serve as External Advisor for the City of Hope NIH fellowship training program in Urologic Oncology.
- For the third consecutive year, I served on the EDRN Standing Review Committee which is responsible for reviewing grant applications for EDRN Associate Member Candidates.
- I was awarded a DOD Prostate Cancer Research grant entitled "Biomarkers in the Detection of Prostate Cancer in African Americans".
- I received an industry sponsored research award from Oncomethylome Sciences entitled "DNA Methylation Markers in High Risk Prostate Cancer Biopsies"
- I was named a judge for the 4th AACR Undergraduate Student Caucus and Poster Competition, 2009 American Association for Cancer Research Annual Meeting.

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Accomplishments by Members of the Laboratory

- Rajiv Nadadur received a Bardos Award from the American Association of Cancer Research to attend the national meeting of the association and present the results of some his work in my laboratory. His poster presentation was entitled "Expression of the Metastatic Prostate Cancer Biomarker miR-141 and Other Members of the miR-200 Family in Prostate Biopsy Tissues"

Invited Presentations (Local, National, and International)

Sandra Gaston, PhD

"Expression of the Metastatic Prostate Cancer Biomarker miR-141 in Prostate Biopsy Tissues". American Association for Cancer Research Minisymposium, Denver, CO; April 21, 2009.

"Building the Interface Between Biomarker Discovery and Clinical Application: Profiling Cancer-Associated microRNAs Using Prostate Biopsy Tissue Prints". Agilent Technologies, Santa Clara, CA; July 31, 2009.

"New Approaches to Molecular Biomarker Analysis of Diagnostic Prostate Biopsies". Oncomethylome Sciences, Leuven, Belgium; October 19, 2009.

"Next Generation Cancer Biomarkers". Principal Investigator Research Forum with Clowes Visiting Professor, BIDMC Surgical Research, Boston, MA; November 3, 2009.

"Using Prostate Needle Biopsies for Gene Expression Profiling". Urology Grand Rounds, Lahey Clinic, Burlington, MA; November 4, 2009.

REPORT OF TEACHING

Harvard Medical School Courses and Research Mentorships

- HMS Molecular and Cellular Basis of Medicine (Randall King, MD, PhD, Director), Tutor, Fall 2009.
- Tutorial Mentor for first year tutor Dr. Simo Arredouani, HMS Molecular and Cellular Basis of Medicine, Fall 2009.
- HST Human Pathology (Richard Mitchell MD, Director), Laboratory Instructor, Fall 2009.
- Research mentor to the following students in 2009:

Rajiv Nadadur
Ashley Hlastava
Maria Pellon Consunji
Maria Bonatsakis

MIT Student
Boston College Student
Wellesley Student
University of Connecticut Student

Plans for the Coming Academic Year

New Recruitment Activities

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

We anticipate recruiting a postdoctoral fellow to join our DOD sponsored study of prostate cancer biomarkers in biopsy tissues from African and European American patients.

Educational Activities

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

This year I joined the Harvard-MIT Health Science Technology (HST) Teaching Faculty as a laboratory instructor in the first year Pathology course. I plan to expand my participation in the HST program.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

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

Mosquera JM, Mehra R, Regan MM, Perner S, Genega EM, Bueti G, Connor M, Shah RB, **Gaston SM**, Tomlins SA, Wei J, Kearney MC, Johnson LA, Tang JM, Chinnaiyan AM, Sanda MG, Rubin MA. Prevalence of TMPRSS2-ERG fusion prostate cancer among men undergoing prostate biopsy in the United States. Clin Cancer Res 2009;15 (14):4706-11.

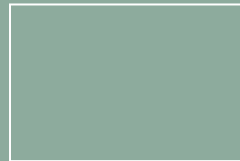
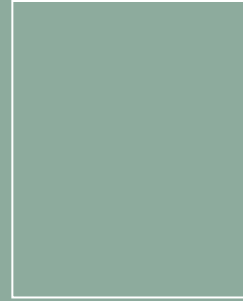
Abstracts

Gaston SM, Guerra A, Meadows J, Bigley J, Renard I, Louwagie J, Bierau K. Molecular biomarker analysis of clinical prostate biopsy specimens: tissue print techniques simplify development of DNA methylation marker tests while preserving the FFPE specimen for histology. Eur J Cancer 2009;7(4): 18A.

RESEARCH SUMMARY

BASIC RESEARCH

Despite that gastric cancer is the 2nd most common cause of cancer deaths worldwide; little is known about its pathogenesis. Thus, our current NIH sponsored research projects are concerned with mechanisms that regulate cancer development and progression in the stomach. Specifically, our focus includes mechanisms that regulate inflammation-induced dysfunction of tight junction organization and permeability in the stomach (barrier disruption), mechanisms that regulate survival and death pathways of gastric epithelial cells, the role of heat shock protein (Hsp) 70 in mucosal protection and its role in gastric cancer progression, and the role of ammonia and glutamate (via epithelia *N*-methyl-D-aspartate receptor activation) in regulating cell physiology in general and during cancer development in the stomach. *Helicobacter pylori* (HP) infection of the stomach is a risk factor for cancer development, so we use HP infection models in collaboration with Dr. James Fox at MIT.



Susan J. Hagen, PhD

LIST OF CURRENT EMPLOYEES

Research Laboratory

Ji Hye Seo, PhD	Sr. Research Fellow
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Core Facilities

Microscopy-Confocal

Lay-Hong Ang, PhD	Confocal Supervisor
Yi Zheng, PhD	Confocal Specialist

Microscopy-Electron Microscopy

Andrea Calhoun, BS	EM Specialist
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Histology

Suzanne White, BS	Supervisor, Research Histotech
Lena Liu, BS	Research Histotech

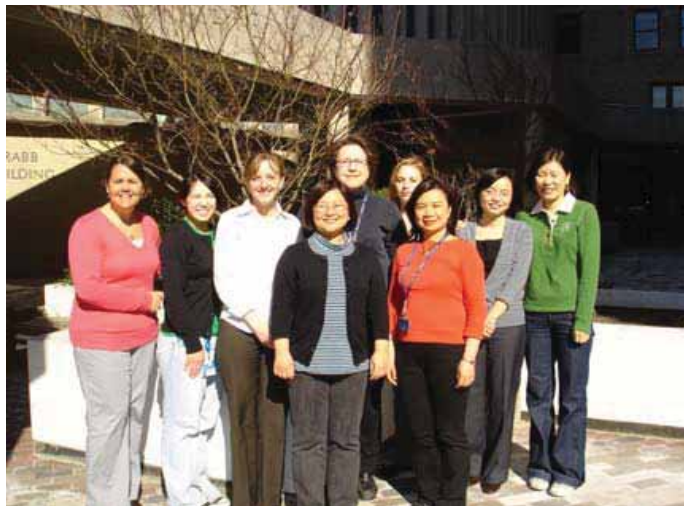
Surgical Research

Wendy Dasgupta, BA, BS	Admin Coordinator
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BASIC RESEARCH CONT'D



Dr. Hagen with the Laboratory and Core Groups

Back (from left): Suzanne White, Elizabeth Christian (until July of 2009), Wendy Dasgupta, Susan Hagen, Andrea Calhoun, Yi Zheng, and JiHye Seo.

Front (from left): Songhua Zhang (until May of 2009) and Lay-Hong Ang.

LIST OF CURRENT FUNDING

“GI mucosal barrier in health and surgical disease”
National Institutes of Health, NIDDK 5 RO1 DK015681-36
Project Period: 2003-2010
PI: Susan Hagen

“Biology of alimentary epithelia in health and disease”
National Institutes of Health, NIDDK P30 DK034854-12
Harvard Digestive Diseases Center Grant
Project Period: 2005-2010
PI: Wayne Lencer, MD (Children’s Hospital)
Subcontract PI: Susan Hagen

RESEARCH GRANTS SUBMITTED AND/OR PENDING FUNDING

“Epithelial cell death in gastric atrophy”
National Institutes of Health, NIDDK 1 R21 DK084196-01
Project Period: 2009-2011
PI: Susan Hagen

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

“Visualization of ATP release”
National Institutes of Health, R01
PI: Wolfgang G. Junger
Co-investigator: Susan Hagen

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

Glutamine protection

In 2009 and in collaboration with George Blackburn and Jin-Rong Zhou (Surgery at BIDMC), we finished a large study that tested whether glutamine protects against HP-induced pathogenesis (below in the list of publications). For this, glutamine was fed as a 5% dietary supplement (1.9% Gln in control and 6.9% Gln in the test diet) to 105 mice that were sham or HP infected and the data were collected and analyzed at 6, 12, and 20 weeks post-infection. We found that the 5% Gln-supplemented diet does not affect body weight, body weight gain, or HP colonization but significantly protects against hyperplasia and inflammation during HP infection in mice. In addition, the cytokine profile was significantly skewed toward a T_H2 -biased response at 6 weeks post-infection, but reverted to a T_H1 response at 12 and 20 weeks post-infection. This work resulted in a number of press releases and journal summaries that include the American Society for Nutrition (May 1, 2009) and Harvard **Science** (May 15, 2009).

The mechanism by which Gln protects against gastric injury may be due to the transcriptional regulation of Hsp expression. Thus, in the past year we initiated studies to explore the role of Hsp 70 expression in cancer progression *in vivo* and *in vitro*. We infected Hsp70^{-/-} mice with HP and collected data at 17, 24, and 34 weeks post-infection. The results showed that cancer progression occurs readily in these knockout mice. We are currently finishing the work on Hsp70^{-/-} mice and cancer progression for publication and the results were submitted in December 2009 for presentation at Digestive Diseases Week 2010.

Tight junction regulation by IL-1 β

Despite taking years of work to complete, we have now demonstrated and published (below in the list of publications) that 1) cultures can be produced from isolated rat chief cells that are > 98% positive for intrinsic factor, a chief cell specific marker; 2) the cultures secrete in an agonist-stimulated manner; 3) production of chief cell cultures requires HGF, which is needed to facilitate proliferation of the isolated cells; and 4) chief cell cultures have a TER of over 2,500 $\Omega \cdot \text{cm}^2$, express occludin, and have very low permeability. Once we had chief cells in culture, we used a mix of T_H1 cytokines (cytomix), containing IL-1 β , IFN- γ , and TNF- α , to show that pro-inflammatory cytokines decreases tight junction integrity in chief cells by reducing transepithelial electrical resistance (TER) and increasing paracellular permeability. Mechanistically the results are quite interesting. In chief cell cultures, the individual cytokines alone do not affect TER or permeability nor do combinations of IFN- γ and IL-1 β or TNF- α and IFN- γ . These results suggest that TNF- α and IFN- γ in the cytomix solution prime cells so that IL-1 β is able to affect tight junction integrity. We determined that this “priming” consists of, at least in part, the transcriptional regulation of IL1RAcP, the accessory protein required for IL-1 signaling. We are currently finishing this work for publication and the results were submitted in December of 2009 for presentation at Digestive Diseases Week 2010.

Administrative Accomplishments

I continued to work as Associate Director for Research in the Department of Surgery. Accomplishments this year were successful completion of, in collaboration with Dr. Per-Olof Hasselgren and with help from Wendy Dasgupta, the “2008 Annual Research Report”. With Wendy’s capable help, we updated the space database for Surgery, maintained HMS appointments and visas, organized space relocations and space backfill, and completed this 2009 Research Report.

I also continued to direct the Microscopy, Histology, and Confocal Core Facilities at BIDMC and to provide oversight and consultation for imaging experiments in the hospital and for members of the Harvard Digestive Diseases Center. In 2009 our center grant was submitted for renewal to the NIH, and I wrote the section for the imaging core B.



Wendy Dasgupta

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Individual Accomplishments

I reviewed grant applications for the ZRG1DKUS-B95S study section and the DKUS-A (58) study section in July 2009.

I served again this year as an elected Councilor for the GI section of the American Physiological Society. This post is for the Steering Committee and will be from 2008-2011. As one job on the committee, I was assigned to run the awards banquet at Experimental Biology in April of 2009, which was at "The Court of Two Sister's" in New Orleans, LA.

I wrote a revised R21 application to study cell death mechanisms in stomach epithelial cells and it received an excellent score—this application is pending a funding decision.

On behalf of the Microscopy core, I was awarded a large shared instrument grant to purchase a new electron microscope. A lot of research was required for this purchase, which took most of the year to accomplish.

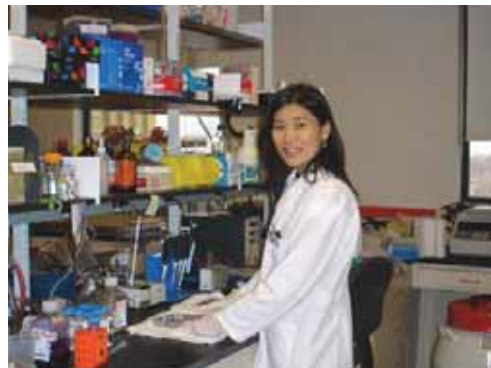
Invited Presentations

"Overview of the BIDMC Morphology Core". Young Investigators Think Tank, Beth Israel Deaconess Medical Center. Jan 22, 2009.

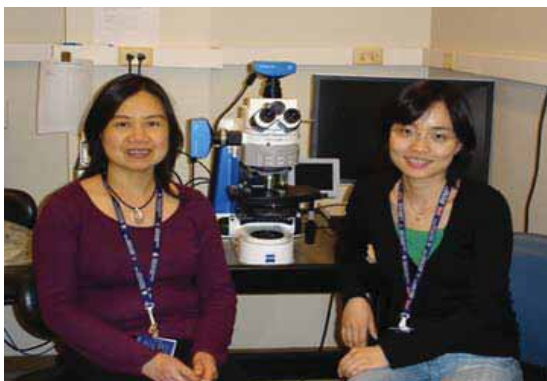
REPORT OF TEACHING

Undergraduate and Medical School Courses

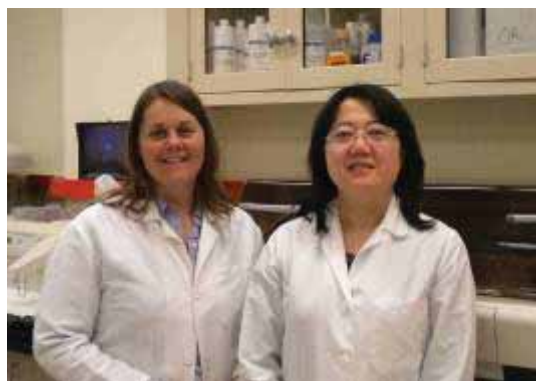
I taught in the Human Body course (IN753.0) at Harvard Medical School from 10/2009- 12/2009 as co-director of the Cannon Society histology laboratory.



JiHye Seo



Lay-Hong Ang (left) and Yi Zheng (right) using the confocal microscope.



Suzanne White (left) Lena Liu (right) in the Histology Core.

BIBLIOGRAPHY (JANUARY-DECEMBER 2009)

Original Articles

Hagen SJ, Ohtani M, Zhou J-R, Taylor NS, Rickman B, Blackburn GL, Fox JG. Inflammation and foveolar hyperplasia are reduced by dietary glutamine during *Helicobacter pylori* infection in the mouse stomach. *J Nutr* 2009; 139(5):912-8.

Kang HW, Ribich S, Kim BW, **Hagen SJ**, Bianco AC, Cohen DE. Increased thermogenesis and turnover of brown fat in mice lacking phosphatidylcholine transfer protein/StarD2. *J Lipid Res* 2009; 50(11):2212-21.

Tashima K*, Zhang S*, Ragasa R, , Nakamura E, Muvaffak A, **Hagen SJ**. Hepatocyte growth factor regulates the development of highly pure cultured chief cells from rat stomach by stimulating chief cell proliferation, in vitro. *Am J Physiol Gastrointest Liver Physiol* 2009;296(2):G319-G329. *Contributed equally to the work.

Original Articles (submitted or in press)

Shanahan MT, Vidrich A, Shirafuji Y, Dubois CL, Henschen-Edman A, **Hagen SJ**, Cohn SM, Ouellette AJ. Elevated expression of Paneth cell CRS4C in ileitis-prone samp1/YitFc mice: regional distribution, subcellular localization, and mechanism of action. *J Biol Chem* 2009; in press.

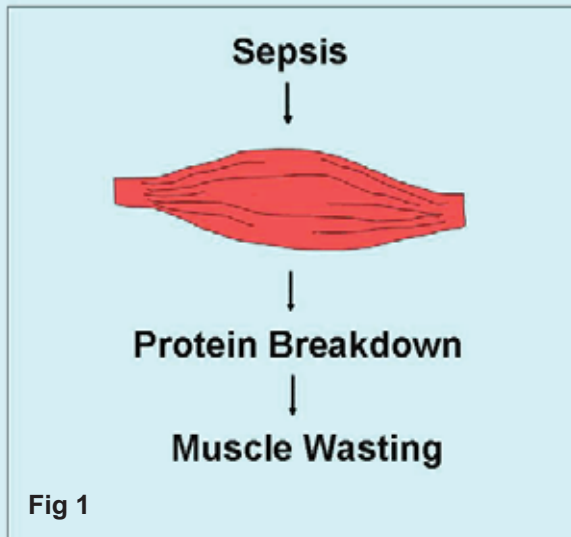


Andrea Calhoun sitting at the JEOL 1200EX II electron microscope

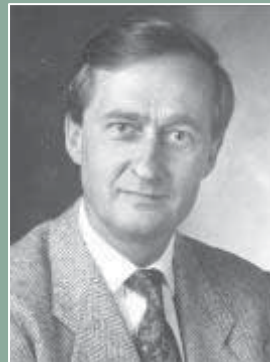
RESEARCH SUMMARY

BASIC RESEARCH

The research in our group is focused on mechanisms regulating the catabolic response to sepsis and injury in skeletal muscle. Sepsis and injury (and a number of other conditions as well, including cancer, AIDS, uremia, and starvation) are associated with muscle wasting (**Fig 1**), mainly reflecting ubiquitin-proteasome-dependent degradation of the myofibrillar proteins actin and myosin. This response in skeletal muscle has severe clinical consequences, including muscle weakness and fatigue, delayed ambulation with risk of thromboembolic and pulmonary complications and prolonged stay in the intensive care unit. Our research supports a model in which myofilaments are released from the sarcomere through a calcium/calpain-dependent mechanism followed by ubiquitination and degradation of actin and myosin by the 26S proteasome. The gene expression of calpains and several components of the ubiquitin-proteasome system, in particular



the ubiquitin ligases atrogin-1 and MuRF1, is upregulated in atrophying muscle, supporting the concept that increased gene transcription is an integral part of muscle wasting mechanisms.



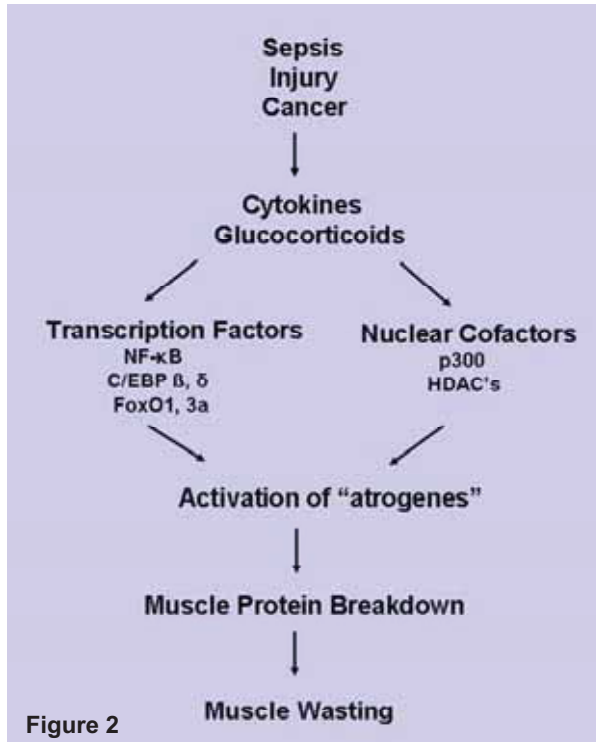
Per-Olof Hasselgren, MD, PhD

LIST OF CURRENT EMPLOYEES

Patricia Gonnella, PhD	Assistant Professor of Surgery
Ira Smith, PhD	Instructor in Surgery
Nima Alamdari, PhD	Research Fellow in Surgery
Steven Tizio, MD	Research Fellow in Surgery/Surgical Resident
Zaira Aversa, MD	Research Fellow in Surgery
Sally Gwin, BS	Administrative Coordinator

BASIC RESEARCH CONT'D

Currently, the transcriptional regulation of genes in the ubiquitin-proteasome pathway is examined. In particular, the roles of the transcription factors C/EBP β and δ and NF- κ B as well as the nuclear co-factors p300 and PGC-1 α and β in the regulation of atrogin-1 and MuRF1 expression are examined. In addition, the role of calcium in sepsis-induced and glucocorticoid-regulated muscle proteolysis is examined, especially with regards to changes in store-operated calcium entry and regulation of calcium-calmodulin protein kinase II and PI3K/Akt/GSK3 β signaling.



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

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

degradation in atrophying muscle is complex and factors influencing protein degradation in catabolic muscle are regulated at multiple levels.

LIST OF CURRENT FUNDING

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

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

"C/EBP, Atrogin-1, and muscle wasting"
National Institutes of Health, R56 NR-08545
Project Period: 2009-2010
PI: Hasselgren, Per Olof

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

“Asthma and glucocorticoid-induced muscle wasting and the potential role of hyperacetylation”

American Asthma Foundation

PI: Hasselgren, Per Olof

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Invited Presentations

Invited Speaker: “Glucocorticoids and the molecular regulation of muscle wasting”. The 5th Muscle Cachexia Meeting. Barcelona, Spain. December 2009.

The Hasselgren Research Team

From left to right: Patricia Gonnella, Nima Alamdari, Steven Tizio, Zaira Aversa and Ira Smith



REPORT OF TEACHING

Graduate School and Graduate Medical Courses

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

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Goldfarb M, **O’Neal P**, Shih J, Hartzband P, Connolly J, **Hasselgren PO**. Synchronous parathyroid carcinoma, parathyroid adenoma, and papillary thyroid carcinoma in a patient with severe and longstanding hyperparathyroidism. *Endocr Pract* 2009;15:463-8.

O’Neal P, Poylin V, Mowschenson P, Parangi S, Horowitz G, Pant P, **Hasselgren PO**. When initial postexcision PTH level does not fall appropriately during parathyroidectomy – what to do next? *World J Surg* 2009;33:1665-73.

O’Neal P, **Alamdari N**, **Smith I**, Poylin V, Menconi M, **Hasselgren PO**. Experimental hyperthyroidism in rats increases the expression of the ubiquitin ligases atrogin-1 and MuRF1 and stimulates multiple proteolytic pathways. *J Cell Biochem* 2009;108:963-73.

Original Articles (submitted or in press)

Gonnella P, **Alamdari**, Petkova V, **Hasselgren PO**. Dexamethasone-induced atrogin-1 expression, protein degradation, and atrophy in cultured L6 muscle cells are C/EBP beta-dependent. 2009; submitted.

Itagaki K, Menconi M, Antoniu B, Zhang Q, **Gonnella P**, Soybel D, Hauser C, **Hasselgren PO**. Dexamethasone stimulates store-operated calcium entry and protein degradation in cultured L6 myotubes through a phospholipase A2-dependent mechanism. *Am J Physiol Cell Physiol* 2009; in press.

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Division of General Surgery

Menconi M, Arany Z, **O'Neal P, Alamdari N, Smith IJ, Hasselgren PO**. Sepsis and glucocorticoids downregulate the expression of the nuclear cofactor PGC-1 beta in skeletal muscle. 2009; submitted.

O'Neal P, Mowschenson P, Connolly J, **Hasselgren PO**. Large parathyroid tumors have an increased risk for atypia and carcinoma. 2009; submitted.

Smith IJ, Alamdari N, O'Neal P, Gonnella P, Aversa Z, Hasselgren PO. Sepsis increases the expression and activity of the transcription factor Forkhead Box O 1 (FOXO1) in skeletal muscle by a glucocorticoid-dependent mechanism. Int J Biochem Cell Biol 2009; in press.

Smith IJ, Aversa Z, Alamdari N, Petkova V, **Hasselgren PO**. Sepsis downregulates myostatin mRNA levels without altering myostatin protein levels in skeletal muscle. 2009; submitted.

Reviews, Chapters, and Editorials

Alamdari N, O'Neal P, Hasselgren PO. Curcumin and muscle wasting – a new role for an old drug? Nutrition 2009;25:125-29.

RESEARCH SUMMARY

BASIC RESEARCH

Our laboratory has continued to study the regulation of innate immunity in trauma with an important emphasis on translational biology. In particular, our major focus concerns the ways in which calcium influx leads to neutrophil (PMN) activation and organ failure after trauma. Our lab discovered the role of lipid metabolites, such as sphingosine 1-phosphate (S1P), as a PMN second messenger, and are currently investigating the hypothesis that S1P triggers calcium signaling and thus PMN conversion to an inflammatory phenotype, which consequently predisposes to organ failure. We have also established systems to evaluate PMN endothelial cell interactions *in vitro* through real time permeability changes, so we can routinely perform *ex vivo* experiments that evaluate interactions between PMN and endothelial cells – the two major cell types involved in inflammatory lung injury.

We have now also established that molecular patterns from mitochondria act as DAMPs (damage-associated molecular patterns, AKA ‘alarmins’) when they are released from injured cells. The DAMPs found so far include mitochondrial DNA that acts on TLR9 and formylated peptides that activate immunity through the formyl peptide receptors (FPR1, FPRL-1 and FPRL-2). These exciting new findings will be published in the March 4 issue of **Nature**. These insights open entire new areas of translational investigation into many disease processes where cell damage and death predispose to inflammation. Mitochondrial DAMPs cause PMN and endothelial cell activation *in vitro* and induce lung injury *in vivo*. These important new finding will lead to better understanding of the pathways by which tissue injury leads to inflammation and organ failure in a wide variety of illnesses.



CARL J. HAUSER, MD

LIST OF CURRENT EMPLOYEES

Kiyoshi Itagaki, PhD	Instructor in Surgery
Qin Zhang, MD	Laboratory Manager
Tolga Sursal, BS	Research Fellow
	Student

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LIST OF CURRENT FUNDING

“Sphingosine-1-phosphate and PMN Ca^{2+} entry in trauma”

National Institutes of Health, R01GM059179

Project Period: 03/01/2006–02/28/2010

PI: Carl J Hauser

“Mitochondrial debris as a discriminator between inflammatory and infectious complications of blast Injuries – the enemy within...”

Department of Defense Deployment Related Medical Research Program

Project Period: 06/01/2009–12/31/2010

PI: Carl J Hauser

“Endothelial cell calcium signaling, sphingosine1-phosphate and ARDS”

BIDMC Department of Surgery/Harvard Medical School

Fellowship Program for Scholars in Medicine

Project Period: 07/01/2008–06/30/2009

PI: Kiyoshi Itagaki

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

“Mitochondrial DAMPS and inflammation after injury”

National Institute of General Medical Sciences (NIH / NIGMS)

PI: Carl J. Hauser

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Invited Presentations

Carl Hauser, MD

“DAMPs and PAMPs: The Role of Mitochondria in SIRS and sepsis”. Surgical Biology Club 3. American College of Surgeons. 2009.

“Moderator: Owen Wangenstein Forum on Basic Surgical Problems in Critical Care I”. American College of Surgeons. 2009.

“General Surgery Review Course: Hemodynamics, Shock, Sepsis and Resuscitation”. American College of Surgeons. 2009.

“DAMPs, PAMPs, Sepsis and SIRS”. Harvard Trauma Symposium. Boston, MA. 2009.

BIBLIOGRAPHY (JANUARY-DECEMBER 2009)

Original Articles

Dutton RP, **Hauser CJ**, Boffard KD, Dimsitts J, Bernard G, Holcomb J, Leppaniemi A, Tortella B, Bouillion B. Scientific and logistical challenges in designing the CONTROL trial: Recombinant factor VIIa in severe trauma patients with refractory bleeding. *Clinical Trials* 2009;6(5):467-79.

Hoyt DB, Dutton RP, **Hauser CJ**, Hess JR, Holcomb JB, Kluger Y, Mackway-Jones K, Parr MJ, Rizoli SB, Yukioka T, Bouillion B. Management of coagulopathy in the patients with multiple injuries: results from an international survey of clinical practice. *J Trauma* 2008;65(4):755-65.

Original Articles (submitted or in press)

Doucet DR, Bonitz RP, Feinman R, Colorado I, Ramanathan M, Feketeova E, Condon M, Machiedo GW, **Hauser CJ**, Xu DZ, Deitch EA. Estrogenic hormone modulation abrogates changes in red blood cell deformability and neutrophil activation in trauma hemorrhagic shock. J Trauma 2009; in press.

Itagaki K, **Hauser CJ**. Sphingosine kinase inhibition alleviates endothelial permeability induced by thrombin and activated neutrophils. Shock 2009; in press.

Itagaki K, Menconi M, Antoniu B, Zhang Q, Gonnella P, Soybel D, **Hauser CJ**, Hasselgren PO. Dexamethasone stimulates store-operated calcium entry and protein degradation in cultured L6 myotubes through a phospholipase A2 -dependent mechanism. Am J Physiol Cell Physiol 2009; in press.

Zhang, Q, Itagaki K, **Hauser CJ**. Mitochondrial DNA activates neutrophils via TLR9 and p38 MAP-Kinase. Shock 2009; in press.

Zhang, Q, Raoof, M, Sursal, T, Chen Y, Sumi Y, Junger W, Brohi K, Itagaki K, **Hauser CJ**. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2009; in press.

Abstracts

Hauser CJ, Boffard K, R. Dutton, G. Bernard et al. Efficacy and safety of recombinant activated factor VII in the management of hemorrhagic shock due to trauma. for the CONTROL Study Group. J Throm Haemostasis 2009; 7 (Supplement 2): OC-TH-069.

Zhang Q, Itagaki K, **Hauser CJ**. Mitochondrial DNA activates neutrophils via TLR9 and p38 MAPK. Shock 2009; 31(S1) P2.

Zhang Q, Itagaki K, **Hauser CJ**. Circulating mitochondrial DNA is increased by trauma/hemorrhagic shock. Shock 2009; 31(S1) P82.

RESEARCH SUMMARY

INNOVATION AND EDUCATION RESEARCH

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 led to innovative endoscopic operations, better models and simulators, and a new understanding of hormonal regulation of obesity.

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

BIDMC was the first Level I Comprehensive Education Institute accredited by the American College of Surgeons in New England. In 2009, BIDMC reaccredited SASC. We continue to collaborate with the Nice Medical School Simulation Center in France.

In collaboration with Dr. Chuttani of GI Endoscopy (Department of Medicine at BIDMC) we have developed new natural orifice transluminal endoscopic approaches to pancreatic resection in an animal model. N.O.T.E.S. techniques may achieve comparable outcomes with faster recuperation.

Collaborative efforts have also worked toward developing better simulators. With S. De, PhD at RPI we have been funded by an NIH R01 grant to create a virtual reality laparoscopic simulator for teaching the technique of the laparoscopic adjustable gastric band using virtual reality and haptic feedback. The newly developed Point-Associated Finite Field (PAFF) approach provides users a smooth visual display and realistic touch response.



Daniel B. Jones, MD, MS, FACS

LIST OF CURRENT EMPLOYEES

Bariatric Program

George Blackburn, MD, PhD	Advisor
Benjamin E. Schneider, MD	Surgeon
Maritza Avedaño	Administrator
Edward Hatchigian, MD, MS	Medical Director
Linda Trainor, RN, BSN	Nurse Educator
Sue Walker, LICSW, MSW	Social Worker
Kelly Moore, RD, LDN	Dietician
June Skoropowski, RD, LDN	Dietician
Amanda Bryant	Program Admin. Assist
Yulissa Sepulveda	Program Admin. Assist
Elizabeth Shenoy	Administrative Assistant
Lisa M. Melville, MS, APRN, BC	Platinum Service General Surgery NP

Simulation and Skills Center

David Fobert	Administrator
Alex Derevianko, MD, MA	Research Assistant
Daren Tavernelli	Coordinator
Ted Korelitz, PhD	Volunteer

Section of Minimally Invasive Surgery

Benjamin E. Schneider, MD
Jonathan Critchlow, MD
Robert Lim, MD
Henry Lin, MD
Jamie Adair, MD
Robert Andrews, MD

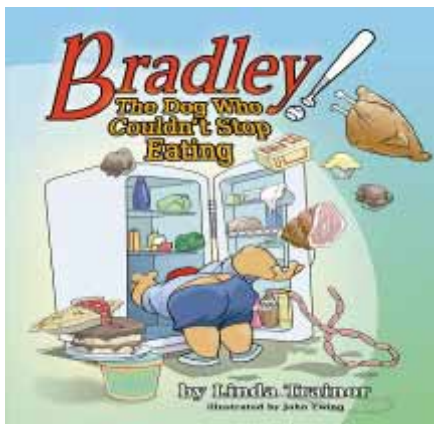
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BASIC RESEARCH CONT'D

We have sought further NIH R01 funding to create a N.O.T.E.S. simulator. Drs. Henry Lin and Jamie Adair have already applied this technology to a VR version (V-BLAST) of Fundamentals of Laparoscopy (FLS) and validated this prototype at SASC. We have applied engineering to create a prototype simulator for teaching laparoscopic adjustable gastric banding operation.

Dr. Robert Andrews and Ted Korelitz have collaborated with industry to create three dimensional models of the breast and aorta using jet printers. We anticipate this type of modeling will change the way surgeons train, provide consent, and perform surgery.



Through the **Program for Obesity and Weight Loss Surgery** we have strived to increase our knowledge of obesity and establish best practice guidelines for bariatric surgery. With Drs. Steven Loring and Stephanie Jones (Department of Anesthesia at BIDMC), we are investigating the use of esophageal pressure measurements as a surrogate of pleural pressure to characterize the effects of obesity on respiratory function. With Dr Christine Wee will are studying the patient's assessment of risk and benefit of weight loss surgery with R01 funding. Drs. George Blackburn, Robert Lim and Jamie Adair have studied impact of exercise on weight loss surgery. In 2009, BIDMC reaccredited with the ACS Bariatric Network.

Educational efforts include a new children's book by Linda Trainer, RN entitled "Bradley-The Dog Who Couldn't Stop Eating" (left). This book was embraced by Project Head Start to teach good health.

COLLABORATORS

Benjamin E. Schneider, MD and Jonathan Critchlow, MD (Surgery, Section of MIS, BIDMC); Steven D. Schwartzberg, MD (Cambridge Health Alliance); George Blackburn, MD, PHD (Surgery, Section of Nutrition, BIDMC); Steven Loring, MD, PHD and Stephanie Jones, MD (Anesthesiology, BIDMC); Ram Chuttani, MD, Christina C. Wee, MD, MPH, and Christos Mantzoros MD (Medicine, BIDMC); Caroline Cao, PhD and Grace Zhou, PhD (Tufts, Human Performance Lab); Suvranu De, ScD (Mechanical, Aerospace and Nuclear Engineering, Rensselaer Polytechnic Institute); Robert Andrews, MD; Jamie Adair, MD; Robert Lim, MD, Henry Lin, MD (Surgery, MIS Clinical Fellows)

LIST OF CURRENT FUNDING

"Physically realistic virtual surgery"
NIH/NIBIB, R01 EB005807-01
Project Period: 06/01/2006-03/31/2010
PI: Suvranu De, PhD
Collaborator: Daniel Jones

"Evaluation of endostapled anastomosis for laparoscopic gastric bypass"
United States Surgical Industry Funding
Project Period: 2007-2009
PI: Daniel Jones

"Understanding how patients value bariatric surgery"
NIDDK, R01 DK073302-01
Project Period: 2007-2009
PI: Christina Wee
Collaborator: Daniel Jones

“AP Lap-Band”

Allergan

Project Period: 2007-2009

PI: Daniel Jones

“Development of a pancreatic tumor animal model and evaluation of the long-term safety of NOTES tumor enucleation as a multidisciplinary approach NOSCARTM”

Project Period 2007-2009

PI: Kai Maithes

Collaborator: Daniel Jones

CRICO-Simulation

Project Period 2009-2010

PI: Daniel Jones

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

- We developed a simulator for teaching the laparoscopic adjustable gastric band operation (right) using VR in collaboration with Dr. De at RPI. The system integrates haptic feedback (sense of touch).



Abstracts Presented at Local, National and International Meetings

Lin H, Ganesh S, Sankaranarayanan G, Arikatla VS, Mulcare M, Zhang L, De S, Cao C, Schneider B, Derevianko A, Lim R, Schwaitsberg S, **Jones DB**. Advances in virtual reality FLS (Fundamentals of Laparoscopic Skills). Presented (as a poster) at SAGES, Phoenix, AZ; April 22, 2009.

Matthes K, Thakker SJ, Lee SH, Lim RB, Janschek J, Devedevianko A, Jones SB, **Jones DB**, Chuttani R. Development of a pancreatic tumor animal model and assessment of feasibility of NOTES tumor enucleation as a multidisciplinary approach – a NOSCARTM funded project. Presented (as a poster) at SAGES, Phoenix, AZ; April 2009.

Conrad C, Konuk Y, Coa C, Warshaw A, Rattner D, **Jones DB**, Gee D. Auditory stress versus mental loading: the effects on laparoscopic motor skill performance. Presented (as a poster) at SAGES, Phoenix, AZ; April 2009.

Lim R, Barrios L, **Jones DB**, Rooks D, Lin H, Schneider B, Dushay J, Corsuro C, Blackburn G. Preoperative exercise on outcomes in bariatric surgery. Presented (as a poster) at SAGES, Phoenix, AZ; April 2009.

Dixon J, **Jones DB**, Oefelein MG. Obesity and weight-loss quality-of-life (OWLQOL) improvement after adjustable gastric banding – 1 year interim results of the APEX study. ASMBS. American Society for Metabolic and Bariatric Surgery (ASMBS) 26th Annual Meeting, Grapevine, TX; June 21, 2009.

Zhou X, Derevianko A, Schneider B, **Jones DB**. Statistical modeling for proficiency assessment on virtual surgical simulators. AAMC. Boston, MA; November 11, 2009.

Individual Accomplishments

- Board of Directors, Association Surgical Education, ASE
- Board of Governors, Society American Gastrointestinal & Endoscopic Surgeons, SAGES
- Vice Chair, ACS Bariatric Advisory Board
- Nominating Committee, SSAT
- Chair, Quality, Outcomes & Safety Committee, SAGES
- Chair, Simulation Committee, ASE

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Individual Accomplishments Cont'd

- ASE Foundation Trustee
- Dinner Chair, Boston Surgical Society
- McEwen Surgery Visiting Professor Lectureship, The UK School of Medicine – Wichita
- Tator Lecture, Canadian University Surgeons
- Visiting Professor, Nice Medical School, Nice, France
- MIS Fellow, Henry Lin, MD awarded second place at SAGES International Top Gun competition

Invited Presentations

Local

“Incorporating simulation into teaching”. Principles of Medical Education: Maximizing Your Teaching Skills, BIDMC, HMS. Boston, MA. 2009.

“Postoperative considerations”. Surgical treatment of severe obesity CRICO, FLS Postgraduate Course for GYN, Practical Approaches to Obesity, HMS. Cambridge, MA. 2009.

“Rationale of the FLS Program”. CRICO, FLS Postgraduate Course for Urologists. Boston, MA. 2009.

“Is it safe? How to make a LSG the safest approach.” Laparoscopic Gastrectomy Postgraduate Course. Boston, MA. 2009.

“Weighing in on obesity surgery”. New England Baptist Hospital, Medicine Grand Rounds. Boston, MA. 2009.

“Weighing in on obesity”.

“Big cases, gaining skills, medical practicing, teamwork and disclosure of bad news”.

“Weight loss surgery cures diabetes too”.

“Betsy Lehman Center for patient safety and error reduction”.

Cassatt RRG Holding Company, Caring for Patients of Size: Patient Safety and Best Practices. Malvern, PA. 2009.

“Surgical approaches to the management of diabetes”. Joslin Advances in Diabetes, Boston, MA. 2009.

National

“ACS educational institute accreditation requirements”.

“MIS simulation: never too early to start”.

“The Current Status and Future of Surgical Simulation - from the Box-trainer to the Human Simulator”.

“Using simulation for medical students”.

Association for Surgical Education, Surgical Education Week. Salt Lake City, UT. 2009.

“Bariatric surgery: Case Presentations”.

“Safer surgery with simulation”.

McEwen Surgery Visiting Professor Lectureship, The University of Kansas School of Medicine – Wichita, Grand Rounds. Wichita, KA. 2009.

“Betsy Lehman Center for patient safety and medical error reduction”. Society of American Gastrointestinal & Endoscopic Surgeons, Best practices for surgical treatment of obesity session. Phoenix, AZ. 2009.

“Centers of excellence concept and Betsy Lehman guidelines”. American Society of Metabolic and Bariatric Surgery, Essentials of bariatric Surgery for Surgeons and Primary Clinicians. Grapevine, TX. 2009.

“Crisis and team training in the simulated OR”. Society of American Gastrointestinal & Endoscopic Surgeons, Surgical education – from here to beyond. Educators Luncheon. Phoenix, AZ. 2009.

"Is bariatric surgery the safest? How can we make it safer?" Annual Surgery of the Foregut Symposium, Coral Gables, FL. 2009.

"SAGES video offerings: changing the format of video education". Society of American Gastrointestinal & Endoscopic Surgeons, From FLS to the web learning center panel: a spectrum of SAGES offerings to enhance your knowledge and skills in MIS. Phoenix, AZ. 2009.

"Science of obesity". Moderator: American College of Surgeons, Surgical Forum. Chicago, IL. 2009.

"Simulation training for laparoscopic colon resection." Society of American Gastrointestinal & Endoscopic Surgeons, Colorectal postgraduate course. Phoenix, AZ. 2009.

"Single-incision laparoscopic surgery, flexible endoscopy and emerging endoluminal procedures".

"Technique of balloon dilation for stomal stenosis."

American Society of Metabolic and Bariatric Surgery, ASMBS/SAGES Postgraduate course.

"Intraoperative Considerations". American College of Surgeons, FLS PG course. Grapevine, TX. 2009.

International

"Abdominal hernia: minimally invasive repair".

"Access and use of simulators for resident education".

"Complications of Bariatric surgery".

"Safer surgery with simulation".

"Tips on difficult laparoscopic inguinal hernia repair".

Mexican Association Endoscopic Surgery. Acapulco, Mexico. 2009.

"Alternatives to gastric bypass for the morbidly obese." 22nd Annual Meeting of Japan Society for Endoscopic Surgery. Tokyo, Japan. 2009.

"Bucking the trend toward more invasive surgery: The US experience."

"Weighing up risk versus benefit: What is the right surgical procedure."

Metabolic Surgery Expert Meeting. Paddington, England. 2009.

"Gastric banding - a procedure in decline? A different perspective".

"Gastric banding – No 1 Procedure in the USA. Managing the load within a large US practice".

14th World Congress of the International Federation for the Surgery Obesity and Metabolic Disorders. Paris, France. 2009.

"Laparoscopic hernia repair education." Canadian Association of General Surgeons, CAGS Symposium, Abdominal Wall Hernia Repair – Controversies, Techniques and Outcomes. Victoria, B.C. 2009.

"Role of centre accreditation and patient safety in bariatric surgery." Imperial College, St Mary's Hospital. London, England. 2009.

"Safer surgery through simulation".

"Surgical simulation: the solution to training and safety or a promise unfulfilled".

Charles Tator Lecturer at the Annual Symposium for the Canadian Association of University Surgeons (CAUS). Victoria, B.C. 2009.

REPORT OF TEACHING

CME Courses

CME Course Director

"Surgical simulation from box trainer to the human simulator". ASE

"Fundamentals of laparoscopy for GYN and urology". CRICO-RMF SAGES

"Fundamentals of laparoscopy for thoracic and vascular surgery". CRICO-RMF SAGES

Associate Course Director

21st annual CME course on "Practical approaches to the treatment of obesity".



BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Hutter MW, **Jones DB**, Riley S, Snow R, Cella RJ, Schneider BE, Clancy K. Best practice updates for weight loss surgery data collection. Obesity 2009;17:924-8.

Lim Y, Deo D, Singh TP, **Jones DB**, De S. In situ measurement and modeling of biomechanical response of human cadaveric soft tissues for physics-based surgical simulation. Surg Endosc 2009;23:1298-1307.

Powers K, Rehrig S, Schwaitzberg SD, Callery MP, **Jones DB**. Seasoned surgeons assessed in a laparoscopic crisis. J Gastrointest Surg 2009;13:994-1003.

Tsuda S, Barrios L, Schneider B, **Jones DB**. Factors affecting rejection of bariatric patients from an academic weight loss program. Surg Obes Relat Dis 2009;5:199-202.

Original Articles (submitted or in press)

Barrios L, Tsuda S, Derevianko A, Barnett S, Moorman D, Cao CL, Karavas AN, **Jones DB**. Framing family conversation after early diagnosis of iatrogenic injury and incidental findings. Surg Endosc 2009; in press.

Conrad C, Konuk Y, Werner P, Coa C, Warshaw A, Rattner D, **Jones DB**, Gee D. The effect of defined auditory conditions vs mental loading on the laparoscopic motor skill performance of experts. Surg Endosc 2009; in press.

Derevianko A, Schwaitzberg S, Tsuda S, Barrios L, Brooks D, Callery M, Dwyer LK, Fobert D, Rattner D, **Jones DB**. Malpractice carrier underwrites FLS training and testing: benchmark for patient safety. Surg Endosc 2009; in press.

Ellsmere J, Mahadevan A, Kellsher T, Jones DB, Chuttani C, Plaskow D. EUS-guided radiotherapy markers for gastrointestinal malignancies. Gastrointest Endosc 2009; in press.

Manning WJ, Jhayeri RR, Pond KK, Kissinger KV, Goepfert L, Schneider B, **Jones DB**. Cardiac remodeling after substantial weight loss: a prospective cardiac magnetic resonance study following bariatric surgery. SOARD 2009; in press.

Nguyen NT, Pomp A, Needleman B, Mikami D, Provost D, Scott D, **Jones DB**, Gallagher S, Dakin G, Gagner M, Murr M. Impact of staple height on the gastro-jejunostomy during laparoscopic gastric bypass: a multicenter prospective randomized trial. SOARD 2009; in press.

Shankaranarayanan G, Lin H, Jones DB, Sreekanth A.V., Mulcare M, Zhang L, Derevianko A, Lim R, Fobert D, Cao C, Schwaitzberg S, De S. Preliminary face and construct validation study of a virtual basic laparoscopic skill trainer. JLAST 2009; in press.

Reviews, Chapters and Editorials

Blackburn GL, Hutter MM, Harvey AM, Apovian CM, Boulton HR, Cummings S, Fallon JA, Greenberg I, Jiser ME, **Jones DB**, Jones SB, Kaplan LM, Kelly JJ, Kruger RS Jr, Lautz DB, Lenders CM, Lonigro R, Luce H, McNamara A, Mulligan AT, Paasche-Orlow MK, Perna FM, Pratt JS, Riley SM Jr, Robinson MK, Romanelli JR, Saltzman E, Schumann R, Shikora SA, Snow RL, Sogg S, Sullivan MA, Tarnoff M, Thompson CC, Wee CC, Ridley N, Auerbach J, Hu FB, Kirle L, Buckley RB, Annas CL. Expert panel on weight loss surgery: executive report update. *Obesity* 2009;17:842-62.

Jones DB. Health economics. In: Jones SB, **Jones DB**, editors. *Obesity surgery: patient safety and best practices*. Cine-Med Publishing; CT; 2009, p. 117-21.

Kelly J, Shikora S, **Jones DB**, Hutter MH, Robinson MK, Romanelli J, Buckley F, Lederman A, Blackburn G, Lautz D. Best practice updates for surgical care in weight loss surgery. *Obesity* 2009; 17: 863-70.

Powers K, Rehrig ST, Owers K, Jones DB. Safer surgery through simulation. In: Jones SB, Jones DB (editors). *Obesity surgery: patient safety and best practices*. Cine-Med Publishing; CT; 2009, p. 355-361.

Rehrig ST, Powers K, **Jones DB**. Simulators and simulation. In: Soper NJ, Swanstrom LL Eubanks S, editors. *Mastery of endoscopic and laparoscopic surgery*. 3rd ed. Lippincott, Williams, and Wilkins; New York; 2009, p. 55-68.

Tsuda S, Scott D, Doyle J, **Jones DB**. New technologies, more complex procedures, and a host of external constraints have changed where and how surgical skills are taught. *Curr Probl Surg* 2009 Apr;46(4):267-9.

Tsuda S, Scott D, Doyle J, **Jones DB**. Surgical skills training and simulation. *Curr Probl Surg* 2009; 46(4):271-370.

Reviews, Chapters and Editorials (submitted or in press)

Barrios L. **Jones DB**. Financial impact of obesity. In: Preedy VR, editor. *Handbook of disease burdens and quality of life measures*. Berlin: Springer-Verlag. 2009; in press.

Jones SB, Schumann R, **Jones DB**. Management in the post anesthesia care unit (PACU): anesthetic and surgical complications. In: Alvarez A, Brodsky JB, Lemmens H, Morton J, editors. *Morbid obesity: peri-operative management* 2nd edition, Cambridge University Press, UK. 2009; in press.

Lim R, Blackburn G, **Jones DB**. Benchmarking best practices in weight loss surgery. *Curr Probl Surg* 2009; in press.

Lim R, **Jones DB**. Ventral hernia. In Ashley S, Vernon A, editors. *Atlas of minimally invasive surgery*, Lippincott. 2009; in press.

Lin H, **Jones DB**. Surgery for peptic ulcer disease. In: Talley N, editor. *Practical gastroenterology and hepatology*, Wiley-Blackwell, Oxford, UK. 2009; in press.

Lin K, Sillin L, **Jones DB**. American College of Surgeons' accreditation of education institutes. In Tsuda S, Scott D, **Jones DB**, editors. *Textbook of simulation, skills and team training*. Connecticut; Cine-Med Publishing. 2009; in press.

Books, Monographs, and Textbooks

Jones SB, **Jones DB**. *Obesity surgery: patient safety and best practices*. Cine-Med Inc. CT Woodbury; 2009.

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Books, Monographs, and Textbooks (submitted or in press)

Jones DB, Torsten A, Schneider B. Atlas of metabolic and weight loss surgery. Cine-Med 2009;in press.

Tsuda S, Scott DJ, **Jones DB**. Textbook of simulation, skills and team training. Cine-Med Inc, Woodbury, CT; in press.

Clinical Communications

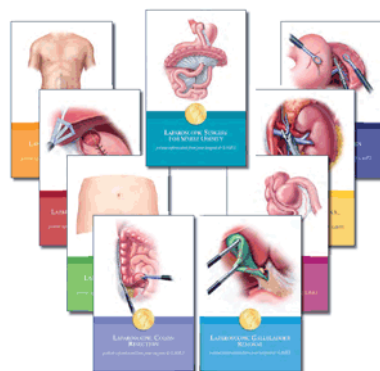
Bhojru S, Dixon JB, Fielding G, Ren C, Patterson E, Grossbard L, Shayani V, Bessler M, Voellinger D, Helmuth B, Cywes R, Ehrlich TB, **Jones DB**, Watkins BM, Ponce J, Brengman M, Schroder G. Safety and effectiveness of bariatric surgery: Roux-en-Y Gastric Bypass is superior to gastric banding in the management of morbidly obese patients. A response. Patient Safety in Surgery 2009;3(17):1-4.

Davis G, DeMaria E, **Jones DB**, Nguyen N, Pomp A. Approaching hiatal hernias during bariatric procedures: what to do? General Surgery News 2009;36(3):24-5.

Gould J, **Jones DB**. SAGES 2009 panel report: best practices for the surgical treatment of obesity. Bariatric Times 2009;6(8):13-8.

Jones DB. Report of the 2008 education committee panel on "teaching safety in the OR". J Gastrointestinal Surg 2009;13:1-2.

Jones DB. Searching for the perfect gastrojejunostomy: commentary 2. Bariatric Times 2009; 6(5) S:17-9.



Educational Materials

SAGES Patient Brochures, Illustrations from **Jones DB**, Maithel S, Schneider BE. Atlas of Minimally Invasive Surgery, Cine-Med 2009.

Abstracts

Lim R, Blackburn G, **Jones DB**, Dushay J, Schneider B, Lin H, Corsaro C. Can healthcare providers increase perioperative exercise behavior in bariatric patients? SOARD 2009; 5(35):S65.

Nguyen NT, Pomp A, Needleman B, Mikami D, Provost D, Scott D, **Jones DB**, Gallagher S, Dakin G, Gagner M, Murr M. Impact of staple height on the gastro-jejunostomy during laparoscopic gastric bypass: a multicenter prospective randomized trial. SOARD 2009; 5(35):S9.

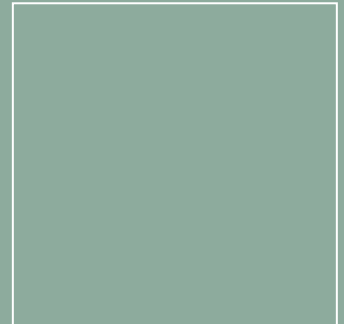
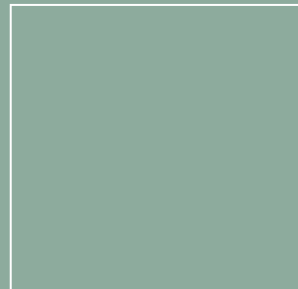
RESEARCH SUMMARY

BASIC RESEARCH

We are interested in the cellular immune response in trauma patients. Inflammation after trauma causes excessive activation of immune cells, such as neutrophils, that damage tissues to result in severe multiple organ failure. In those patients who survive these inflammatory complications, overcompensation then leads to the down-regulation of cellular immunity, which causes immune suppression and reduced host defenses against infections. Consequently, many patients develop infectious complications and sepsis within a week after trauma. These post-traumatic complications are a leading cause of death in those trauma patients who survive the initial injury.

The specific focus of my group is to study the molecular and cellular mechanisms involved in neutrophil activation and in the suppression of T cells with the ultimate goal in mind to develop potential therapeutic strategies to improve the clinical outcome in trauma patients. We are currently working on several different projects to pursue that goal as follows: 1) to determine mechanisms by which hypertonic resuscitation fluids suppress neutrophil activation. For this, we found that hypertonic stress induces the release of cellular ATP from neutrophils and that subsequent activation of A2a adenosine receptors blocks neutrophil functions in an autocrine fashion; 2) to examine the role of purinergic signaling in the control of neutrophil chemotaxis and other functional cell responses that mediate the inflammatory processes in trauma patients; and 3) to determine the role of purinergic signaling in T cell activation processes, specifically at the immune synapse, and on the cell-to-cell interactions between specific T cell subsets (e.g., gamma delta T cells) and neutrophils.

Results from the studies described above have already yielded a number of important discoveries that may ultimately lead to the development of novel therapeutic strategies to reduce the inflammatory complications seen in trauma patients.



Wolfgang G. Junger, PhD, DI

LIST OF CURRENT EMPLOYEES

Yu Chen, MD	Instructor in Surgery
Abdala Elkhail, PhD	Instructor in Surgery
Yuka Sumi, MD, PhD	Research Fellow in Surgery
Tobias Woehrle, MD	Research Fellow in Surgery
Yongli Yao, MD	Research Fellow in Surgery
Rahul Gupta, PhD	Research fellow in Surgery
Monali Bhate	Student
Ariana Brooks-James	Student
Anartya Mandal	Project Success Student

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CLINICAL RESEARCH

We are currently investigating if our laboratory research findings have clinical relevance using patient material from a large-scale multi-center trial. The aim of this trial is to test the immunomodulatory effects and clinical efficacy of hypertonic resuscitation fluids in trauma patients admitted to 11 different level-1 trauma centers in Canada and the United States of America. In association with our collaborators at the University of Washington, Seattle and at the University of Toronto, Canada, we are currently testing how hypertonic resuscitation of trauma patients affects neutrophil, monocyte, and T cell responses.



The Junger Laboratory Group

from left: Wolfgang, Yongli, Yu, Tobi, Abdala, Monali, and Yuka.

LIST OF CURRENT FUNDING

“Hypertonic saline and neutrophil function”
National Institutes of Health, R01 GM060475-06
04/01/2006-03/31/2010
PI: Wolfgang Junger

“Autocrine control of neutrophil chemotaxis”
National Institutes of Health, R01 AI072287
05/15/2009-04/30/2011
PI: Wolfgang Junger, PhD

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

“Hypertonic saline resuscitation, gamma-delta T cell function, and post-traumatic organ failure”
Department of Defense, W81XWH-05-1-0488
09/15/2005-09/14/2010
PI: Wolfgang Junger

“Hypertonic modulation of inflammation”
National Institutes of Health, R01 GM076101-01
06/11/2007-06/10/2011
Subcontract PI: Wolfgang Junger

“Hemorrhagic shock and hemostasis”
Shock Society Novo Nordisk, Grant 2007-2008
10/01/2007-09/31/2009
PI: Yu Chen, MD
Mentor: Wolfgang Junger

“Role of Th17 cytokines and Invariant Natural Killer (iNKT) cells in patients affected by COPD”
National Institutes of Health, R03 HL095426
08/04/2009-07/31/2011
PI: Abdallah Elkhail, PhD



Yuka Sumi



Tobi Woehrle



Yu Chen



Yongli Yao



Abdallah Elkhail

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

“Visualization of ATP release”

National Institutes of Health, R01

PI: Wolfgang G. Junger, PhD

“Purinergic signaling and multi-organ failure”

Department of Defense

PI: Wolfgang G. Junger, PhD

“Improved hypertonic resuscitation fluid”

National Institutes of Health, R01

PI: Wolfgang G. Junger, PhD

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

We made a number of important discoveries pertaining to the autocrine feedback mechanisms that control neutrophil chemotaxis. Dr. Yu Chen identified pannexin-1, a gap junction molecule, as a key player in the release of ATP from stimulated neutrophils. In addition, she could show that P2Y2 receptors closely co-localize with formyl peptide receptors (FPR) on the cell surface of human neutrophils (**Fig 1**). Our findings suggest that pannexin-1 and P2Y2 receptors are indispensable for the activation of neutrophils by formyl peptides. Manuscripts describing the roles of these molecules in neutrophil activation and chemotaxis are in preparation.

Dr. Tobias Woehrle has been studying purinergic signaling events in T cells and he found that P2X7 and P2X4 receptors determine how T cells respond to external stimuli. His findings indicate that both purinergic receptor subtypes play important roles in the influx of calcium during T cell activation and that P2X4, but not P2X7 receptors translocate to the immune synapse during T cell activation. A paper with Dr. Woehrle and our former team member Dr. Linda Yip as lead authors is being prepared for publication.

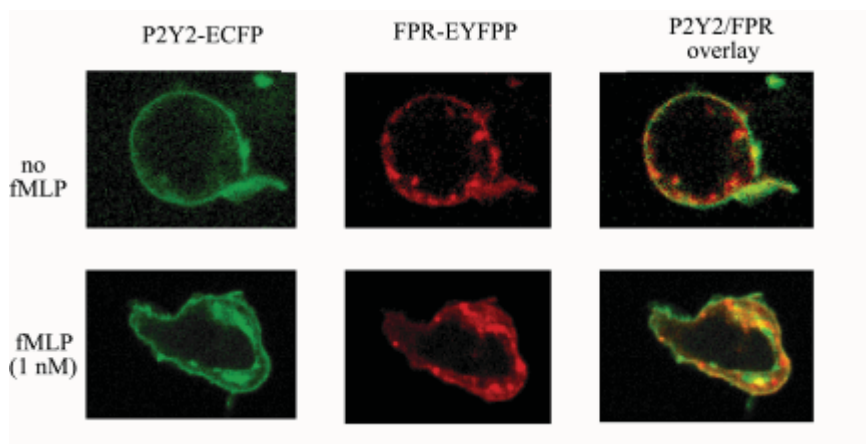


Fig 1 Formyl peptide receptors (FPR) and P2Y2 receptors co-localize on the cell surface of neutrophils.

Dr. Yu Chen has been studying the role of A2a adenosine receptors in neutrophil chemotaxis. Initial data suggest that these receptors are involved in uropod retraction of migrating cells. Dr. Yongli Yao, who contributed to all the studies described above, has also been instrumental in improving a high performance liquid chromatography (HPLC) method, which we now use frequently in our laboratory. This technique has allowed us to study the concentrations of ATP and related nucleotides in complex biological samples, including blood, with a high degree of accuracy. We are using this method to investigate if trauma, sepsis, and shock influence plasma ATP concentrations. Dr. Yuka Sumi has utilized this method to establish that different purinergic signaling mechanisms are required for cellular responses to different types of adrenergic stimuli and that these mechanisms control complex physiological responses such as smooth muscle contraction and relaxation.

Dr. Abdala Elkhail and Ms. Monali Bhate joined our laboratory this year and they have focused their work on gamma delta T cells as well as Th17 cells. Dr. Elkhail has been able to show that these cells play a critical role in the primary and secondary inflammatory responses in sepsis.

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Individual Accomplishments

- Editorial Board Member, The Open Critical Care Medicine Journal
- Ad hoc reviewer for Science, Shock, Journal of Immunology, Journal of Surgical Research, Journal of Leukocyte Biology, American Journal of Physiology, FASEB Journal, Cytokine, and others)
- Grant Reviewer for Wellcome Trust grant applications, DoD US ARMY grant applications, NIH ARRA grant applications, and the NIH-ZRG1-BST and NIH-CSR-RC1 study sections.
- Elected Councilor, Shock Society

Invited Presentations

"Purinergic signaling and inflammation", Hepatology Retreat, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

"Purinergic receptors control neutrophil migration", Department of Biochemistry, Boston University School of Medicine, Boston, MA

"Hypertonic resuscitation and neutrophil responses", Department of Surgery, University of Washington, Seattle, WA

REPORT OF TEACHING

Undergraduate Courses:

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

Graduate School and Graduate Medical Courses:

Faculty advisor to medical students at UCSD School of Medicine

- Andrew Li, MD (completed his independent study project at BIDMC and obtained his MD degree from UCSD)

Other Teaching Contributions

Mentoring junior faculty and residents: Ionita Ghiran, MD, BIDMC (submitted four grant application); Yu Chen, MD, BIDMC (submitted one grant application); Abdallah Elkhail, PhD, BIDMC (submitted one grant application); Marco Heft, MD, BIDMC (submitted 2 fellowship applications).

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Yip L, Woehrle T, Corriden R, Hirsh M, Chen Y, Inoue Y, Ferrari V, Insel PA, **Junger WG**. Autocrine regulation of T-cell activation by ATP release and P2X7 receptors. FASEB J 2009; 23:1685-93

Original Articles (submitted or in press)

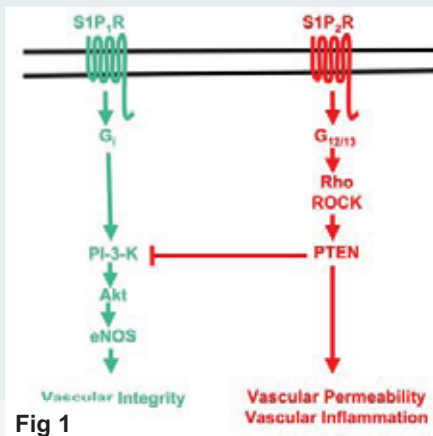
Beldi G, Banz Y, Kroemer A, Sun X, Wu Y, Graubardt N, Rellstab A, Enjyoji K, Li X, **Junger WG**, Candinas D, Robson SC. Deletion of CD39 on natural killer cells attenuates hepatic ischemia reperfusion injury. Hepatology 2009; in press.

Yu T, **Junger W**, Yuan C, Jin A, Zhao Y, Zheng X, Zeng Y, Liu J. Shockwaves increase the T-cell proliferation and IL-2 expression through ATP release, P2X7 receptor and FAK activation. Am J Physiol Cell Physiol 2009; in press.

RESEARCH SUMMARY

BASIC RESEARCH

My laboratory investigates the signaling pathways which regulate the responses of the vascular endothelium to injury. Endothelial cells are constantly adapting to changes within the extracellular environment and responding in ways that are usually beneficial but at times, could be deleterious to the organism. Dysregulation of these tightly regulated physiological events gives rise to many different disorders including tissue edema, inflammation, atherosclerosis or pathological angiogenesis. More specifically, we are focused on the signaling pathways activated by sphingosine-1-phosphate (S1P). S1P, a bioactive sphingolipid present at high levels in plasma and lymph, regulates multiple cellular responses, by activating the endothelial differentiation gene family of G protein-coupled receptors (EDG-1-5, renamed S1P1-5R).



To better understand the role of S1P in the regulation of endothelial cell function, we have established several *in vitro* and *in vivo* systems. Using pharmacological modulators of S1P receptors and genetic models, we have shown that S1P is a critical modulator of endothelial cell migration and endothelial barrier function *in vitro*, as well as angiogenesis, vascular permeability and vascular inflammation *in vivo*. Interestingly, we found that vascular responses to S1P depend on the balance of expression of two of its receptors, S1P1R and S1P2R. Indeed, while activation of S1P1R *inhibits* vascular permeability and inflammation, activation of S1P2R *promotes* vascular permeability and endothelial inflammation (**Fig 1**).



Teresa Sanchez, PhD

List of Current Employees

Bonnie Wang, MD
Kieran Ryan, BS
Guoqi Zhang, MD, PhD

Honggang Zhao, MD, PhD

Research Assistant
Research Assistant
Research Fellow in
Surgery
Research Fellow in
Surgery

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BASIC RESEARCH CONT'D

In addition, our studies have revealed the molecular mechanisms underlying the antagonistic effects of S1P1R and S1P2R in the regulation of endothelial responses. While S1P1R activates phosphatidylinositol-3-kinase (PI3K), S1P2R counteracts the actions of S1P1R by activating the phosphatase PTEN, which antagonizes the actions of PI3K. In agreement with this model, we found that PTEN activity was required for the inhibition of endothelial cell migration and induction of endothelial permeability by S1P2R.

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

LIST OF CURRENT FUNDING

"Regulation of Vascular Permeability and Angiogenesis by S1P2 Receptor and its Downstream Effector PTEN"
American Heart Association, National Scientist Development Grant 0630384N
Project Period: 1/1/2006-12/31/2010
PI: Teresa Sanchez

"Sphingolipid signaling in endothelial responses to injury"
National Institutes of Health, NHLBI 1R01HL094465-01
Project Period: 8/1/09-7/31/14
PI: Teresa Sanchez



Dr. Sanchez with the laboratory at the 2009 Center for Vascular Biology Retreat
From left to right: Guoqi Zhang, Teresa Sanchez, Bonnie Wang, and Kieran Ryan.

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

After setting up my new laboratory at BIDMC, with support from the Departments of Surgery and Emergency Medicine, I obtained NIH funding to study the role of Sphingolipid Signaling in the Regulation of Endothelial Responses to Injury. Guoqi Zhang and Kieran Ryan joined the lab in the summer of 2009 to work on this newly NIH-funded project. Later in the year, Honggang Zhao joined the lab to study the role of Sphingolipid Signaling in Ischemia-Reperfusion Injury, with support from the Departments of Surgery and Emergency Medicine.

In addition, I have been collaborating with Dr. Ferrer, Director of Pediatric Urologic Surgery at Connecticut Children's Medical Center, on a project focused on understanding the role of sphingolipid signaling in Wilms tumor progression. Wilms tumor is the most common malignant renal tumor in children and our understanding of the events leading to Wilms tumor progression and metastasis is still limited. We characterized the S1P receptor expression profile in Wilms tumor and elucidated the mechanisms whereby S1P/S1P1R signaling promote migration and invasion of WIT49 cells, while S1P/S1P2R signaling has an opposite effect and inhibits migration and invasion of these cells. In addition, we characterized the signaling pathways that lead to the expression of the anti-proliferative connective tissue growth factor by S1P/S1P2R in Wilms tumor cells.

Abstracts Presented at Local, National and International Meetings

Wang B, Hla T, **Sanchez T**. Induction of Endothelial Inflammatory and Coagulation Pathways by Sphingosine-1-phosphate Receptor-2 (S1P2R). Presented as a poster at the Annual Meeting of the Society of Academic Emergency Medicine, New Orleans, LA, May 2009.

Wang B, Hla T, **Sanchez T**. Induction of Endothelial Inflammation By the Sphingosine-1-phosphate Receptor-2. Presented as a poster at the Annual Center for Vascular Biology Research Summer Retreat, North Falmouth, MA, June 2009.

Administrative Accomplishments

I was a member of the organizing Committee for the Annual Center for Vascular Biology Research Summer Retreat, which was held in North Falmouth, MA, in June 2009.

I was a member of the Seminar Committee for the Center for Vascular Biology Research. This Committee is in charge of organizing the seminar Series that take place in the Center: This includes the Translational Seminar Series, Visiting Professor Series, CVBR Research Seminar Series, and Journal and Data Club.

Individual Accomplishments

- Reviewer for the American Heart Association Molecular Signaling study section, April 23-24, 2009, Philadelphia, PA.
- Peer reviewer (ad-hoc) for the journals: British Journal of Pharmacology, Cell Biology International, Cancer Research, Journal of Biological Chemistry, Journal of Cellular Physiology, Journal of Molecular Histology, Microvascular Research, Therapeutics and Clinical Risk Management, Trends in Endocrinology and Metabolism.
- Abstract reviewer for American Heart Association, Arteriosclerosis Thrombosis and Vascular Biology Annual Conference 2009, Washington D.C.
- Abstract reviewer and grader for the Annual Center for Vascular Biology Research Summer Retreat, North Falmouth, MA, June 2009.
- Moderator of the afternoon Scientific Sessions, Annual Center for Vascular Biology Research Summer Retreat, North Falmouth, MA, June 2009.

REPORT OF TEACHING

Graduate School and graduate medical courses:

External Examiner, PhD Thesis Defense, Akua Kusi Fordjour. "The effect of PKC isoform expression on p190 RhoGAP activity and endothelial barrier function". Pathobiology PhD Graduate Program, Brown University, Providence RI. (May, 2009).

Other Teaching Contributions:

This year, together with Dr. Ruhul Abid (Department of Medicine), I have been coordinator and instructor of the Center for Vascular Biology Research (CVBR) Journal Club and Data Club. The CVBR Data and Journal Club consists of presentations by students, post-doctoral and research fellows in the Center. The Data club gives our students and fellows the opportunity to present and discuss their latest research findings, receive feedback from faculty members and enhance their presentation skills. In the Journal Club, students and fellows present a recent high impact article in Vascular Biology and related disciplines. The objectives of the Data and Journal Club are to promote interactions and collaborations among our junior scientists, as well as encourage critical thinking in a relaxed and friendly atmosphere. The Data and Journal Club takes place every Friday from 12:00pm-1:00pm. We have around 45 speakers per academic year.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Li MH, **Sanchez T**, Milne GL, Morrow JD, Hla T, Ferrer F. S1P/S1P2 signaling induces cyclooxygenase-2 expression in Wilms tumor. *J Urol*. 2009; 181(3):1347-52.

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Li MH, **Sanchez T**, Yamase H, Hla T, Oo ML, Pappalardo A, Lynch KR, Lin CY, Ferrer F. S1P/S1P1 signaling stimulates cell migration and invasion in Wilms tumor. *Cancer Lett.* 2009; 276(2):171-9.

DIVISION OF PLASTIC AND RECONSTRUCTIVE SURGERY

Robert A. Frankenthaler, MD
Acting Chief, Division of Plastic and Reconstructive Surgery
Chief, Division of Otolaryngology
Assistant Clinical Professor of Surgery
Harvard Medical School

DIVISION OF PLASTIC AND RECONSTRUCTIVE SURGERY MEMBERS

Bernard T. Lee, MD
Samuel J. Lin, MD
Sumner A. Slavin, MD

Ami Taghinia, MD
Adam M. Tobias, MD
Joseph Upton, MD
Geoffrey Brahmer, MDiv
Maria Semnack, RN

Tolulope Adesiyun
Mark Bishara, MD
Matthew Carty, MD
Jerry Chang, MD
Mary Chen (Chen Chen)
Salih Çolakoğlu, MD
Michael Curtis, MD
Faraz Mahmood
Minh-Doan Nguyen, MD
Adeyemi Ogunleye, MD
Amr Rabie, MD
Carolyn Schook
David Tomich
Janet Yueh, MD

Instructor in Surgery
Assistant Professor of Surgery
Associate Clinical Professor of Surgery
Division Chief through June 30, 2009
Instructor in Surgery
Instructor in Surgery
Associate Clinical Professor of Surgery
Educational & Research Coordinator
Nurse Manager

HMS Student (III)
Clinical Fellow in Surgery-Body Contouring
Hand Microsurgery Fellow
Aesthetic Plastic Surgery Fellow
HMS Student (IV)
Research Fellow
Peter Jay Sharp Reconstructive Breast Fellow
Summer Research Intern, Brandeis University
Aesthetic & Reconstructive Breast Surgery Fellow
Harvard School of Public Health
Research Fellow
HMS Student (III)
Summer Intern, Case Western Reserve University
HMS Student (IV)

RESEARCH SUMMARY

BASIC RESEARCH

The Division of Plastic Surgery focused primarily on the following basic research projects in 2009:

1. Perforator Identification Using Near-Infrared Imaging (NIR)
2. Perforator Flap Perfusion Assessment Using Near-Infrared Imaging (NIR)
3. Neural Prosthetics with Chemical Harvesting and Stimulation for Facial Nerve Reanimation.

1. Perforator Identification Using Near-Infrared Imaging (NIR)

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

2. Perforator Flap Perfusion Assessment Using Near-Infrared Imaging (NIR)

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

3. Neural Prosthetics with Chemical Harvesting and Stimulation for Facial Nerve Reanimation.

This project is being done by Dr. Samuel Lin in collaboration with Drs. Amr Rabie, Jongyoon Han, Rahul Sarpeshkar, and Yong-Ak Song at the Massachusetts Institute of Technology (MIT).

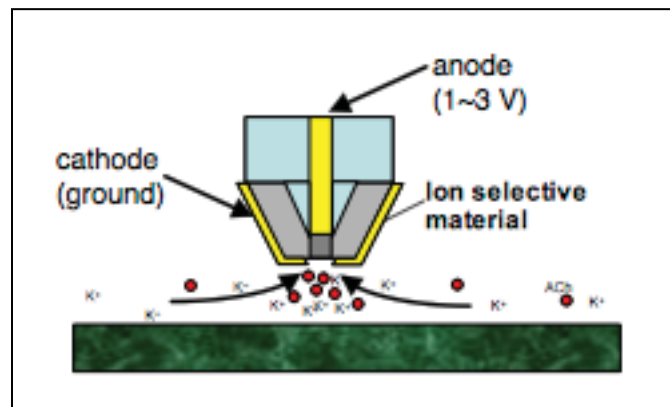


Fig 1 Schematic of a concentration device used in the collaborative project with MIT.

CLINICAL RESEARCH

The Division of Plastic Surgery focused on the following clinical research areas in 2009:

ViOptix Monitoring in Perforator Flap Surgery: This project further refines our clinical pathway through the utilization of a vioptix monitoring in perforator flap surgery. The project utilizes a tissue oximeter (ViOptix) monitoring device to detect early vascular compromise leading to flap loss and subsequent patient distress. The ViOptix device is a non-invasive monitor of real-time flap perfusion. Using the emission of near-infrared light, it measures local tissue oxygen saturation. This approach offers a more objective method than the more traditional clinical assessment for the detection of vascular compromise after perforator breast reconstruction surgery.

The study, utilizing a retrospective database review of 448 perforator flaps (from 356 patients) will compare the detection of vascular compromise between the ViOptix monitoring device versus the more traditional clinical

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assessment. It is hoped that the results from this study will lead to earlier detection of vascular problems and clinical intervention before significant flap ischemia or necrosis occurs. In addition, the study will further refine the parameters of our Clinical & Intraoperative Pathway. Dr. Bernard Lee is the project leader.

Infectious Complication of AlloDerm in Breast Reconstruction: An IRB is being prepared to look more carefully at this issue. The project will evaluate the outcomes and cost related to the use of AlloDerm in breast surgery. AlloDerm is established as a highly successful modality for managing implant-based breast reconstruction, complications and contour irregularities from breast surgery. Known benefits of the use of AlloDerm in breast reconstruction include: decreasing the number of times expansion is needed, allowing for a more immediate breast contour and correcting implant malposition when tissue is deficient. Our study will involve the comparison of the outcomes and health care costs of patients in which AlloDerm was used and a historical control group. Dr. Bernard Lee is the project leader.

Breast Cancer Recurrence: This project, which has just been initiated, will focus on breast cancer recurrence after mastectomy (with or without breast reconstruction). The study will compare recurrence rates between some of the following patient groups:

- Patients having breast reconstruction with patients who have elected not to have reconstruction after a mastectomy.
- Patients having perforator breast reconstruction with patients having implant reconstruction.

The study will also look at what types of radiographic imaging (CT scans, mammograms, and bone-scans) are most effective to detect cancer recurrence with different types of reconstruction. Dr. Bernard Lee is the project leader.

The Use of Vasopressors to Microsurgical Breast Reconstruction: The use of vasopressors during microsurgery is still being debated. General anesthesia often induces hypotension in patients during surgery, but micro surgeons are reluctant to use intraoperative vasopressors. The theoretical risk of vasoconstriction in the flap can potentially cause vascular spasm, stasis, and potentially ischemia and necrosis. The team conducted a retrospective analysis of the effects of ephedrine and/or phenylephrine on microsurgical breast reconstructions. We found no statistically significant differences in major complications in patients receiving and not receiving vasopressors. Previously reported animal and laboratory model experiments that showed negative effects of vasopressors may not accurately correlate to clinical scenarios. Further studies are necessary to determine the exact mechanisms of vasopressors on flaps in clinical use. Dr. Bernard Lee is the project leader.

The Use of Human Acellular Dermis for Secondary Breast Deformities: This project looks at the surgical technique of using human acellular dermis to correct secondary breast deformities. The study looked at 23 patients and 39 reconstructed breasts. Deformities consisted of surface irregularities, implant malposition, and hyperdynamic deformities. The use of human acellular dermis resulted in the improvement of 87% of the breasts reconstructed (33 out of 39). There was a complication rate of 2.6% (1/39). This study validates the use of human acellular dermis for the difficult problems of revision for cosmetic breast surgery. Dr. Sumner Slavin is the project leader for the study.

Real-time Intraoperative Computed Tomography Monitoring of Fractures: The project utilizes intraoperative computer tomography in the OR for monitoring fractures, including both facial fractures, as well as fractures of the upper extremity. The team is trying to assess the impact of intraoperative computer tomography in the reduction of facial and hand fractures. This will enable the surgeon to monitor intraoperatively with the possibility of immediate revision, if needed. The principal investigator is Dr. Samuel Lin.

Common Patterns of Reconstruction for Mohs Defects: The project outlined reconstructive trends for Mohs defects to help in preoperative planning. 245 patients, who received Mohs defect reconstruction, were categorized according to the reconstructive technique used, the anatomical location, and the size of the defect. Conclusions of the study were as follows: the most common reconstructive techniques according to the sites of the defects were bilobed flaps for the nasal ala, tip and sidewall defects and forehead flaps for the nasal dorsum; composite grafts for the nasal columella, FTSG for the nasal sill and STSG for the scalp. Linear closure was the most common technique for cheek, forehead, chin, lip, auricle, eyelid and temporal defects. Knowing the trends of

the closure for Mohs defects may help in planning the methods of reconstructions. The principal investigator for the study was Dr. Samuel Lin.

LIST OF CURRENT FUNDING

“Aesthetic Plastic Surgery Fellowship”
Ethicon Foundation
07/01/2007- 06/30/2010
PI: Samuel Lin, MD

“Real-time Intraoperative Computed Tomography Monitoring of Fractures”
Harvard Catalyst Pilot Grant
06/2009 – 06/2010
PI: Samuel Lin, MD

“Perforator identification using near-infrared imaging (NIR)”
NIH, R01 EB005805-01A1
07/01/2006-06/30/2010
PI: John Frangioni, MD
Co-PI: Bernard Lee, MD

“Peter Jay Sharp Program for Aesthetic and Reconstructive Breast Surgery”
Peter Jay Sharp Foundation
2005-2009
PI: Adam Tobias, MD

APPLICATIONS SUBMITTED AND PENDING REVIEW / FUNDING

“Renewal Grant for Aesthetic Plastic Surgery Fellowship”
Ethicon Foundation
07/01/2010- 06/30/2014
PI: Samuel J. Lin, MD

“Peter Jay Sharp Program for Aesthetic and Reconstructive Breast Surgery”
Peter Jay Sharp Foundation
2009-2013
PI: Adam Tobias, MD

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

Research efforts in the Division of Plastic Surgery have led to a host of presentations, papers, and other scholarly activities at the local, regional, national and international areas. In all of our research, we have invited and incorporated the participation of medical students, residents, and fellows.

One of the major ongoing accomplishments as a Division is our ongoing ability and commitment to work with residents, medical students, and researchers, helping mentor them to be future leaders in surgery, medical education, and research. This collaborative model extends to all of our work, including our ongoing fellowship programs: body contouring, aesthetic and reconstructive breast surgery, and hand/microsurgery fellowships.

Breast Reconstructive Surgery Research: Dr. Bernard Lee continues to lead an active research team dedicated to research on reconstructive breast surgery. In 2009, the team consisted of Drs. Bernard Lee, Minh-Doan Nguyen, Michael Curtis, and Adam Tobias, as well as HMS medical student, Mary Chen and international research fellow, Dr. Salih Çolakoğlu. Three summer research interns were also recruited Mr. David Tomich, a medical student at Case

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Western Reserve University in Cleveland, Ohio, Adeyemi Ogunleye, an MD at the Harvard School of Public Health in Boston, and Mr. Faraz Mahmood, a student at Brandeis University. In autumn, the team also took on board another HMS student: Mr. Charles Carspecken. The research team maintains ongoing research relationships with former Doris Duke fellows, Harvard Medical School graduates, Harvard Plastic Surgery residents, and Peter Jay Sharp Reconstructive Breast Surgery Fellows. Dr. Lee has also begun the process to recruit an additional international fellow.

Members of the research team meet every week on Friday afternoon to brainstorm new potential studies, to evaluate current projects, and to develop research time-lines and strategies in moving the projects forward, including the formulation of presentations, abstracts, and original articles. Current research projects include the following:

- Vioptix monitoring in perforator flap surgery
- Infectious complication of AlloDerm in breast reconstruction
- The use of vasopressors to microsurgical breast reconstruction
- Breast cancer recurrence

Dr. Sumner Slavin also recruited a team to look at the use of human acellular dermis for secondary breast deformities. This project, which was a multi-year study, validates the use of human acellular dermis for the difficult problems of surgical revisions for cosmetic breast surgery. The study has led to several presentations at national and international meetings. It has also been submitted to a journal for publication. In addition to Dr. Slavin, other team members included Drs. Amir Taghinia, Jerry Chang, Samuel Lin, and Tristan Hartzell.

Lymphedema Research: Until June of 2009, **Drs. Sumner Slavin** and **Arin Greene** continued to see patients and educate residents and medical students at the monthly BIDMC lymphedema clinic. They supported **Carolyn Schook**, a Harvard Medical Student (HMS III), who submitted IRB's at Children's Hospital and the BIDMC to study lymphedema in patients. The team continued to make linkages with *Norma-Tec*, a medical rehabilitation company that works closely with patients for treatment and rehabilitation needs.

In July, the lymphedema clinic moved to Children's Hospital / Waltham, MA. The clinic has expanded its clinic to two afternoons a month. At this new site at Children's Hospital, the lymphedema team continues to see patients and be involved in the education of residents and medical students. New lymphedema patients, as well as patients in need of follow up, are now referred to the clinic at Children's Hospital. Since opening the BIDMC lymphedema clinic (one afternoon a month) in 2004, the team treated 175 patients. Under the directorship of Dr. Sumner Slavin for this time period, lymphedema patients were treated, residents and medical students were educated, numerous presentations took place, and original publications were published.

Facial Plastic & Reconstructive Surgery Research: Dr. Samuel Lin, as Principal Investigator, aided by Dr. Amr Rabie, an International Research Fellow, from Egypt, were successful in submitting and obtaining a Harvard Catalyst Pilot Grant to study the *Real-time Intraoperative Computed Tomography Monitoring of Fractures*. This project will utilize intraoperative computerized tomography to monitor the reduction of facial and hand fractures in the operating room. In addition to Drs. Lin and Rabie, other BIDMC plastic surgery and orthopedic surgery faculty are also participating in the study including Bernard Lee, MD; Adam Tobias, MD; Amir H Taghinia, MD; Joseph Upton, MD and Charles Day, MD.

Another project initiated by Drs. Lin and Rabie is a collaborative research endeavor with scientists and engineers at the Massachusetts Institute of Technology. The project will focus upon *Neural Prosthetics with Chemical Harvesting and Stimulation for Facial Nerve Reanimation*. In addition to Drs. Lin and Rabie, other members of the team from include: Jongyoon Han, PhD; Rahul Sarpeshkar, PhD; Yong-Ak Song, PhD, Massachusetts Institute of Technology (MIT).

Drs. Samuel Lin and Rabie, with other faculty, completed a study on *Common Patterns of Reconstruction for Mohs Defects*. An IRB was submitted for the study and the charts of 245 patients were reviewed. The results of the study will lead to better preoperative planning for reconstruction following Mohs surgery. The principal investigator for the study was Dr. Samuel Lin. Co-investigators included, Amr Rabie, MD, Adam Tobias, MD, Bernard Lee, MD, and Loren Borud, MD.

Abstracts Presented at Local, National and International Meetings

Chen C, Nguyen MD, Lee BT. New Monitoring System to Decrease Microsurgical Flap Loss in Breast Reconstruction. Presented (as a poster) at Silverman Institute for Health Care Quality and Safety, Beth Israel Deaconess Medical Center, Boston, MA; March 2009.

Adesiyun T , Lee BT, Nguyen MD, Çolakoğlu S, Yueh J, Tobias A, Recht A. Postmastectomy Radiation Therapy and Breast Reconstruction: An Analysis of Complications and Patient Satisfaction. Presented (as a poster) at San Antonio Breast Cancer Symposium, San Antonio, TX; December 2009.

Individual Accomplishments

Geoffrey Brahmer

- Researched, prepared and presented four different talks on the Holocaust at venues in both the U.S. and Israel including at the BIDMC General Surgery Grand Rounds, Medical Grand Rounds, Leonard Morse Hospital, BIDMC, Plastic Surgery Division Rounds, Bar-Ilan University, Yod YaSharon Community Cultural Center (Israel) , Conservative Rabbinic Yeshiva (Jerusalem) International Child's Survival Conference, as well as other venues, including high schools, community groups, hospice ethics committees, seniors' groups, and synagogues.
- "Health Care in the Ghetto of Lodz". presented with Dr. Harold Bursztajn at BIDMC General Surgery Grand Rounds, led to major story by Globe and LA Times staff reporter, Judy Foreman, "A Healing Hope" in the Boston Globe (August 10) and the LA Times (August 31).

Robert Frankenthaler, MD

- Appointed Acting Chief, Division of Plastic Surgery
- Actively involved in giving presentations and the writing of original articles and book chapters otolaryngology.

Bernard Lee, MD

- Served as Co-Director for the Peter Jay Sharp Reconstructive & Aesthetic Breast Surgery Program.
- Served as primary academic and clinical mentor to the Peter Jay Sharp Aesthetic & Reconstructive Breast Surgery Fellows.
- Served as the supervising mentor to two HMS Research Fellows, four summer intern fellows, and an international research fellow.
- Served as Faculty Advisor for Harvard Medical School, Holmes Society.
- Served as editor for "Encyclopedia of Flaps, 3rd edition." Strauch B, Vasconez L, Hall-Findlay E, Lee BT, editors.
- Served as Associate Editor of the Journal of Reconstructive Microsurgery.
- Primary surgical investigator on the following projects:
 - Perforator identification using Near-Infrared Imaging (NIR).
 - Vioptix monitoring in perforator flap surgery.
 - Infectious complications of AlloDerm in breast reconstruction.
 - Ultrasonic liposuction as a treatment of fat necrosis after perforator breast reconstruction.
 - Use of vasopressors to microsurgical breast reconstruction.
- Served as Member, National Inservice Examination Committee, American Society of Plastic Surgeons / Plastic Surgery Educational Foundation.
- Actively involved in giving presentations and the writing of original articles and book chapters on aesthetic & reconstructive plastic surgery.

Samuel Lin, MD

- Promoted to Assistant Professor of Surgery, HMS.
- Served as Director of the Aesthetic Plastic Surgery Fellowship.
- Appointed BIDMC Residency Site Director for the Harvard Plastic Surgery Residency Program

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Samuel Lin, MD, contd.

- Obtained funding for Harvard Catalyst Pilot Grant, also serving as lead-investigator for the project “Real-time Intraoperative Computed Tomography Monitoring of Fractures”.
- Lead investigator for “Neural Prosthetics with Chemical Harvesting and Stimulation for Facial Nerve Reanimation”, a project being done in collaboration with investigators from MIT.
- Established and mentored an International Research Fellow within the Division.
- Edited, 1) Plastic and Reconstructive Surgery Pearls of Wisdom – 2nd edition, 2) An Aesthetic Atlas of the Head and Neck, and wrote a chapter on Minimally Invasive Techniques, for a book entitled, Aesthetic Head and Neck Surgery.
- Actively involved in giving presentations and the writing of original articles and book chapters on aesthetic & reconstructive plastic surgery.

Sumner Slavin, MD

- Completed term as Chairman, Executive Board, Harvard Plastic Surgery Residency Program.
- Served as Chief of the Division through the end of the academic year (2008-2009)
- Served as an Associate Editor for the British Journal of Plastic Surgery and as a member of the Breast Committee, American Society of Plastic Surgeons.
- Served as Chairman for International Symposium “Plastic Surgery at the Red Sea” Eilat, Israel.
- Served as the Co-Director of the Aesthetic Plastic Surgery Fellowship.
- Served as Director (BIDMC) and co-Director (Children’s Hospital) of the Lymphedema Clinic.
- Actively involved in giving presentations and the writing of original articles and book chapters on aesthetic & reconstructive plastic surgery.

Amir Taghinia, MD

- Started Plastic Surgery Faculty practice at Children’s Hospital and the Beth Israel Deaconess Medical Center.
- Served as attending supervisor at the BIDMC weekly hand clinic.
- Started academic work for a Masters in Public Health at Harvard University.
- Published several original papers.

Adam Tobias, MD

Served as the Director of the Peter Jay Sharp Program for Aesthetic and Reconstructive Breast Surgery. In this position, he was actively involved in all aspects and phases of the program including: funding, program organization and development, staffing, public relations, recruitment and mentoring of the breast surgery fellow, development of clinical and intraoperative pathways, and the ongoing education of residents and medical students. Over the course of the year, Dr. Tobias has also been active in research and in the mentoring of fellows, residents, and medical students.

Joseph Upton, MD

- Served as the Director of the Hand/Microsurgery Fellowship Program. In this position, he was in charge of all of the aspects of the program, including administration, fellowship recruitment and mentoring, and research activities. He also worked closely with Dr. Charles Day, in the integration of the plastic surgery and orthopedic surgery hand fellowships.
- Served as attending faculty at the weekly BIDMC hand clinic.
- Actively involved in giving presentations and the writing of original articles and book chapters on hand and microsurgery.

Invited Presentations

Geoffery Brahmer

“Lamentation for Lodz”.

Plastic Surgery Division Rounds, Boston, MA. March 3, 2009.

Conservative Rabbinic Yeshiva, Jerusalem. March 31, 2009.

Ethics Committee, Hospice Compasses, Lakeside, AZ. July 23, 2009.

“In the Eye of the Storm: 6 Photographers in the Nazi Era”. Yod YaSharon Community Cultural Center, Israel. April 1, 2009.

“Return to the Warsaw Ghetto”. Bar-Ilan University, Israel. April 2, 2009.

“Health Care in the Ghetto of Lodz: Care, Compliance, Conscience and Resistance” (Presented with Bursztajn H).

Surgery Grand Rounds, BIDMC, Boston, MA. July 8, 2009.

World Federation of Child Survivors of the Holocaust, Newton, MA. Nov. 1, 2009

Maimonides Club, Harvard Medical School, Boston, MA. November 10, 2009.

Medical Grand Rounds, Leonard Morse Hospital, Natick, MA. December 9, 2009.

Tolulope Adesiyun

“Postmastectomy radiation therapy and breast reconstruction: An analysis of complications and patient satisfaction”. Plenary Presentation, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

“Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction”. American Society for Therapeutic Radiology and Oncology, Annual Meeting, Chicago, IL. November 2, 2009.

Mary Chen (Chen Chen)

“Infectious complications leading to explanations in implant-based breast reconstruction with and without Alloderm” and “Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction”. Plastic Surgery Research Council. Pittsburg, PA. May 26-31, 2009.

“Computer-based learning module increases shared decision making in breast reconstruction” and “ViOptix monitoring system decreases flap loss in microsurgical in breast reconstruction”. New England Society of Plastic and Reconstructive Surgeons. Boston, MA. June 4-7, 2009.

“A comparative analysis of perioperative complications between breast reconstruction, mastectomy, and lumpectomy”. Plenary Session, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

“Computer-based learning module increases shared decision making in breast, reconstruction”. Plenary, American College of Surgeons. Chicago, IL. October 11-15, 2009.

“Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction”. American Society for Therapeutic Radiology and Oncology, Annual Meeting, Chicago, IL. November 2, 2009.

Salih Çolakoğlu

“Postmastectomy radiation therapy and breast reconstruction: An analysis of complications and patient satisfaction” and “A comparative analysis of perioperative complications between breast reconstruction, mastectomy, and lumpectomy”. Plenary Session, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

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"Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction". American Society for Therapeutic Radiology and Oncology, Annual Meeting, Chicago, IL. November 2, 2009.

Michael Curtis

"A comparative analysis of perioperative complications between breast reconstruction, mastectomy, and lumpectomy". Plenary Session, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

"Non-abdominal perforator flap breast reconstruction". Plastic Surgery Division Rounds, Beth Israel Deaconess Medical Center, Boston, MA. December, 15, 2009.

Bernard T. Lee

"The posterior tibial artery perforator flap: An Alternative to Free Flap Closure in the Co-Morbid Patient, American Society for Reconstructive Microsurgery" and "The influence of infonomic and sociodemographic factors on shared decision making in microsurgical breast reconstruction". American Society for Reconstructive Microsurgery. Maui, HI. January 10-13, 2009.

"Abdominal wall reconstruction". Core Curriculum Session, Plastic Surgery Residents, Harvard Medical School. Boston, MA. Spring, 2009.

"Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction". Plastic Surgery Research Council. Pittsburg, PA. May 26-31, 2009.

"Infectious complications leading to explanations in implant-based breast reconstruction with and without Alloderm".

Plastic Surgery Research Council. Pittsburg, PA. May 26-31, 2009.

Plenary Session, American Society of Plastic Surgeons. Seattle, WA. October 23-27, 2009.

"Computer-based learning module increases shared decision making in breast reconstruction".

New England Society of Plastic and Reconstructive Surgeons. Boston, MA. June 4-7, 2009.

Plenary, American College of Surgeons. Chicago, IL. October 11-15, 2009.

"ViOptix monitoring system decreases flap loss in microsurgical in breast reconstruction" and "Ectropion and entropion incidence after facial fracture repair: A retrospective study and meta-analysis comparing sub tarsal, sulciary, and transconjunctival incisions". Plenary Presentation, New England Society of Plastic and Reconstructive Surgeons, Annual Meeting. Boston, MA. June 4-7, 2009.

"Stress and burnout among surgeons". Core Curriculum, Plastic Surgery Residents, Harvard Medical School, Boston, MA. 2009.

"New opportunities in breast reconstruction". Multidisciplinary Conference, Departments of Medicine and Surgery, Beverly Hospital. Beverly, MA. 2009.

"Complications in breast surgery and how to approach them". Plastic Surgery Division Rounds, BIDMC. Boston, MA. December 22, 2009.

"Postmastectomy radiation therapy and breast reconstruction: An analysis of complications and patient satisfaction" and "A comparative analysis of perioperative complications between breast reconstruction, mastectomy, and lumpectomy". Plenary Session, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

"Common patterns of reconstruction for Mohs defects". AAO-HNSF Annual Meeting & OTO EXPO. San Deigo, CA. October, 2009.

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"Comparison of Morbidity, Functional Outcome, and Satisfaction Following Bilateral TRAM or Bilateral DIEP Flap Breast Reconstruction". Plenary Presentation, American Society of Plastic Surgeons. Seattle, WA. October 23-27, 2009.

"Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction". American Society for Therapeutic Radiology and Oncology, Annual Meeting. Chicago, IL. November 2, 2009.

Samuel J. Lin

"Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction". Plastic Surgery Research Council. Pittsburg, PA. May 26-31, 2009.

"The effect of rhinoplasty on the internal nasal valve: A comparison between internal continuous osteotomy and external perforating osteotomy". Plastic Surgery Research Council (PSRC), 54th Annual Meeting. Pittsburgh, PA. May, 2009.

"ViOptix monitoring system decreases flap loss in microsurgical in breast reconstruction". New England Society of Plastic and Reconstructive Surgeons. Boston, MA. June 4-7, 2009.

"Effects of rhinoplasty on the internal nasal valve: A comparison between internal continuous osteotomy and external perforating osteotomy". Northeastern Society of Plastic Surgeons (NESPS), 26th Annual Meeting. Charleston, SC. September, 2009.

"Common patterns of reconstruction for Mohs defects". AAO-HNSF Annual Meeting & OTO EXPO. San Deigo, CA. October, 2009.

Minh-Doan Nguyen

"Latissimus and local flaps for breast reconstruction". Journal Club: Plastic Surgery Division Rounds, BIDMC. Boston, MA. January 6, 2009.

"Autologous breast reconstruction". Plastic Surgery Division Rounds, BIDMC. Boston, MA. April 7, 2009.

"Abdominal wall reconstruction". Core Curriculum Session, Plastic Surgery Residents, Harvard Medical School. Boston, MA. Spring, 2009.

"Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction" and "Infectious complications leading to explanations in implant-based breast reconstruction with and without Alloderm". Plastic Surgery Research Council. Pittsburg, PA. May 26-31, 2009.

"Peter Jay Sharp aesthetic & reconstructive breast surgery fellowship: program overview". Plastic Surgery Division Rounds, BIDMC. Boston, MA. May 26, 2009.
Harvard Plastic Surgery Grand Rounds, Shriners Burns Hospital. Boston, MA. June 3, 2009.

"Computer-based learning module increases shared decision making in breast reconstruction" and "ViOptix monitoring system decreases flap loss in microsurgical in breast reconstruction". New England Society of Plastic and Reconstructive Surgeons. Boston, MA. June 4-7, 2009.

"Postmastectomy radiation therapy and breast reconstruction: An analysis of complications and patient satisfaction". Plenary Presentation, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

"Infectious complications leading to explanation in implant-based breast reconstruction with and without AlloDerm". Plenary Session, American Society of Plastic Surgeons. Seattle, WA. October 23-27, 2009.

"Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction". American Society for Therapeutic Radiology and Oncology, Annual Meeting, Chicago, IL. November 2, 2009.

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Adeyemi Ogunleye

"A comparative analysis of perioperative complications between breast reconstruction, mastectomy, and lumpectomy". Plenary Session, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

Amr Rabie

"The effect of rhinoplasty on the internal nasal valve: A comparison between internal continuous osteotomy and external perforating osteotomy". Plastic Surgery Research Council (PSRC), 54th Annual Meeting. Pittsburgh, PA. May, 2009.

"Effects of rhinoplasty on the internal nasal valve: A comparison between internal continuous osteotomy and external perforating osteotomy". Northeastern Society of Plastic Surgeons (NESPS), 26th Annual Meeting. Charleston, SC. September, 2009.

"Common patterns of reconstruction for Mohs defects" and "Surgical management of tinnitus due to high jugular bulb". Oral AAO-HNSF Annual Meeting & OTO EXPO. San Deigo, CA. October, 2009.

Sumner A. Slavin

"Surgical treatment of lymphedema, DIEP (Deep Inferior Epigastric Perforator) flap breast reconstruction". Invited Faculty: 26th Annual Miami Breast Cancer Conference. Miami, FL. March, 2009.

"Correction of contour deformities following breast cosmetic surgery with human acellular dermis", "Correction of contour deformities following breast reconstruction with DIEP flaps using fat injections", and "A family operation: plastic surgeons who perform cosmetic surgery on family members". Invited Faculty: Plastic Surgery at the Red Sea – International Symposium. Eilat, Israel. March, 2009.

"Correction of contour deformities following breast cosmetic surgery with human acellular dermis", "Correction of contour deformities following breast reconstruction with fat grafts", and "A family operation: plastic surgeons who perform cosmetic surgery on family members". Invited Faculty: 23rd Annual Virgin Islands Workshop in Plastic Surgery, St John US Virgin Islands. January, 2009 and Invited Speaker: Harvard Plastic Surgery Grand Rounds, Shriner's Burns Hospital. Boston, MA. April, 2009.

"The New England experience with DIEP flap breast reconstruction". Invited Speaker: RamBam Medical Center, Technion University. Haifa, Israel. April, 2009.

"Reconstruction with the latissimus dorsi myocutaneous flap and saline breast prosthesis: Oncological risks and aesthetic results". New England Society of Plastic and Reconstructive Surgeons. Boston, MA. June 4-7, 2009.

Adam M. Tobias

"The influence of infonomic and sociodemographic factors on shared decision making in microsurgical breast reconstruction". American Society for Reconstructive Microsurgery. Maui, HI. January 10-13, 2009.

"ViOptix monitoring system decreases flap loss in microsurgical in breast reconstruction" and "Computer-based learning module increases shared decision making in breast reconstruction". New England Society of Plastic and Reconstructive Surgeons, Boston, MA. June 4-7, 2009.

"Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction". Plastic Surgery Research Council. Pittsburg, PA. May 26-31, 2009.

"Postmastectomy radiation therapy and breast reconstruction: An analysis of complications and patient satisfaction" and "A comparative analysis of perioperative complications between breast reconstruction, mastectomy, and lumpectomy". Plenary Presentation, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

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"Common patterns of reconstruction for Mohs defects". AAO-HNSF Annual Meeting & OTO EXPO. San Deigo, CA. October, 2009.

"Infectious complications leading to explanation in implant-based breast reconstruction with and without AlloDerm". Plenary Session, American Society of Plastic Surgeons. Seattle, WA. October 23-27, 2009.

Joseph Upton

"Microsurgical cranial base reconstruction: a 30 year experience", "Quad toe transfer to the hand", "Fascial flap application", and "Salvage lower extremities". Invited Speaker: American Society for Reconstructive Microsurgery. Maui, HI. January 10-13, 2009.

"Fascial flaps in the hand: a series of 60 patients" and "Post graduate medical education: plastic surgery fellowship". Invited Speaker: American Association of Plastic Surgeons. Rancho Mirage, CA. March 21-24, 2009.

"Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction". Plastic Surgery Research Council. Pittsburg, PA. May 26-31, 2009.

Janet Yueh

"The influence of infonomic and sociodemographic factors on shared decision making in microsurgical breast reconstruction". American Society for Reconstructive Microsurgery. Maui, HI. January 10-13, 2009.

"Computer-based learning module increases shared decision making in breast reconstruction". New England Society of Plastic and Reconstructive Surgeons, Boston, MA. June 4-7, 2009.

"Postmastectomy radiation therapy and breast reconstruction: An analysis of complications and patient satisfaction". Plenary Presentation, Northeastern Society of Plastic Surgeons. Charleston, SC. Sept. 23-27, 2009.

"Comparison of morbidity, functional outcome, and satisfaction following bilateral TRAM or bilateral DIEP flap breast reconstruction". Plenary Presentation, American Society of Plastic Surgeons. Seattle, WA. October 23-27, 2009.

"Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction". American Society for Therapeutic Radiology and Oncology, Annual Meeting, Chicago, IL. November 2, 2009.

REPORT OF TEACHING

Undergraduate and Medical School Courses

1. Medical students were introduced to the diagnosis, treatment, and management of lymphedema at the monthly clinic.
2. The Division of Plastic Surgery was active in teaching student clerkships and 4th year medical students for HMS course, SU514M.1, a course that was directed by Dr. Slavin, Dr. Lee and Dr. In 2009, we had 15 student clerks rotate through the Division. Each student spent 1 month in the Division. We had hosted 3 international medical students who were on observational rotations.
3. The Division was part of the Dept. of Surgery's elective rotation for 2-week rotations of Harvard Medical Students, HMS III's. In 2008, we helped mentor 2 students. In addition to mentoring ongoing students, the Division sponsored 3-hour wound healing and suturing training seminars for each group of rotating students assigned to the BIDMC. This one-half day seminar takes place quarterly, about 4 times a year.
4. Sponsored, Mary Chen, HMS clinical Researcher, two international Research Fellows and 4 student clinical research interns.

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Graduate School and Graduate Medical Courses

1. Drs. Slavin and Greene introduced surgical interns and plastic surgery residents to the special challenges and approaches in clinically treating patients with lymphedema. Residents / medical students are now involved in writing papers/abstracts for papers and presentations.
2. Drs. Tobias and Lee introduced surgical interns and plastic surgery residents to the special challenges and approaches in microsurgery and working with perforator flaps. Residents, a breast surgery fellow and medical students are now involved in writing papers/abstracts for papers and presentations.
3. Dr. Sumner Slavin and Dr. Richard Bartlett taught a training session in the use of plastic surgery fillers for both aesthetic and reconstructive purposes.
4. Drs. Slavin, Lee, Lin, Taghinia, Tobias, and Upton all participated in the Core Curriculum and Journal Club of the Combined Harvard Plastic Surgery Residency Program.
5. In 2009, the Division helped mentor 24 interns (General Surgeons and EMEDS), 2 podiatry residents, and 21 plastic surgery residents. We also sponsored 3 fellows: aesthetic and reconstructive breast surgery, body contouring, and hand/microsurgery, and were also actively involved in training the BIDMC Orthopedic Hand Fellow and the MGH Hand / Plastic Surgery Fellow.
6. In 2009, the Division also hosted 3 visiting surgeons/residents for observational / elective / sabbatical rotations.

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Original Articles

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Burga LN, Tung NM, Troyan SL, Bostina M, Konstantinopoulos PA, Fountzilas H, Spentzos D, Miron A, Yassin YA, **Lee BT**, Wulf GM. Altered proliferation and differentiation properties of primary epithelial cells from BRCA1 mutation carriers. *Cancer Res* 2009;69(4):1273-8.

Carty MJ, Ferraro N, **Upton J**. Reconstruction of pediatric cranial base defects: A review of a single microsurgeon's 30-year experience. *J Craniofac Surg* 2009;20(Suppl1): 639-45.

Chun YS, **Taghinia A**. Hyperprolactinemia and galactoceles formation after augmentation mammoplasty. *Ann Plast Surg* 2009;62(2):122-3.

Karnes JC, **Lee BT**, Phung T, Alomari AI, Mulliken JB, Greene AK. Adult-onset kaposiform hemangioendothelioma in a posttraumatic site. *Ann Plast Surg* 2009;62(4):456-8.

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Lee BT, **Yueh JH**, **Chen C**, **Lin SJ**, **Tobias AM**, **Slavin SA**. Establishment of perforator flap programs for breast reconstruction: the New England program experience. *Plast Reconstr Surg* 2009;124(5):1410-8.

McCafferty LR, Casas LA, Stinnett SS, **Lin SJ**, Rho J, Skiles M. Multisite analysis of 177 consecutive breast augmentations: predictors for reoperation. *Aesthet Surg J* 2009;29(3):213-20.

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Ridgway EB, **Chen C**, Colakoglu S, Gautam S, **Lee BT**. The incidence of lower eyelid malposition after facial fracture repair: a retrospective study and meta-analysis comparing subtarsal, subciliary, and transconjunctival incisions. *Plast Reconstr Surg* 2009;124(5):1578-86.

Taghinia AH, Movassaghi K, Wang AX, Pribaz JJ. Reconstruction of the upper aerodigestive tract with the submental artery flap. *Plast Reconstr Surg* 2009;123(2):562-70.

Yueh JH, Houlihan MJ, **Slavin SA**, **Lee BT**, Pories SE, Morris DJ. Nipple sparing mastectomy: evaluation of patient satisfaction, aesthetic results, and sensation. *Ann Plast Surg* 2009;62(5):586-90.

Yueh JH, **Slavin SA**, Bar-Meir ED, Merali HS, Houlihan MJ, Gautam S, Morris DJ, **Tobias AT**, **Lee BT**. Impact of regional referral centers for microsurgical breast reconstruction: the New England perforator flap program experience. *J Am Coll Surg* 2009;208(2):246-54.

Original Articles (submitted or in press)

Carty MJ, **Taghinia A**, **Upton J**. Facial flap reconstruction of the hand. *Plast Reconstr Surg* 2009, in press.

Chen C, **Nguyen MD**, Bar-Meir ED, Hess PA, **Lin SJ**, **Tobias AM**, **Upton J**, **Lee BT**. Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction. *Ann Plast Surg* 2009; in press.

Cooper JS, **Lee BT**. Treatment of facial scarring - lasers, filler, and non-operative techniques. *Facial Plast Surg* 2009; in press.

Fang R, **Lin SJ**, Mustoe TA. Abdominoplasty flap elevation in a more superficial plane: decreasing the need for drains. *Plast Reconstr Surg* 2009; in press.

Lee BT, Matsui A, Winer JH, Laurence RG, Frangioni JV. Submental perforator flap design using near-infrared fluorescence imaging: the relationship among number of perforators, flap perfusion, and venous drainage. *Plast Reconstr Surg* 2009; in press.

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Lee BT, **Chen C**, **Nguyen MD**, **Lin SJ**, **Tobias AM**. A new classification system for muscle and nerve preservation in DIEP flap breast reconstruction. *Microsurgery* 2009; in press.

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Lee BT, Matsui A, Winer JH, Laurence RG, Frangioni JV. Intraoperative near-infrared imaging in perforator flap reconstruction: a review of current research and literature. *J Reconstr Microsurg* 2009; in press.

Lee BT, **Yueh JH**, **Chen C**, **Lin SJ**, **Tobias AM**, **Slavin SA**. A Blueprint of the New England perforator flap program at 400 Flaps: if you build it will they come? *Plast Reconstr Surg* 2009; in press.

Lin SJ, Butler CE. Subtotal thigh flap and bioprosthetic mesh reconstruction of large, composite abdominal wall defects. *Plast Reconstr Surg* 2009; in press.

Lin SJ, **Rabie AN**, Yu P. Unusual anterolateral thigh donor site complications: Intraneural hemangioma and traumatic neuroma. *Plast Reconstr Surg* 2009; in press.

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Makhni EC, **Taghinia A**, Ewald T, Zurkaowski D, Day CS. Comminution of the dorsal metaphysis and its effects on the radiographic outcomes of distal radius fractures. J Hand Surg 2009; in press.

Matros E, **Yueh JH**, Bar-Meir ED, **Slavin SA**, **Tobias AM**, **Lee BT**. Sociodemographics, referral patterns, and internet use for decision-making in microsurgical breast reconstruction. Plast Reconstr Surg 2009; in press.

Nguyen MD, **Chen C**, **Lin SJ**, **Tobias A**, **Upton J**, **Lee BT**. Vasopressin and flap elevation. Ann Plast Surg 2009; in press.

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Reviews, Chapters and Editorials

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Lee BT. Computer and data disposal in plastic surgery: guidelines for health insurance portability and accountability act compliance. Plast Reconstr Surg 2009;124(1):186e-7e.

Lee BT, Matsui A, Winer JH, Vooght CS, Laurence RS, Frangioni JV. Real-time intraoperative near-infrared fluorescence angiography for perforator identification and flap design. Plast Reconstr Surg 2009;123(3):125e-7e.

Lin SJ, **Frankenthaler R**. Free tissue transfer in the head and neck of a cancer patient with graft versus host disease. J Otolaryngol Head Neck Surg 2009;38(2):E42-4.

Lin SJ, **Lee BT**. The intrinsic tying platform in microsurgery. Plast Reconstr Surg 2009;123(6):223e-4e.

Lin SJ, Yu P. Free tissue transfer in a head and neck cancer patient with polycythemia vera. Plast Reconstr Surg 2009;124(1):169e-70e.

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Upton J, Garcia J, Liao E. Botox to the rescue. Plast Reconstr Surg 2009;123(1):38e.

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Cooper JS, **Lee BT**, Fillers. In: Mustoe TA, **Lin SJ**, editors. Aesthetic head and neck: an operative atlas. New York: McGraw-Hill Publishing; 2009; in press.

Lin SJ. Plastic and reconstructive surgery pearls of wisdom. 2nd ed. New York: McGraw-Hill Publishing; 2009; in press.

Lin SJ. An aesthetic atlas of the head and neck. New York: McGraw-Hill Publishing; 2009; in press.

Lin SJ. Minimally invasive techniques. In: Aesthetic head and neck surgery. London: Elsevier Publishing; 2009; in press.

Raskin ER, **Slavin SA**, Borud LJ. Lymphedema. In: Guyuron B, Eriksson E, Persing J, Chung K, Disa J, Gosain A., Kinney B, Rubin JP, editors. Plastic surgery: indications and practice. London: Elsevier; 2009; in press.

Upton J, Chiu D, Littler JW, Wei F-C, Foucher G. Reconstruction of the thumb and digits, London: Martin Dunitz, Co.; 2009; in press.

DIVISION OF PODIATRY

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Chief, Division of Podiatry
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Harvard Medical School



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Research Coordinator

Suzy Wu

Research Assistant

Sarada Kuchibhotla

Research Assistant

Ermelindo Leal, PhD

Research Fellow

RESEARCH SUMMARY

BASIC AND CLINICAL RESEARCH

Our research program continues to be strongly influenced by projects involving diabetes and the problems expressed in the feet. We continued to investigate new approaches for dealing with diabetic ulcers through clinical trials this year. Both extra-corporeal shock wave therapy and dietary supplements were used to enhance wound closure. We also continued to study the use of collagen and negative pressure wound therapy to treat diabetic ulcers.

Clinical applications for collagen continue to be a central aspect of our research program. New surgical procedures involving joint resurfacing and fat pad augmentation have been developed as a result of preliminary studies conducted last year. In addition, we have expanded our use of collagen to include treatments for venous leg ulcers. This year, I was also fortunate enough to edit an issue of Clinics in Podiatric Medicine and Surgery, which focused on collagen bioscaffolds and advanced biologics used in foot surgery and wound care. Based on these experiences, we have just begun to formulate a new program which will explore new applications for fresh cryopreserved human allograft skin, in order to deliver cellular components along with the collagen scaffold.

This year, we also conducted clinical research on laser treatments for onychomycosis. As the national principal investigator, I led a team of sites to complete the first study of its kind to be submitted to the FDA for evaluation. Our first public presentation on this topic drew standing room only crowds at the national meeting of the American Podiatric Medical Association national convention.

Finally, our fellowship in Reconstructive Podiatric Surgery and Research is now in its third year. Our first two fellows, Emily Cook, DPM, MPH and Jeremy Cook, DPM, MPH, successfully completed their program, and joined our division as attending physicians. We recently learned that they have also been awarded their first grant from the American College of Foot and Ankle Surgeons. Our new fellow, Kevin Riemer, DPM, is now working on several research programs as well.



Adam Landsman, DPM, PhD

LIST OF CURRENT EMPLOYEES

Kevin Riemer, DPM	Research Fellow
Valentina Conant, MS	Clinical Res Admin

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LIST OF CURRENT FUNDING

“Evaluation of a medical food for chronic wounds”

Abbott Laboratories

Project Period: 2008-2010

PI: Adam Landsman

“Use of the dermaPACE (pulsed acoustic cellular expression) device in conjunction with standard of care in the treatment of diabetic foot ulcers”

Sanuwave, Inc

Project Period: 2008-2010

PI: Adam Landsman

“A Prospective, Multi-center, Randomized, Controlled Clinical Investigation of Dermagraft® in Subjects with Venous Leg Ulcers DEVO-Trial”

Advanced BioHealing, Inc.

Project period: 2010-2011

PI: Adam Landsman

“A Multi-center, randomized study with Integra bilayer matrix wound dressing for the treatment of neuropathic diabetic foot ulcers”

Integra Lifesciences Corp.

Project period: 2010-2012

PI: Adam Landsman

“Does Ketorolac Delay Bone Healing and Improve Post-Operative Pain? A Prospective Double-Blind Placebo-Controlled Randomized Clinical Trial.”

American College of Foot and Ankle Surgeons

Project period: 2010-2012

PI: Emily Cook

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

Our research involving collagen has led to several new surgical procedures, including a new technique for resurfacing of metatarsal phalangeal joints, and a new method for augmentation of the plantar fat pad of the foot. Our work with laser therapy for onychomycosis has also been widely recognized.

We received an award for our abstract, presented at the American Podiatric Medical Association, National Scientific Conference, for our work on HgA1C and its relationship to the development of diabetic foot ulcers.

Abstracts Presented at Local, National and International Meetings

Landsman A. What does the literature tell us about mechanically induced ulcerations and how do force absorbing materials work? Presented at the Biomechanical Implications of Foot Surgery, Samuel Merritt University, Oakland, CA; February 28, 2009.

Landsman A. New trends in rheumatologic medications. Presented at the 67th ACFAS Scientific Conference, Washington, DC; March 4-8, 2009.

Landsman A. Hallux abducto valgus controversies; does hypermobility exist? Presented at the 67th ACFAS Scientific Conference, Washington, DC; March 4-8, 2009.

Landsman A. Update on 5th metatarsal osteotomies. Presented at the 67th ACFAS Scientific Conference, Washington, DC; March 4-8, 2009.

Landsman A. A prospective analysis of 22 patients treated with percutaneous RF nerve ablation for prolonged moderate to severe heel pain associated with plantar fasciitis. Presented at the 67th ACFAS Scientific Conference, Washington, DC; March 4-8, 2009.

Landsman A. Optimizing adherence of skin grafts, living skin equivalents, and collagen bioscaffolds with smart dressings. Presented at the 2009 APMA Annual Scientific Conference, Toronto, Canada; July 30-August 2, 2009.

Landsman A. Laser therapy for the treatment of onychomycosis. Presented at the 2009 APMA Annual Scientific Conference, Toronto, Canada; July 30-August 2, 2009.

Landsman A. Hemoglobin A1C as an independent predictor of wound healing: a preliminary case report. Presented at the 2009 APMA Annual Scientific Conference, Toronto, Canada; July 30-August 2, 2009.

Administrative Accomplishments

Adam Landsman and **Philip Basile** continue to serve as co-directors of the Podiatric Reconstructive Surgery and Research Fellowship program. Under our direction, we were able to recruit our third fellow to this program. Our total training program is one of the most comprehensive and highly sought training programs in the country, for podiatric surgery. With the strong emphasis on research, we anticipate that the program will continue to attract the most qualified candidates, nationwide, and will flourish and grow.

Valentina Conant remains as our lead Clinical Research Assistant, and has helped to structure the clinical research projects of our fellows as well as our very active clinical research activities.

Individual Accomplishments

- Appointed as guest editor for "Clinics in Podiatric Medicine and Surgery"

REPORT OF TEACHING

Graduate School and Graduate Medical Courses

- **Adam Landsman, Jeremy Cook, Emily Cook**; Harvard Medical School; "Clinical Epidemiology and Population Health"; Course Tutor.
- **Adam Landsman and Philip Basile**; Co-Directors, Podiatric Reconstruction and Research Fellowship. This year, we expanded our program designed to teach advanced surgical techniques for the management of complex foot deformities. Our fellow participated in clinical trials and reconstructive surgical procedures.

Other Teaching Contributions

Residency Training Attending Physician, Division of Podiatric Surgery, Beth Israel Deaconess Medical Center, Boston, MA; Training of podiatric surgical residents and visiting medical students from Harvard Medical School and from the Colleges of Podiatric Medicine. This residency program is 3 years in length, and includes 6 residents.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Cook E, Cook J, Rosenblum B, Basile P, **Landsman A**, Giurini J. Meta-analysis of first metatarsophalangeal joint implant arthroplasty. J Foot Ankle Surg 2009;48(2):180-90.

Hall PB, **Landsman A**, Banks AS, Dalmia L. Thermal properties of first metatarsal osteotomies. J Foot Ankle Surg 2009;48(4):432-8.

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Landsman A, DeFronzo D, Anderson J, Roukis, T. A scientific assessment of over-the-counter foot orthoses to determine their effect on pain, balance, and foot deformities. J Am Podiatr Med Assoc 2009;99(3):206-15.

Liden B, Simmons M, **Landsman A**. A prospective analysis of 22 patients treated with percutaneous RF nerve ablation for prolonged moderate to severe heel pain associated with plantar fasciitis. J Foot Ankle Surg 2009;48(6):642-7.

Original Articles (submitted or in press)

Landsman A, Agnew P, Joseph R, Parish L, Galiano R; A randomized, multi-center, prospective analysis of diabetic foot ulcers treated with TheraGauze alone or TheraGauze and Becaplermin. J Am Podiatr Med Assoc 2009; in press.

Landsman A, Angelina PF, Wu CC, Cook J, Robbins AH, Bornstein ES; Treatment of moderate to severe onychomycosis using a dual wavelength laser: A retrospective review of 27 cases with $\geq 50\%$ nail involvement. J Am Podiatr Med Assoc 2009; in press.

Reviews, Chapters and Editorials

Cornwell KG, **Landsman A**, James KS. Extracellular matrix biomaterials for soft tissue repair. Clin Podiatr Med Surg. 2009;26(4):507-23.

Landsman A. Advances in wound and bone healing [preface]. Clin Podiatr Med Surg 2009;26(4):xiii-xv.

Landsman A. Mechanical loading of collagen bioscaffolds for tendon and ligament repair why is prestressing important? Foot Ankle Spec. 2009;2(1):51-2.

Landsman A. Preoperative and perioperative management of the high-risk patient with diabetes mellitus. In: Zgonis T, editor. Surgical reconstruction of the diabetic foot and ankle. Philadelphia : Lippincott Williams & Wilkins Pub; 2009. p. 7-12.

Landsman A, Taft D, Riemer K. The role of collagen bioscaffolds, foamed collagen, and living skin equivalents in wound healing. Clin Podiatr Med Surg 2009; 26(4):525-33.

RESEARCH SUMMARY

BASIC RESEARCH

My main interest lies in studying the pathophysiology of diabetic wound healing in animal models. This work is being conducted with Drs. Frank W. LoGerfo and Leena Pradhan from the Division of Vascular Surgery.

CLINICAL RESEARCH

My main research interest is the vascular reactivity of micro- and macrocirculation. 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 in 2009 was mainly funded by grants from the NIH.

My clinical research interest is in the relationship between functional changes in vascular reactivity and structural changes of the skin. Other interests include the effect of c-nociceptive fiber dysfunction of wound healing and the diabetes-related impairment of angiogenesis.

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

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

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



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

LIST OF CURRENT EMPLOYEES

Adrian Krutz	Research Coordinator
Carlie Dice	Research Coordinator
Suzy Wu	Research Assistant
Sarada Kuchibhotla	Research Assistant
Ermelindo Leal, PhD	Research Fellow

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CLINICAL RESEARCH CONT'D

In addition, in collaboration with Roy Freeman, MD, our research examines the natural history of the progression of peripheral neuropathy in diabetic patients. Finally, I am collaborating very closely with Dr. Atul Malhotra, MD from the Harvard Center on Sleep Neurobiology and Sleep Apnea to examine the effects of sleep apnea on vascular reactivity. I currently serve as co-mentor for two fellows who work with Dr. Malhotra.

LIST OF CURRENT FUNDING

"Natural history of small fiber diabetic neuropathy"

NIH: 1 R01 NS046710-01

Project period: 2/1/05-1/31/10

PI: Aristidis Veves

"Sleep apnea and obesity: cardiovascular risk assessment"

NIH: 1 R01 HL073146-01

Project period: 7/1/05-6/30/10

PI: Atul Malhotra

Co-Investigator: Aristidis Veves

"Impaired wound healing in diabetic foot ulceration"

NIH: 1R01DK076937-01

Project period: 12/1/06-11/30/11

PI: Aristidis Veves

"Metabolic MRI of diabetic lower extremity disease"

NIH: 1R01 DK071569-01

Project period: 12/1/06-11/30/11

PI: Robert L. Greenman

Co-Investigator: Aristidis Veves

"Biochemics study to investigate the mechanisms through which a biochemics cream promotes wound healing in an in vivo rabbit model of neuroischemic wound healing"

Biochemics Inc.

Project period: 01/22/2008-12/31/2010

PI: Aristidis Veves

"The effect of diabetes, neuropathy, and arterial disease in lower extremity energy"

NIH: 1R21DK082987-01

Project period: 6/1/09 - 5/31/11

PI: Aristidis Veves

"The effect of Aliskiren on endothelial function in pre-diabetes and diabetes (investigator initiated research, Novartis Pharma Inc.

Project period: 09/01/09-08/31/11

PI: Aristidis Veves

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

"Role of neuropeptides in diabetic foot problems."

NIH: 1R01NS066205-01

Project period: 07/01/10-06/30/15

Co-PI: Aristidis Veves

“Interaction between obstructive sleep apnea and diabetes in cardiovascular risk”

NIH: 1R01HL102754-01

Project period: 07/01/10-06/30/15

Co-PI: Aristidis Veves

“Development of novel biomaterials for diabetic wound healing”

NIH: 1R41DK

Project period: 07/01/10-06/30/11

Co-PI: Aristidis Veves

“Contractile hydrogel dressing for primary wound closure”

Project period: 07/01/10-06/30/11

NIH: 1R41DK

Co-PI: Aristidis Veves

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

During the past year, we continued two prospective studies that are funded by two NIH R01 grants. We completed a study that was funded by an NIH STTR grant. We also initiated an R21 study and an investigator initiated study funded by Novartis Pharma.

The Veves Research Team

Back row from left to right: Rachel Cloutier, Aristidis Veves, Thomas E. Lyons, Szuhuei Wu.
Front row from left to right: Sarada Kuchibhotla, Thanh Dinh, Adrian Krutz.



Abstracts Presented at Local, National, and International Meetings

Leena Pradhan, Szuhuei Wu, Patrick Guthrie, Michelle Martin, Sarada Kuchibhotla, Frank Logerfo, **Aristidis Veves**. Neuropathic and Ischemic Models of Diabetic Wound Healing. Presented at the 69th ADA Scientific Sessions, New Orleans, LA; June 2009.

Thanh Dinh, John Doupis, Thomas E. Lyons, Sarada Kuchibhotla, Walker Julliard, Charalambos Gnardellis, Barry I. Rosenblum, Xiaoen Wang, John M. Giurini, Robert L. Greenman, **Aristidis Veves**. Foot Muscle Energy Reserves Are Reduced in Diabetic Patients without and with Peripheral Neuropathy. Presented at the 69th ADA Scientific Sessions, New Orleans, LA; June 2009.

Individual Accomplishments

- Member of the NHLBI Mentored Patient Oriented Research Career Development Award Panel for K23, K24 and K25 applications and R13 Conference Grants, and ad hoc member for ACTS Study Section panel.
- Scientific Committee member, 8th International Symposium on Diabetic Neuropathy and 19th Annual Meeting of the Diabetic Neuropathy Study Group of the EASD, October 2009, Toronto, Canada.

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Individual Accomplishments Cont'd

- Member of the Neurodiab Consensus Workshop on Diabetic Neuropathy, October 2009, Toronto, Canada.
- I continue to serve as an Associate Editor for the journal: *Wounds: A Compendium of Clinical Research and Practice* (2000-).
- I was asked to act as a peer reviewer for the journals: the Diabetes, Diabetologia, Diabetes Care, Diabetic Medicine, Wound Repair and Regeneration and Wounds.
- Series Editor, Contemporary Diabetes, Humana Press, Totowa, NJ (2003-).

Invited Presentations

"Vascular Dysfunction, Neuropeptides and Inflammation in Wound Healing in Diabetes". 1st National Symposium of the Greek Association for the study of Diabetic Foot. Athens, Greece. February 2009.

"The Role of Vascular Function and Inflammation in the Development and Healing of DFU". 2009 Symposium on Advanced Wound Care and Wound Healing Society (SAWC/WHS) meeting. Dallas, TX. April 2009.

"The Role of Vascular Function and Inflammation in the Development and Healing of DFU". 2009 Autumn Symposium on Advanced Wound Care and Wound Healing Society (SAWC/WHS) meeting. Washington, DC. September 2009.

REPORT OF TEACHING

Other Teaching Contributions

In the past year I was involved in the following teaching responsibilities:

Dr. Ermelindo Leal, PhD, post doc research fellow worked September to December directly under me in basic research.

Dr. Francesco Tecilazich, MD, is a research fellow from Italy working directly under me in clinical research. I am member of the mentoring committee in the K23 award of Dr. Christopher Gibbons, MD, Department of Neurology.

I was involved in the mentoring of Dr. Lora Kesselman, PhD, Department of Neurology for her F32 award.

I worked closely in common research projects with Drs. Susie Yim Yeh, MD, Department of Medicine, Brigham and Women's Hospital, Shilpa Rahangdale MD, Department of Medicine, Brigham and Women's Hospital and Thanh Dinh, DPM, Department of Surgery, Beth Israel Deaconess Medical Center, all at the Instructor level. My role includes supervision in research design and conduction and manuscript and research application writing

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Cloutier R, Horr S, Niemi JB, Scoffone H, D'Andrea S, Lima C, Harry JD, **Veves A**. Prolonged mechanical noise restores tactile sense in diabetic neuropathic patients. *Int J Low Extrem Wounds* 2009;8:6-10.

Dinh T, Doupis J, Lyons TE, Kuchibhotla S, Julliard W, Gnardellis C, Rosenblum BI, Wang X, Giurini JM, Greenman RL, **Veves A**. Foot muscle energy reserves are reduced in diabetic patients without and with clinical peripheral neuropathy. *Diabetes Care* 2009;32:1521-4.

Doupis J, Lyons TE, Wu S, Gnardellis Ch, Dinh T, **Veves A**. Microvascular reactivity and inflammatory cytokines in painful and painless peripheral diabetic neuropathy. *J Clin Endocrinol Metab* 2009;94(6):2157–2163.

Khaodhiar L, Brennan AM, Lima C, Chan JL, Mantzoros CS, Manning WJ, Danias PG, **Veves A**. Effect of Valsartan on left ventricular anatomy and systolic function and aortic elasticity. *Metabolism* 2009;58:682–688.

Rutkove SB, **Veves A**, Mitsa T, Nie R, Fogerson P, Costa M, Garmirian L, Nardin RA. Impaired distal thermoregulation in diabetes and diabetic polyneuropathy. *Diabetes Care* 2009;32:671-6.

Yim Yeh S, Doupis J, Rahangdale S, Horr S, Malhotra A, **Veves A**. Total serum bilirubin does not affect vascular reactivity in patients with diabetes. *Vasc Med* 2009;14:129-36.

Original Articles (submitted or in press)

Chin MS, Ogawa R, Lancerotto L, Pietramaggiore G, Schomacker K, Scherer SS, Mathews JC, Van Duyn P, Prsa MJ, Ottensmeyer MP, **Veves A**, Orgill DP. In vivo acceleration of skin growth using a servo-controlled stretching device. *Tissue Eng Part C Methods* 2009; in press.

Doupis J, Rahangdale S, Gnardellis C, Pena SE, Malhotra A, **Veves A**. Effects of diabetes and obesity on vascular reactivity, inflammatory cytokines and growth factors. *Circulation* 2009; submitted.

Kasselman L, **Veves A**, Gibbons C, Rutkove SB. Repeated cold exposure hastens the development of diabetic polyneuropathy in the rat. *Exp Diabetes Res* 2009; in press.

Pradhan L, Cai X, Wu S, Andersen ND, Martin M, Malek J, Guthrie P, **Veves A**, LoGerfo FW. Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing. *J Surg Res* 2009; in press.

Rajesh M, Mukhopadhyay P, B tkai S, Patel V, Becker L, Hask  G, Liaudet L, **Veves A**, Mechoulam R, Pacher P. Cannabidiol attenuates myocardial dysfunction, fibrosis, inflammation, cell death and interrelated signaling pathways associated with diabetic cardiomyopathy. *J Am Coll Cardiol* 2009; submitted.

Yim Yeh S, Rahangdale S, Nguyen A, Jordan A, Novack V, **Veves A**, Malhotra A. In obese individuals, obstructive sleep apnea is associated with impaired endothelial function in younger subjects. *Chest* 2009; submitted.

Yim Yeh S, Rahangdale S, Nguyen A, Stevenson K, Jordan A, Novack V, **Veves A**, Malhotra A. Endothelial dysfunction in obstructive sleep apnea and type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2009; submitted.

Reviews, Chapters and Editorials

Pradhan L, Nabzdyk C, Andersen ND, LoGerfo FW, **Veves A**. Inflammation and neuropeptides: the connection in diabetic wound healing. *Expert Rev Mol Med* 2009;11:e2.

Dinh T, Scovell S, **Veves A**. Peripheral arterial disease and diabetes: a clinical update. *Int J Low Extrem Wounds* 2009;8(2):75-81.

Rahangdale S, Yeh SY, Malhotra A, **Veves A**. Therapeutic interventions and oxidative stress in diabetes. *Front Biosci* 2009;14:192-209.

Reviews, Chapters and Editorials (submitted or in press)

Dinh T, Snyder G, **Veves A**. Current techniques to detect foot infection in the diabetic patient. *Int J Low Extrem Wounds* 2009; in press.

Tellechea A, Leal E, **Veves A**, Carvalho E. Inflammatory and angiogenic abnormalities in diabetic wound healing: role of neuropeptides and therapeutic perspectives. *Open Circ and Vasc J* 2009; in press.

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Abstracts

Yeh S, Rahangdale S, Stevenson KE, Jordan A, Novack V, **Veves A**, Malhotra A. In obese individuals, OSA is associated with impaired endothelial function in younger subjects. Am J Respir Crit Care Med 179;2009:A5326.

Yeh S, Rahangdale S, Stevenson KE, Jordan A, Novack V, **Veves A**, Malhotra A. In obese individuals, the effect of OSA on vascular function is modulated by age and gender. SLEEP 2009;32: A174.

DIVISION OF TRANSPLANTATION

Douglas W. Hanto, MD, PhD
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Research Fellow in Surgery
Senior Research Associate
Research Assistant
Research Student

Associate Professor of Surgery and Psychology

Departments of Psychiatry and Surgery
Director, Outcomes for Transplant (as of October 2009)

Professor of Medicine and Surgery

Co-Director, The Transplant Institute

Lecturer on Medicine

Co-Director, The Transplant Institute

Professor of Medicine
Associate Professor of Medicine
Assistant Professor of Medicine
Administrative Coordinator

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RESEARCH SUMMARY

BASIC RESEARCH

My current laboratory research is focused on the ability of carbon monoxide (CO) at low concentrations to be protective in rodent and large animal models of ischemia-reperfusion injury (IRI) and delayed graft function (DGF), allograft rejection and survival, and in hepatic regeneration. CO is a product of HO-1 action on heme and has potent anti-inflammatory, anti-apoptotic, and anti-proliferative effects. It is of great interest that the CO effects are observed with intermittent exposure, e.g., 1 hour per day. DGF is a common complication of kidney transplantation, occurring in 20%-50% of deceased donor kidneys, and is associated with decreased short-term and long-term function, decreased graft survival, increased risk of rejection, and increased costs. We have developed a novel kidney allograft model of DGF in swine that allows us to examine the ability of CO to prevent IRI and the resulting DGF, as well as acute and chronic rejection. We have shown that treatment of the recipient with intra-operative inhaled CO using a novel CO gas delivery system is effective in restoring kidney function more rapidly than in non-CO treated animals and accelerating the recovery of renal function post-transplant. We are currently determining the optimal treatment regimen (dose, duration, timing), studying whether CO treatment will allow longer cold storage time, what role O₂ plays in the efficacy of CO, and importantly, whether treatment of the donor and the allograft will further limit DGF. We are also examining the potential usefulness of non-invasive real time imaging (MRI) to evaluate renal function over time in recipients. We believe the mechanisms of protection in the recipient and donors are different with regard to the innate immune response to IRI. We are currently investigating the molecular mechanisms by which CO decreases DGF utilizing immunopathology and gene expression profiling using highly sensitive RT-PCR and Affymetrix gene arrays. Preliminary data has shown decreased cell death and enhance epithelial cell repair in CO treated animals with a likely component being more rapid recruitment and differentiation of stem cells.



Douglas W Hanto, MD, PhD

LIST OF CURRENT EMPLOYEES

Kaori Kuramitsu, MD, PhD	Research Fellow in Surgery
Helen Snook	Administrative Coordinator

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BASIC RESEARCH CONT'D

In our rodent models we know that CO enhances endothelial cell (EC) repair that is otherwise lost as a result of warm and cold ischemia followed by reperfusion injury. CO treatment of the recipient is unlikely to have an impact on EC preservation, but rather influences a repair process of the lost endothelium and subsequent epithelial renal tubule cells. Such a mechanism would be different yet complemented by donor treatment that would be likely to prevent IRI-induced cell death through prophylactic cell preservation. We are planning to test whether CO treatment of the recipient will augment EC repair and whether treatment of the donor plus recipient results in additive repair. From a cell signaling and molecular standpoint, we are also examining *in vitro* the role of RhoA, Akt, and eNOS/NO in the ability of CO to augment motility and proliferation of EC that has been shown to be important in EC preservation and proliferation. This work has been the basis for planned human clinical trials of CO in organ donation and transplantation to prevent DGF that will take place in part under my direction at BIDMC. This work is being done in collaboration with Leo Otterbein, PhD in our Division, who has made seminal contributions to our understanding of the biological effects of CO in many different animal models and is recognized as one of the world's experts in CO. Taken together, we have the unique opportunity to study a truly novel gaseous molecule therapy with a true bench to bedside application.

CLINICAL RESEARCH

A complication of immunosuppression is the development of post-transplant lympho-proliferative diseases (PTLD). We were the first to clearly describe the clinical syndromes associated with these PTLD, their association with the Epstein-Barr virus (EBV), and that they were polyclonal B-cell proliferations that could evolve into monoclonal B-cell proliferations. We were the first to define the morphological features of these polymorphic lymphoproliferations and to propose their classification as polymorphic diffuse B-cell hyperplasia or polymorphic B-cell lymphoma. The two papers published in *Cancer Research* remain the classic descriptions and have been the basis for many subsequent clinical, immunopathologic, and virologic studies of these diseases. We were also the first to report the clinical use of acyclovir in a patient with EBV infection and showed suppression of oropharyngeal shedding of EBV during acyclovir therapy and regression of a polyclonal B-cell proliferation. By examining immunoglobulin gene rearrangements and cytogenetic abnormalities, we were able to demonstrate in predominantly polyclonal B-cell proliferations, a subpopulation of B-cells that were monoclonal and in some cases oligoclonal. Polyclonal proliferations were shown to evolve into monoclonal B-cell lymphomas and were no longer responsive to anti-viral therapy. The elucidation of the pathogenesis of the EBV-related PTLD has improved the ability to prevent and treat these diseases leading to improved patient survival. Recent studies have been focusing on the relative risks of various immunosuppressive drugs and combinations of drugs in the development of PTLD. We have also published data defining when it is safe to retransplant patients with a history of PTLD.

I am also actively involved in other clinical trials examining the safety and efficacy of kidney and liver transplantation in HIV+ patients, examining the safety and efficacy of various new immunosuppressive drugs and combinations in kidney and liver transplant patients, and assessing the role of clinical pathways in improving the quality and consistency of transplant patient care. We have developed over 25 comprehensive clinical pathways that begin during the pre-transplant evaluation phase and include the peri-operative, inpatient, and post-transplant phases of kidney, liver, and pancreas transplant recipients and living donors. I have also written and spoken about some of the ethical challenges and controversies in transplantation such as solicitation of donor organs, buying and selling of organs, as well as others.

We have also established a "Center for Transplant Outcomes and Quality Improvement" within the Transplant Institute at BIDMC that has been supported by a generous gift from a liver transplant recipient and her husband. The purpose of this center is to develop a comprehensive database on pre- and post-transplant patients and to provide regular and timely analyses that will be geared to identifying opportunities for enhancing the quality of care delivered to inpatients and outpatients and improving outcomes. Interactive adult learning educational programs and tools for patients and their families that involve them in their care are being developed. We are examining the challenges presented by patients and families who struggle financially and socially in order to determine their impact on access to transplant, quality of care, and outcomes. These disparities and how to intervene to reverse them will be a major focus of the Center.

LIST OF CURRENT FUNDING

"Solid organ transplantation in HIV: Multi-site study"

NIH/NIAID AI052748

Project Period: 2004-2012

PI: Peter G. Stock (University of California San Francisco)

Site Principal Investigator: Douglas W. Hanto

"Randomized double-blind study to assess the efficacy and safety of prophylactic use of Maribavir versus oral gancyclovir for the prevention of cytomegalovirus disease in recipients of orthotopic liver transplants"

Viro Pharma

Project Period: 2007-2010

Co-Investigator: Douglas W. Hanto

"A 12-month open-label randomized multi-center sequential cohort dose-finding study to evaluate the efficacy, safety, and tolerability of oral AEB071 versus tacrolimus in combination with Myfortic, Simulect, and corticosteroids in de novo adult renal transplants"

Novartis

Project Period: 2007-2010

Co-Investigator: Douglas W. Hanto

"Neoadjuvant sorafenib prior to RFA in HCC, a randomized controlled phase II trial"

Bayer/Onyx

Project Period: 2008-

Co-Investigator: Douglas W. Hanto

"Placebo-controlled, safety and tolerability study of the effects of carbon monoxide for inhalation in patients receiving kidney transplantation"

Ikaria C201

Project Period: 2008-

Site Principal Investigator: Douglas W. Hanto

"Social networks and socialized risk: Understanding and mitigating disparities in renal transplantation."

Harvard Catalyst Pilot Grants Program

Project Period: 2009-2010

Principal Investigator: Douglas W. Hanto

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Abstracts Presented at Local, National and International Meetings

Croome KP, Chudzinski R, **Hanto DW**. Increasing time delay from presentation until referral to tertiary care surgeons for hepatobiliary (HPB) malignancies. Presented at the University of Western Ontario Research Day, London, ON; April 29, 2009.

Stock P, Roland M, **Hanto D**, Johnson S, Pavlakis M, Light J, Barin B, Jayaweera D, Murphy B. Early and unexpected results in a multicenter study of kidney transplantation in HIV-infected recipients. Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #23.

Dib MJ, Kennealey PT, Farrell ML, Mandelbrot D, Curry M, Hertl M, Ko DSC, Cosimi AB, Tsoulfas G, Saidi R, Elias N, Johnson SR, **Hanto DW**, Markmann JF, Karp SJ. Risk factors for chronic kidney disease (CDK) after liver transplantation: implications for performing combined liver and kidney transplantation (CLKT). Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #247.

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Mandelbrot D, Pavlakis M, Johnson S, Karp S, **Hanto D**, Rodrigue J. Practices and barriers in living kidney donor follow-up: a survey of U.S. transplant centers. Presented at the American Transplant Congress 2009. Boston, MA; May 30-June 4. abstract #416.

Dib MJ, Ferrada P, Challies T, Nasser I, Brennan DD, Goldberg SH, Chudzinski R, Karp SJ, Johnson SR, **Hanto DW**, Curry MP. Tumor burden as determined by radiological volumetry is an accurate predictor of recurrence after liver transplantation for HCC utilizing RFA as a bridging therapy. Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #888.

Kuramitsu K, Wegiel B, Csizmadia E, Otterbein LE, **Hanto DW**. Exposure to carbon monoxide enhances liver regeneration in mice. Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #896.

Rogers C, Bain B, Johnson S, Wong M, Stablein D, Stock P, Frassetto L, **Hanto D**, Roland M. Rapamycin fails to yield a renal sparing effect in HIV+ transplant recipients. Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #1082.

Chudzinski R, Khwaja K, Teune P, Tang H, Pavlakis M, Rogers C, Johnson S, Karp S, **Hanto D**, Mandelbrot D. Successful DCD kidney transplantation using early corticosteroid withdrawal. Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #1336.

Hanto DW, Maki T, Thomas M, Wegiel B, Gallo D, Bersenbrugge A, Cooreman M, Szabo C, Otterbein LE. Carbon monoxide reduces delayed graft function of a kidney allograft in swine by reducing cell death and inflammation and by enhancing repair. Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #1391.

Abdul Q, Chudzinski R, Tang H, Mandelbrot D, Wong M, Karp S, Johnson S, **Hanto D**, Pavlakis M. Infection incidence in pancreas after kidney transplantation compared to simultaneous kidney pancreas transplantation. Presented at the American Transplant Congress 2009, Boston, MA; May 30-June 4. abstract #1891.

Croome KP, Chudzinski R, **Hanto DW**. Increasing time delay from presentation until referral to tertiary care surgeons for hepatobiliary (HPB) malignancies. Presented (as a poster) at the Canadian Surgery Forum, Victoria, BC; September 11, 2009.

Kuramitsu K, Wegiel B, Csizmadia E, Otterbein LE, **Hanto DW**. The effect of carbon monoxide on liver regeneration after hepatectomy. American Association for the Study of Liver Diseases. Presented at The Liver Meeting 2009, Boston, MA; October 30-November 3, 2009. abstract #713.

Invited Presentations

"Transplantation: State of the Art (and Science)". Medical Grand Rounds, Saint Vincent Hospital. Worcester, MA. January 29, 2009.

"Protective Effects of Carbon Monoxide". Grand Rounds, Department of Anesthesia, Beth Israel Deaconess Medical Center. Boston, MA. April 1, 2009.

"Ethical Issues in Transplantation". Medical Grand Rounds, Saints Medical Center. Lowell, MA. April 2, 2009.

"Protective Effects of Carbon Monoxide". Research and Academic Affairs All Staff Meeting, Beth Israel Deaconess Medical Center. Boston, MA. May 1, 2009.

Key Opinion Leaders Conference. The Transplantation Society, Jackson Hole, WY. July 16-19, 2009.

"Carbon monoxide in health and disease." Grand Rounds, Department of Surgery. Beth Israel Deaconess Medical Center. Boston, MA. September 23, 2009.

"The Role of the Surgeon in Patients with Hepatobiliary Cancer". AASLD/ASGE Endoscopy Course. The Liver Meeting (AASLD Annual Meeting), Boston, MA. October 30, 2009.

Team Chair, Classification of PTLT and the Impact of EBV. PTLT Consensus Conference (Genzyme). Seville, Spain. November 12-15, 2009.

"Case Presentations: Surgical Management of Metastatic Colon Cancer to the Liver." Tumor Board for Oncology Fellows, Division of Hematology-Oncology, Beth Israel Deaconess Medical Center. Boston, MA. November 23, 2009.

REPORT OF TEACHING

Graduate School and Graduate Medical Courses:

2001-present Harvard Medical School; Boston, MA
Core Clerkship in Surgery
Teaching role: Attending
Type of students: Average of 10 HMS students per year
Preparation and contact time: Average 2 hours per week

2001-present Transplant Elective
Teaching role: Attending
Type of students: Average of 2-4 HMS students per year
Preparation and contact time: Average 2 hours per week

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Egbuna O, Davis RB, Chudzinski R, Pavlakis M, Rogers C, Molakatalla P, Johnson SR, Karp S, Monaco AP, Tang H, **Hanto DW**, Mandelbrot DA. Outcomes with conversion from calcineurin inhibitors to sirolimus after renal transplantation in the context of steroid withdrawal or steroid continuation. Transplantation 2009; 88:684-92.

Ladin K, Rodrigue JR, **Hanto DW**. Framing disparities along the continuum of care from chronic kidney disease to transplantation: barriers and interventions. Am J Transplant 2009; 9:669-74.

Mandelbrot DA, Pavlakis M, Johnson SR, Karp SJ, **Hanto DW**, Rodrigue JR. Practices and barriers in long-term living kidney donor follow-up: a survey of US transplant centers. Transplantation 2009; 88:855-60.

Rogers CC, Johnson SR, Mandelbrot DA, Pavlakis M, Horwedel T, Karp SJ, Egbuna O, Rodrigue JR, Chudzinski RE, Goldfarb Rumantzev AS, **Hanto DW**, Curry MP. Timing of sirolimus conversion influences recovery of renal function in liver transplant recipients. Clin Transplant 2009; 23:887-96.

Reviews, Chapters and Editorials

Hanto DW. Book Review: When altruism isn't enough: The case for compensating donors. Am J Transplant 2009; 9:2855.

Hanto DW, Chudzinski R. What does the CONVERT trial data really tell us about conversion from calcineurin inhibitors to sirolimus? [Editorial]. Transplantation 2009;87:164-5.

Hanto DW. Historical aspects of post-transplant lymphoproliferative disorders (PTLD). In: Dharnidharka V, Green M, Webber S, editors. Post-transplant lymphoproliferative disorders. Heidelberg: Springer; 2009. p. 5-15.

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Miksad R, **Hanto D**, Timmerman RD, Come S. Management of isolated liver metastases. In: Harris JR, Lippman ME, Morrow M, Osborne CK, editors. Diseases of the breast, fourth edition. Baltimore: Lippincott Williams & Wilkins; 2009. p. 1030-7.

Clinical Communications

Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MM, D'Alessandro A, Pomfret EA, Freeman RB, Markmann JF, **Hanto DW**, Matas AJ, Roberts JP, Merion RM, Klintmalm GB, ASTS Standards on Organ Transplantation Committee. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. Am J Transplant 2009; 9:2004-2011.

Tilney N, Murray J, Thistlethwaite R, Norman D, Delmonico F, **Hanto D**, Leichtman A, Danovitch G, Sayegh M, Shapiro R, Harmon W, Salvatierra O, Brennan D, McDiarmid S, Stock P, Pomfret L, Bennett W, Conti D, Metzger B, Sarwal M, Cosimi AB. Promotion of altruistic donation [Letter]. Transplantation 2009; 88(9):1145-7.

RESEARCH SUMMARY

BASIC RESEARCH

Research in my laboratory concerns the biology of liver development and liver regeneration, with the goal of understanding the molecular basis of these processes and then applying this knowledge to strategies for liver renewal or replacement. Preparation for this research focus included work in molecular biology and limb development. Contributions included the cloning and characterization of a subunit of the human NMDA receptor and publications elucidating the signaling pathways critical for cartilage and bone development. Specifically, we established the role of indian hedgehog in a feedback loop involving parathyroid hormone-related protein which regulates chondrocyte differentiation and maturation. Further studies demonstrated that Noggin antagonism of bone morphogenetic protein 4 controls development of the axial skeleton through mesoderm patterning.



Seth J. Karp, MD

LIST OF CURRENT EMPLOYEES

Karen Ho, MD	Research Fellow in Surgery
Martin Dib, MD	Research Fellow in Surgery
Nhue Do, MD	Research Fellow in Surgery
Rita Gottschalk, MS	Research Assistant
Lynne Mosher	Administrative Associate

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CLINICAL RESEARCH

Clinical contributions involve expertise in liver, kidney, and pancreas transplantation, vascular access, and general surgery. I developed a novel procedure for vascular access involving use of the renal vein for outflow that is particularly suitable for patients who present difficult access problems. Other clinical contributions include a novel method for diagnosing gastrointestinal bleeding, which has proven successful in animal models, and demonstration that acute renal failure should not preclude use of kidneys for transplantation. Recent research identifies novel methods for determining the suitability of livers for donation after cardiac death transplantation.

LIST OF CURRENT FUNDING

"Activin signaling in liver development and regeneration"

NIH K08

Project Period: 2003-present

Principal Investigator: Seth J. Karp

"Lineage analysis of the developing and regenerating liver"

American Society of Transplant Surgeons

Project Period: 2005-present

Principal Investigator: Seth J. Karp

Collaborative Scientist Award

American Society of Transplant Surgeons

Project Period: 2008-present

Principal Investigator: Seth J. Karp

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Mandelbrot DA, Pavlakis M, **Karp SJ**, Johnson SR, Hanto DW, Rodrigue JR. Practices and barriers in long-term living kidney donor follow-up: a survey of U.S. transplant centers. *Transplantation* 2009; 15;88(7):855-60.

Original Articles (submitted or in press)

Dib MJ, Ho KJ, Hanto DW, **Karp SJ**, Johnson SR. Roux limb volvulus after pancreas transplantation: an unusual cause of pancreatic graft loss. *Clin Transplant* 2009; in press.

Rogers CC, Johnson SR, Mandelbrot DA, Pavlakis M, Horwedel T, **Karp SJ**, Egbuna O, Rodrigue JR, Chudzinski RE, Goldfarb-Rumyantsev AS, Hanto DW, Curry MP. Timing of sirolimus conversion influences recovery of renal function in liver transplant recipients. *Clin Transplant* 2009; in press.

Reviews, Chapters and Editorials

Karp SJ. Clinical implications of advances in the basic science of liver repair and regeneration. *Am J Transplant*. 2009;9(9):1973-80.

RESEARCH SUMMARY

BASIC RESEARCH

The aims of my research are to understand the molecular and cellular basis of tolerance to islet allograft and xenograft rejection. By necessity this includes an understanding of the molecular and cellular basis of diabetogenic autoimmunity. In particular I am pursuing a promising new area for translation application to understand the mechanism and role of inflammation in transplants. In using these two tools, my aim is to design new therapeutic and diagnostic approaches and test them in animal models. I believe that it is necessary to later the balance of inflammation from pro- to anti-inflammatory model as a means to establish tolerance to islets in an autoimmune host. Thus I aim to follow extremely exciting data, concentrating my efforts to cure diabetes through the prevention of islet graft rejection or recurrence of autoimmune disease. My aim is to find protocols for tolerance induction in clinical transplantation.

The following represents a list of funded projects in my laboratory:

- 1) Tolerance induction for primate islet transplantation
- 2) New strategy of tolerance induction in non-human primate islet allograft model
- 3) Tolerance induction for primate islet
- 4) Thoracic allograft tolerance in non-human primates
- 5) Human islet transplant center – a pipeline to induce tolerance
- 6) A new approach to reverse the onset of autoimmune diabetes
- 7) Inflammation and T cell memory: inter-related barriers to allograft tolerance
- 8) On the role of reg T cells in transplantation
- 9) To test the new Aralast-NP on the role of inflammation and autoimmunity in the NOD mouse

Area being developed for funding

Imaging of islet transplant using “color-coded” T-cells. In this system, T-cell subsets express different colors and can be followed *in vivo* after islet transplantation.



Maria Koulmanda, MSc, PhD

LIST OF CURRENT EMPLOYEES

Zhigan, Fan MD, Ph.D	Research Fellow
Dusan Hanidziar, MD	Research Fellow
Derek Liu, PhD	Research Fellow
Babak Movahedi, MD	Research Fellow
Rebecca Sampathkumar, PhD	Research Fellow
Singh Gurbakhish, MD	Research Fellow
Naved Munir, Msc	Research Fellow
Nipun Goel, MSc	Research Associate

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BASIC RESEARCH CONT'D

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

In 1995, while writing my PhD dissertation part-time, I was recruited as an Overseas Research Associate by Professor David White of Cambridge University, UK. Using the transgenic pig-to-monkey model, we demonstrated that hyperacute rejection, the barrier that prevents xenogeneic organ transplants, is not a barrier to islet transplants. In 1998 I was recruited by Dr. Hugh Auchincloss to establish non-human primate and NOD mouse core programs for the Juvenile Diabetes Foundation (JDF) Center for Islet Transplantation at Harvard Medical School. In collaboration with Dr. Terry Strom, we achieved remarkable prolongation (ca. 300 days) of allogeneic monkey islets following a short course of novel co-stimulatory based therapy. Indeed, the grafts failed due to non-immune related islet loss that also destroyed a similarly sized autologous pancreas. We subsequently tested the effect of short-term treatment with IL-2.Ig mutant antagonist type IL-15.Ig plus sirolimus in the monkey islet allograft and new-onset Type 1 (T1) diabetes mellitus (DM) NOD models. In treated monkey recipients, long-term drug free graft survival, a cardinal achievement in this extremely difficult model, is routine. In the new-onset T1DM NOD model this regimen restores normoglycemia, immune tolerance to islets, and abolishes a previously unrecognized inflammatory state that impairs insulin signaling, thereby causing insulin resistance. This regimen has been approved for an Immune Tolerance Network funded clinical trial in T1DM.

Next we hypothesized that agents that tilt the balance of pro- to anti-inflammatory molecules toward an anti-inflammatory state would prove similarly effective in these models. Hence, new-onset T1DM mice were treated short-term with alpha-1-anti-trypsin (AAT), an acute phase reactant. Although this agent does not directly act upon T cells, AAT promotes rapid restoration of normoglycemia and islet cell tolerance in the NOD model. In fact, the remnant islet cell mass rapidly tripled in size in the AAT-treated mice. In AAT-treated monkey islet allograft recipients, insulin levels rise substantially ca. 30 days post-transplantation. In contrast, insulin levels insidiously decrease in other islet (even autologous) transplant models. While this work is not yet published, the Immune Tolerance Network has approved an AAT clinical trial in new-onset T1DM. As hypoxic- and ischemic-reperfusion type injuries lead to amplified expression of pro-inflammatory cytokines in human transplants, these findings open new opportunities for clinical application of inflammation-altering cytoprotective strategies. Going forward I am concentrating on the study of allogeneic and xenogeneic (both fetal and conventional) islet transplants placed into cynomolgus monkey recipients. I will pay particular attention to the study of novel anti-inflammatory (cytoprotective) strategies as a means to enable immune tolerance and nurture resilient ("cytoprotected") islets as a means to cure T1DM in new-onset diabetics or in recipients of islet transplants.

LIST OF CURRENT FUNDING

"Inflammation and T cell memory: inter-related barriers to allograft tolerance"

National Institutes of Health, 1-U19 DK080652

Project Period: 07/01/2007-06/30/2012

PI: Maria Koulmanda

"New strategy to induce islet allograft tolerance"

Juvenile Diabetes Foundation 1-2007-52

Project Period: 12/01/2007 -11/30/2010

PI: Maria Koulmanda

"JDRF center for diabetes research: human islet transplantation"

Juvenile Diabetes Research Foundation

Project Period: 04/01/2006- 03/31/2011

Pilot study "New strategy of tolerance induction using DC's.

PI: Maria Koulmanda

“New strategy to induce islet allograft tolerance in NHP model”

Juvenile Diabetes Research Foundation

Project Period: 04/01/2008-03/31/2011

Co-PIs: Maria Koulmanda and Xin Xiao Zheng

“Thoracic allograft tolerance in non-human primates”

National Institutes of Health, NIAID U19 AI066705-01

Project Period: 07/02/ 2005-06/30/2010

PI: Joren Madsen

Collaborator: Maria Koulmanda

“On the role of regulatory T cells in transplantation”

National Institutes of Health, PO1 AI041521

Project Period: 07/01/2007-06/30/2012

PI: Terry Strom

Co-Investigator: Maria Koulmanda

Project 8: “The autoimmunity/inflammation connection in type-1 diabetes”

JDRF Center on Immunological Tolerance in Type 1 Diabetes at Harvard Medical School (response to RFA)

Juvenile Diabetes Foundation 4-2007-1057

Project Period: 01/10/2008-12/31/2013

PI: Terry Strom

Co-investigator: Maria Koulmanda

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Accomplishments in the Laboratory

We were fortunate to have our work on in vivo tracking of “color-coded” effector, natural, and induced regulatory T cells in allograft response accepted for publication in Nature Medicine; see the Bibliography below.

Abstracts presented at Local, National and International Meetings

Hanidziar D, Fan Z, Strom TB, **Koulmanda M**. The reciprocal relationship between Th17 immunity and Foxp3-expressing Tregs in the allograft response. Concurrent session 53: Tolerance II: (Pre)Clinical/Th17. Presented as oral presentation at the American Transplant Congress. June 1, 2009.

Fan Z, Spencer J, Lu Y, Pitsillidis C, Singh G, Kim P, Yun S, Strom TB, Lin C, **Koulmanda M**. In vivo tracking of “color-coded” effector, natural and induced regulatory T cells in allograft response. Session: Stem Cells, Tolerance and Immunity. Abstracts, p. 326. Oct 13th. Presented as oral presentation at International Pancreas and Islet Transplantation Association – International Xenotransplantation Association. October 12th-16th, 2009.

Koulmanda M, Qipo A, Fan Z, Singh G, Movahedi B, Kaiw T, Strom TB. Prevention of non-immunologic loss of transplanted islets in monkeys. Session: Islet Engraftment. Presented as an oral presentation at International Pancreas and Islet Transplantation Association – International Xenotransplantation Association. October 12th-16th, 2009.

Movahedi B, Singh G, Qipo A, Strom TB, **Koulmanda M**. In vivo assessment of functional beta cell mass in macaques. Session 1 Islet Xenotransplantation I and Encapsulation. Presented as oral presentation at International Pancreas and Islet Transplantation Association – International Xenotransplantation Association. October 12th-16th, 2009.

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Individual Accomplishments

Invited Plenary Speaker

- “New biotherapeutics that control inflammation and immunity”; Austin Research Institute; Melbourne, Australia, January 9th.
- “T1DM, T cell directed Rx strategies and the confounding role of inflammation”. Beta cell replacement in diabetic patient; Session: Open Questions in Islet Transplantation. June 19th. Fifteenth N.A.T. Meeting, Program Nantes, France; June 18-19.
- “Self-Tolerance in Type 1 Diabetes can be restored by reversal of adverse Inflammation” Global Hellenic Medical & Biosciences Network; Athens, Greece; September 2-5.

Invited Speaker

- “Prevention of Non-Immunologic Loss of Transplanted islets in Monkeys”; Joint Meeting IPITA-IXA; Venice, Italy; October 12th-16th
- “In vivo tracking of “color-coded” effector, natural and induced regulatory T cells in allograft response”; Joint Meeting IPITA-IXA; Venice, Italy; October 12th-16th

Invited Chair

- New Approaches in islet Xenotransplantation. International Pancreas and Islet Transplantation Association – International Xenotransplantation Association Venice, Italy; October 12th-16th 2009

Other Accomplishments

- Appointed as an Associate Professor of Surgery, Melbourne University, Melbourne, Victoria, Australia
- Appointed to the editorial board of Xenotransplantation and Transplantation
- Ad Hoc Reviewer for Journals:
 - Nature Biotechnology, Cell Transplantation, Xenotransplantation, Transplantation
 - Clinical and Experimental Immunology, Diabetologia, American Journal of Transplantation
- International Committee Member for the Cell Transplantation Society
- Co-sponsored an NIH F32 application for Dusan Hanidziar MD entitled “Role of IL-21 in the Allograft Response”.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles (submitted or in press)

Fan Z, Spencer JA, Lu Y, Pitsillides CM, Singh G, Kim P, Yun SH, Toxavidis V, B. Strom TB, Lin CP, **Koulmanda M**. In vivo tracking of “color-coded” effector, natural and induced regulatory T cells in allograft response. Nature Med 2009; in press.

Papas KK, Colton CK, Qipo A, Wu H, Nelson RA, Hering BJ, Weir GC, **Koulmanda M**. Prediction of marginal mass required for successful islet transplantation. J Inv Surg 2009; in press.

Reviews, Chapters and Editorials

Strom TB, **Koulmanda M**. Recently discovered T cell subsets cannot keep their commitments: J Am Soc Nephrol 2009;20:1677-80.

Weir GC, **Koulmanda M**. Control of inflammation with alpha 1-antitrypsin: a potential treatment for islet transplantation and new-onset type 1 diabetes. Curr Diabetes Reports 2009;9(2):100-2.

Abstracts

Hanidziar D, Fan Z, Strom TB, **Koulmanda M**. The reciprocal relationship between Th17 immunity and Foxp3-expressing Tregs in the allograft response. Am J Transplant 2009; 9 (s2): 301A.

RESEARCH SUMMARY

BASIC RESEARCH

Currently my time is exclusively devoted to research that includes the training of postdoctoral fellows and surgical residents. My research has been focused on understanding the role of the enzyme heme oxygenase and the products of its activity, particularly carbon monoxide, in models of oxidative stress. While my experience has been primarily in models of acute lung injury and inflammation, it has recently diverged to include transplant and vascular biology and models of liver injury. My research has evolved into the study of carbon monoxide as a protective molecule, much like nitric oxide (in fact, my laboratory is now involved in exploring the interrelationship between these two gas molecules), with current studies looking at the cellular mechanisms and targets of action. In addition, the translation of this research toward clinical application has directed collaborations with investigators into the initiation of human testing.



Leo E. Otterbein, PhD

LIST OF CURRENT EMPLOYEES

Beek Yoke Chin, PhD	Instructor in Surgery
Barbara Wegiel, PhD	Instructor in Surgery
Daniel Doberer, MD	Research Fellow in Surgery
Rodrig Marculescu, MD	Research Fellow in Surgery
Eva Czismadia	Senior Research Associate
Clair Harris	Research Assistant
Andreas Hedblom	Research Student

BASIC RESEARCH CONTD.

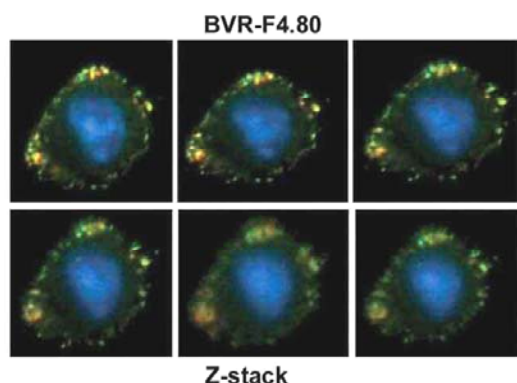


Fig 1 Demonstrates 3-D reconstruction of TLR4 and BVR colocalization in macrophages. Functionally, this interaction prevents the upregulation of pro-inflammatory cytokines and improves survival in a model of acute hepatitis in mice.

My group focuses primarily on the gas molecule carbon monoxide (CO) and the potent therapeutic effects it has when used at low concentrations in models of shock, transplantation and vascular injury. This work stems from the study of heme oxygenase-1 (HO-1), also a focus of the laboratory, as this inducible enzyme, which has been labeled a protective gene that generates CO as a product during the catalysis of heme. This year we have added the investigations of a second product of HO-1 activity, biliverdin (BV) and more specifically biliverdin reductase (BVR) that converts BV to bilirubin (BR). BV has been shown to exert potent protective effects in a number of *in vitro* and *in vivo* models with the assumption that it is the powerful anti-oxidant effects that underlie the

mechanism of action. We tested the hypothesis that BVR can act as a receptor and, in addition to converting BV to BR, initiates, via the binding of BV, a signaling cascade through PI3K and Akt activation. Moreover, that this occurs because BVR, in part, is

localized on the external surface of cells. More recently we have discovered that BVR colocalizes with Toll-like receptor-4 (TLR4) and regulates the response of the cell to bacterial endotoxin.

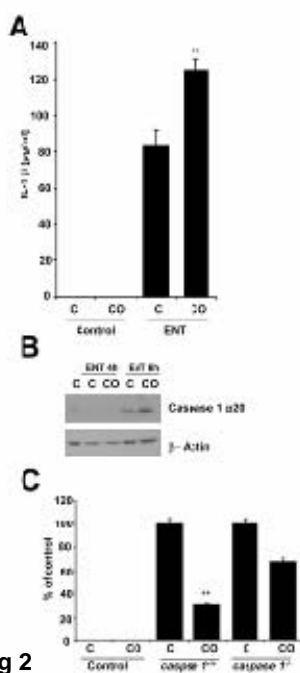


Fig 2

Ongoing in the laboratory is a very active bacterial sepsis program where we have shown that inhaled CO can protect mice from acute severe bacterial sepsis and shock. One mechanism by which CO provides protection is via enhanced activation of the inflammasome. This is evidenced by augmented caspase-1 activation and IL-1β expression as well as bacterial clearance in the peritoneum. We have shown that PPARγ and HIF1-α are both regulated by CO, likely in sync. We are currently investigating their potential role in bacterial clearance as well as end-organ preservation that is otherwise compromised in the septic animals. Functionally, CO improves survival (100% of CO-treated vs. 20% air-treated septic animals). Shown in **Fig 2** is evidence of inflammasome activation in macrophages treated with *E. coli* ± CO. Panel A shows enhanced IL-1β expression while Panel B and C show evidence of caspase-1 activation which is augmented in CO-treated cells. Note that CO is unable to kill bacteria in caspase-1 null macrophages (C).

In a collaborative effort with Dr. Simon Robson, Department of Medicine at BIDMC, we demonstrated that the anti-inflammatory effects of adenosine in macrophages occur in part by increasing the expression of HO-1. The endogenous CO generated via HO-1 in turn upregulates the selective expression of the A2a adenosine receptor that drives the anti-inflammatory response. These effects were lost in A2a deficient macrophages. These data exemplify the close and complex interrelationship between these protective genes and their products.

Ongoing studies in models of vascular injury related to both arteriosclerosis that leads to chronic rejection as well as balloon angioplasty have elucidated that CO augments vascular repair via select targeting of calcium channels which lead subsequently to downstream activation of Akt and NO generation via eNOS. Further that CO enhances recruitment of endothelial progenitor cells to repair the injured vessel in mice.

Preclinical research –large animal model of kidney transplantation

A large animal study was completed this year that has led to a clinical trial for CO in organ transplantation to prevent early loss of function and ultimately chronic rejection. The hope is that CO can be used to increase the donor pool and permit the use of extended criteria donors. In collaboration with Doug Hanto, we developed a model of delayed graft function (DGF) following kidney transplantation in swine, which is primarily due to

ischemia/reperfusion injury. We demonstrate that CO now known as Covox when administered to recipients transplanted with a compromised kidney (IRI injury in the donor) reduces the time to normal function from 5-6 days to 3-4 days effectively limiting DGF when CO is administered only to recipients. Our data suggests that intraoperative administration of CO to the recipient through the ventilator as a one-time exposure, reduces DGF. Mechanistically, histopathology, gene arrays and PCR show that CO blocks inflammation and apoptosis and increases epithelial cell repair in the proximal tubules. Phase II clinical trials are currently underway at the BIDMC and many centers nationwide. We continue to study additional treatment modalities including donor treatment and increasing cold storage preservation time.

LIST OF CURRENT FUNDING

“Gas Molecules as Transcriptional Regulators”

NIH R01 GM088666-01

Project Period: 2009-2013

PI: Leo E. Otterbein

“Heme Oxygenase-1 in Transplantation”

NIH 1R01HL077721-02

Project Period: 2005-2010

PI: Fritz H. Bach

Collaborator: Leo E. Otterbein

“Molecular Mechanisms of Protection Afforded by CO to prevent DGF in swine”

iNO Therapeutics

Project Period: 2007-2010

PI: Leo E. Otterbein

“Inhalation of Medicinal Gases Targeting new Pathways for the Treatment of Sepsis.”

CIMIT (DoD)

Project Period: 2009-2010

PI: Leo E. Otterbein, PhD

“Carbon Monoxide to prevent Velcade-Induced Neuropathy.”

Takeda/Millennium

Project Period: 2009-2010

PI: Leo E. Otterbein

“Preclinical Evaluation of Carbon Monoxide to Prevent Delayed Graft Function of a Kidney Allograft in Swine.”

Project Period: 2009-2010

PI: Leo E. Otterbein

“Training in Transplant Immunology”

NIH- 5T32AI070085-02

Project Period: 2007-2011

PI: John Iacomini (BWH)

Preceptor: Leo E. Otterbein

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

“Carbon Monoxide and Host Defense: Role of the Inflammasome.”

NIH R01

Project Period: 10/1/10-9/31/15

PI: Leo Otterbein

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"Heme Oxygenase-1 and Transplant Tolerance"

NIH R01

Project Period: 10/1/10-9/31/15

PI: Leo Otterbein

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress in the Past Year

- Immune Regulation of Carbon Monoxide (Principal Investigator) for shock in vitro and in vivo in models of bacterial infection, transplantation, vascular disease, acute liver failure and fibrosis and cancer.
- Vascular injury response (Principal Investigator) to test the effects of carbon monoxide on endothelial progenitor cell function.
- Liver regeneration in the setting of fibrosis investigating the role of heme oxygenase and carbon monoxide to enhance repair and remodeling.
- Human Kinome Project – (Principal Investigator). We are evaluating the expression and functional profiling of all known human kinases in response to endotoxin in macrophages. In collaboration with the Broad Institute at MIT.

Abstracts Presented at Local, National and International Meetings

Presented 3 abstracts at the American Transplant Society, Boston, MA; 2009.

Presented 5 abstracts and 2 oral presentations at the International Heme Oxygenase Congress, Miami, FL; 2009.

Individual Accomplishments

- Awarded New Key Opinion Leader Recognition by the American Transplant Society
- Front page report of research in the Boston Globe. September.
- I am a member of the NIH study section Special Emphasis Panel/Scientific Review Group for KO2, K23 and KO8 awards. This committee meets three times a year for grant review. This is an ongoing commitment that began in 2004.
- On the review committee for the James & Ester King Biomedical Research Program.
- Full member in the BIDMC IACUC.

Invited Presentations

"CO Releasing Molecules as Novel Therapeutics". North Shore Technology Council. Beverly, MA. May, 2009.

"Inhaled Carbon Monoxide to Improve Transplant Tolerance". Key Opinion Leaders Meeting of the American Transplant Society. Jackson Hole, WY. July, 2009.

"Role of Heme Oxygenase-1 in Diabetes, Obesity and Inflammatory Disorders". Heme Oxygenases in Medicine International Conference. Miami, Fla. September, 2009.

"Natural Genetic Protection: Heme Oxygenase-1". Pharmanex Inc. Provo, UT. October, 2009.

"Anti-Inflammatory and Cytoprotective Effects of Carbon Monoxide". Clowes Visiting Professor Faculty Lecture Presentation, Department of Surgery. Beth Israel Deaconess Medical Center, Boston, MA. November, 2009.

Patent Disclosures

I have continuing involvement in the litigation of nine patent applications for the use of carbon monoxide as a therapeutic. Four of the nine patents were approved thus far titled. "*Carbon monoxide improves outcomes in tissue and organ transplants and suppresses apoptosis.*" and "*Methods of treating vascular disease.*". The remaining 5 are expected to be approved in 2009.

REPORT OF TEACHING

I am currently on staff for the Harvard Medical School Human Body Course for first year medical students. The course covers gross anatomy, physiology and cell biology for which I serve as a faculty member and tutor.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Bilban M, Haslinger P, Prast J, Klinglmüller F, Woelfel T, Haider S, Sachs A, **Otterbein LE**, Desoye G, Hiden U, Wagner O, Knöfler M. Identification of novel trophoblast invasion-related genes: Heme oxygenase-1 controls motility via PPAR γ . *Endocrinology* 2009; 150:1000-13.

Wegiel B, Jiborn T, Abrahamson M, Helczynski L, **Otterbein L**, Persson JL, Bjartell A. Cystatin C is downregulated in prostate cancer and modulates invasion of prostate cancer cells via MAPK/Erk and androgen receptor pathways. *PLoS One* 2009; 4: e7953.

Wegiel B, Baty CJ, Gallo D, Csizmadia E, Scott JR, Akhavan A, Chin BY, Kaczmarek E, Alam J, Bach FH, Zuckerbraun BS, **Otterbein LE**. Cell surface biliverdin reductase mediates biliverdin-induced anti-inflammatory effects via phosphatidylinositol 3-kinase and Akt. *J Biol Chem* 2009;284:21369-78.
This article was highlighted in *Science Signaling*.

Reviews, Chapters and Editorials

Otterbein LE. The evolution of carbon monoxide into medicine. *Respir Care* 2009;54:925-32.

Chin BY, **Otterbein LE**. Carbon monoxide is a poison....to microbes! *Current Opinion In Pharm* 2009;9:490-500.

Educational Materials

Wegiel B, **Otterbein LE**. Heme oxygenase-1. *Nature Signaling Gateway on-line Molecule Pages Database*. 2009;10.1038.

RESEARCH SUMMARY

CLINICAL RESEARCH

My research focuses on the behavioral health aspects of organ transplantation and organ donation. There are four primary objectives of this research program: (1) identification of the psychological and behavioral health sequelae associated with solid organ and stem cell transplantation, (2) examination of the relationship between behavioral health variables and primary transplant outcomes (e.g., morbidity, mortality), (3) development, implementation, and evaluation of psychological and behavioral health interventions designed to enhance primary transplant outcomes (e.g., morbidity, mortality), and (4) identification of factors influencing organ and tissue donation consent decisions and the evaluation of interventions to increase rates of donation. In addition to my current NIH R01 funded study on strategies to reduce racial disparity in live donor kidney transplantation, I recently submitted a K24 application to the NIDDK. If funded, this would allow me to further develop my research program in transplant disparities by evaluating the effectiveness of a patient navigation program in transplantation.



James R. Rodrigue, PhD

LIST OF CURRENT EMPLOYEES

Matthew Paek, MS Clinical Research Assistant

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LIST OF CURRENT FUNDING

"A randomized trial to reduce the disparity in live donor kidney transplantation"

NIH/NIDDK R01DK079665

Project Period: 2007-2012

PI: James R. Rodrigue

"Quality of life therapy for adults with ESRD awaiting renal transplantation"

NIH/NIDDK R21DK077322

Project Period: 2006-2009

PI: James R. Rodrigue

"HCV in children: Quality of life, cognitive, and emotional outcomes"

NIH/NIDDK U01DK067767

Project period: 2002-2010

PI: Regino Gonzalez-Peralta

Co-PI: James R. Rodrigue

"Increasing enrollment in Donate Life Florida organ and tissue donor registry"

Health Resources and Services Administration D71HS08576

Project Period: 2007-2010

Co-PI: James R. Rodrigue

"Social networks and socialized risk: Understanding and mitigating disparities in renal transplantation"

Harvard Catalyst/Harvard Clinical and Translational Science Center

Project Period: 2009-2010

PI: Douglas W. Hanto

Investigator: James R. Rodrigue

"Cognitive function in dialysis patients: Ancillary study to FHN trial"

NIH/NIDDK DK074715

Project Period: 2010-2012

PI: John Stokes

Site PI: James R. Rodrigue

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

"Kidney Donor Outcomes Cohort (KDOC) Study"

NIH/NIDDK DK-085185 (revision submitted 3/5/10)

Project Period: 2011-2015

PI: James R. Rodrigue

"Quality of Life Therapy for Adults with Chronic HCV (QOLT-HCV Trial)"

NIH/NINR NR012305 (under review)

Project Period: 2011-2013

PI: James R. Rodrigue

"Patient-Oriented Research to Reduce Transplant Disparities"

NIH/NIDDK DK090296 (under review)

Project Period: 2011-2015

PI: James R. Rodrigue

"Effectiveness of a Navigation Program to Reduce Transplant Disparities for Adults with HIV"
Harvard Catalyst/Harvard Clinical and Translational Science Center (under review)
Project Period: 2011-2012
PI: James R. Rodrigue

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress in the Past Year

In addition to my current funded projects, I have a large number of ongoing unfunded projects. Please see the list below.

- Rate and risk factors for nonadherence to immunosuppression medications after liver transplantation.
- Liver disease severity at time of transplant and post-transplant quality of life.
- Living kidney donor evaluation and selection.
- Tobacco use before and after kidney transplantation.
- Patients' willingness to accept liver transplantation from expanded criteria donors.
- Longitudinal assessment of live donors and transplant recipients.
- Evaluating the psychometric properties of the Living Donation Expectancies Questionnaire.
- Follow-up medical care of living donors.
- Quality of life therapy for adults with Hepatitis C virus and cirrhosis awaiting liver transplantation.
- Fatigue and quality of life in liver transplant candidates and recipients.
- Fatigue and quality of life in kidney transplant candidates and recipients.
- Quality of life, mood, caregiving strain and benefit, and social intimacy of transplant spouses.
- Outcomes following living kidney donation.
- Kidney disease severity at time of transplant and post-transplant quality of life.
- Patients' willingness to accept kidney transplantation from expanded criteria donors.
- Psychosocial outcomes of kidney donation: Good Samaritan versus traditional donors.
- Living and deceased kidney donation among diverse populations in Europe.

Abstracts Presented at Local, National and International Meetings

Rodrigue JR, Mandelbrot DA, Pavlakis M, Johnson SR, Antonellis T, Whiting J, Vella J, Reed AI, Kaplan B. A prospective, multi-site evaluation of psychosocial outcomes of living kidney donors. Presented to the American Transplant Congress, Boston MA, 2009.

Rodrigue JR, Antonellis T, Dimitri N, Reed A, Mandelbrot DA, Pavlakis M, Curry M. Psychosocial impact of transplantation on spouse caregivers. Presented to the American Transplant Congress, Boston MA, 2009.

Westermann-Clark E, Hanto R, **Rodrigue JR**. Survey of U.S. transplant centers on barriers to implementation of kidney paired donation, list paired donation, and desensitization protocols. Presented (as a poster) to the American Transplant Congress. Boston MA, 2009.

Rodrigue JR, Antonellis T, Dimitri N, Reed A, Mandelbrot DA, Pavlakis M, Curry M. Are there any benefits to being a transplant caregiver? A study of kidney and liver transplant spouses. Presented (as a poster) to the American Transplant Congress. Boston MA, 2009.

Westermann-Clark EV, Hanto R, Donelan K, McMahon PM, Weinstein MC, Gazelle GS, **Rodrigue JR**. Three Kidney Transplant Controversies: Results of a National Survey of Transplant Center Directors. Presented (as a poster) to the American Transplant Congress. Boston MA, 2009.

Mandelbrot D, Pavlakis M, Johnson S, Karp S, Hanto D, **Rodrigue JR**. Practices and barriers in living kidney donor follow-up: A survey of U.S. transplant centers. Presented (as a poster) to the American Transplant Congress. Boston MA, 2009.

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Division of Transplantation

Rodrigue JR. PegInterferon Alfa-2a with or without Ribavirin results in minimal effect on quality of life, emotional, and cognitive outcomes: Results of the Peds-C Trial. Presented to the American Association for the Study of Liver Diseases, Boston MA, 2009.

Invited Presentations

"Transplantation and nonadherence: Ethical and clinical considerations". Weekly conference series, the Liver Center, Beth Israel Deaconess Medical Center. Boston, MA. 2009.

"Living kidney donor program review, FY 2008". Transplant Institute, Beth Israel Deaconess Medical Center. Boston, MA. 2009.

"Minority populations and attitudes toward organ donation". The Many Faces of Organ and Tissue Donation: A collaborative Conference of the New England Organ Bank and Beth Israel Deaconess Medical Center. Boston, MA. 2009.

"Alcohol relapse rates following liver transplantation: Policy considerations". The Transplant Institute, Beth Israel Deaconess Medical Center. Boston, MA. 2009.

"Strategies for increasing live donor kidney transplantation". Nephrology Grand Rounds. University of Iowa, Iowa City, IA. 2009.

"Implementing a behavioral health service in your transplant program". American Transplant Congress, Boston, MA. 2009.

"Living kidney donation and transplantation: Is it time for a new collaborative?" Plenary talk, World Organ Donation Congress, Berlin, Germany. 2009.

"Deceased organ donation and the family system: What have we learned?" Keynote talk, World Organ Donation Congress, Berlin, Germany. 2009.

REPORT OF TEACHING

2009-2010 Clinical and Ethical Dilemmas in Liver Transplantation
Brigham and Women's Psychosomatic Fellowship Program
Psychiatry Fellows
2-hour lecture

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Ladin K, **Rodrigue JR**, Hanto DW. Framing disparities along the continuum of care from chronic kidney disease to transplantation: Barriers and interventions. *Am J Transplant* 2009; 9:1-6.

Mandelbrot DA, Pavlakis M, Karp SJ, Johnson SR, Hanto DW, **Rodrigue JR**. Practices and barriers in long-term living kidney donor follow-up: A survey of U.S. transplant centers. *Transplantation* 2009;88:855-60.

Rodrigue JR, Balistreri W, Haber B, Jonas M, Mohan P, Molleston JP, Murray KF, Narkewicz MR, Rosenthal P, Smith LJ, Schwarz KB, Robuck P, Barton B, González-Peralta RP. Impact of hepatitis C virus infection on children: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol Nutr* 2009; 48:341-7.

Rodrigue JR, Cornell DL, Howard RJ. Relationship of exposure to organ donation information to attitudes, beliefs, and donation decisions of next-of-kin. *Progr Transplant* 2009;19:173-9.

Rogers CC, Johnson SR, Mandelbrot D, Pavlakis M, Horwedel T, Karp SJ, Egbuna O, **Rodrigue JR**, Chudzinski RE, Goldfarb-Rumyantzev A, Hanto DW, Curry M. Timing of Sirolimus conversion influences recovery of renal function in liver transplant recipients Clin Transplant 2009;23:887-96.

Original Articles (submitted or in press)

Rodrigue JR, Cornell DL, Howard RJ. Family initiated discussions about organ donation. Clin Transplant 2009; in press.

Reviews, Chapters and Editorials

Rodrigue JR, Zelikovsky N. Pediatric organ transplantation. In: Roberts MC, Steele RG, editors. Handbook of pediatric psychology, 4th ed. New York: Guilford; 2009. p. 392-402.

Waterman AD, **Rodrigue JR**. Transplant and organ donation education: what matters? Progr Transplant 2009; 19:7-8.

Reviews, Chapters and Editorials (submitted or in press)

Waterman AD, **Rodrigue JR**, Purnell TS, Ladin K, Boulware LE. Addressing racial disparities in live donor kidney transplantation: priorities for research and intervention. Semin Nephrol. in press.

Waterman AD, Stanley S, **Rodrigue JR**. Ethically and effectively promoting live donor kidney transplantation. In: Alvaro EM, Siegel JT (eds). Applied psychology and organ donation: Implementing and evaluating health behavior interventions. Boston, MA: Blackwell. in press.

Clinical Communications

Rodrigue JR, Crist K, Roberts JP, Freeman RB, Merion RM, Reed AI. Stimulus for organ donation: A survey of the American Society of Transplant Surgeons membership. Am J Transplant 2009; 9:2172-6.

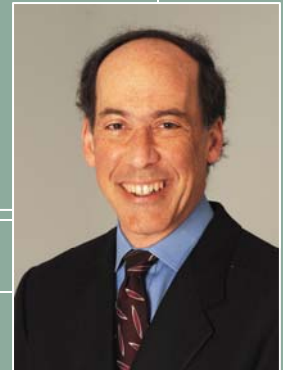
RESEARCH SUMMARY

BASIC RESEARCH

The Division of Transplant Immunology is both an independent entity and a major component of Beth Israel Deaconess Medical Center's Transplant Institute. The division employs 5 Research Faculty members, 28 Research Fellows, and 3 Research Technicians. The Division serves a research, not clinical, function.

Quality Improvement

Laurence A. Turka joined the Division in 2009 as the Co-Scientific Director with Terry B. Strom. Dr. Turka is a nephrologist and research investigator and currently the C. Mahlon Kline Professor of Medicine and Surgery, Pediatrics and Pathology and Laboratory Medicine at the University of Pennsylvania. Dr. Turka is an internationally known and respected immunologist who has made seminal contributions to our understanding of the immunobiology of T cells and transplantation. He is currently the Editor-in-Chief of the Journal of Clinical Investigation, one of the most prestigious research journals as well as a member of the Executive Committee of the Immune Tolerance Network. He has been Chief of the Division of Nephrology at UPenn, President of the American Society of Transplantation and has held numerous other leadership positions in transplantation and immunology in the United States and abroad. He will be bringing and recruiting new faculty and post-doctoral fellows that will strengthen and expand the scope of research being done in the Division.



Terry B. Strom, MD (*upper left*)

Laurence A. Turka, MD (*lower right*)

LIST OF CURRENT EMPLOYEES

Simon C. Robson, MBChB, PhD	Professor of Med
Xian C. Li, MD, PhD	Assoc. Professor of Med
Wenda Gao, PhD	Assist. Professor of Med
Savithri Bala-subramanian, PhD	Research Fellow
Gulcin Demirci, MD, PhD	Research Fellow
Glen Doherty, MD, PhD	Research Fellow
Keiichi Enjyoji, PhD	Research Fellow
Zhigang Fan, MD	Research Fellow
Zemin Fang, MD, PhD	Research Fellow
Lili Feng, MD, PhD	Research Fellow
Shipra Gupta, PhD	Research Fellow
Dusan Hanidziar, MD	Research Fellow
Imad Harmouch, M.D	Research Fellow
Nasim Kassam, PhD	Research Fellow
Garrett Lawlor, MD	Research Fellow
Derek Liu, PhD	Research Fellow
Wentao Liu, MD	Research Fellow
Babak Movahedi, MD	Research Fellow
Martina Nowak, MD	Research Fellow
Prabhakar Putheti, PhD	Research Fellow
Andi Qipo, MD	Research Fellow
Steven Salhanick, MD	Research Fellow
Moritz Schmelzle, MD	Research Fellow
Gurbakhshish Singh, MD	Research Fellow
Xiaofeng Sun, MD	Research Fellow
Thomas B. Thornley, PhD	Research Fellow
Yan Wu, PhD	Research Fellow
Xiang Xiao, PhD	Research Fellow
Jun Yan, MD	Research Fellow
Jian Zhang, MD, PhD	Research Fellow
Qiang Zhou, MD, PhD	Research Fellow
Brunilda Ramos-Perez	Admin Coordinator

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LIST OF CURRENT FUNDING

“JDRF center on immunological tolerance in type 1 diabetes”

JDRF 4-2004-368

Project Period: 01/1/08-12/31/12

Principal Investigator: Terry B. Strom

“Human islet transplantation at BIDMC”

JDRF 7-2005-1329

Project Period: 04/1/06-4/30/11

Principal Investigator: Terry B. Strom

“On the role of regulatory T cells in transplantation”

NIH P01 AI041521

Project Period: 07/01/07–6/30/12

Principal Investigator: Terry B. Strom

“New NAPRTCS in steroid free immunosuppression”

NIH U01 AI 055795

Project Period: 09/01/03-02/28/09

Principal Investigator: Terry B. Strom

“Inflammation and T cell memory: inter-related barriers to allograft tolerance”

NIPH PPG U19 DK080652

Project Period: 08/20/07-06/30/12

Principal Investigator: Terry B. Strom

“Molecular profiling and immunomodulatory intervention (CTOT)”

NIH U01 AI063589

Project Period: 09/15/04-08/31/09

Principal Investigator: Terry B. Strom

“Novel therapies of chronic allograft dysfunction (CTOT)”

NIH U01 AI063589

Project Period: 09/01/04-08/31/09

Principal Investigator: Terry B. Strom

“Cardiac allograft tolerance in non-human primates”

NIH U19 AI066705

Project Period: 07/01/05-06/30/10

Principal investigator: Terry B. Strom

“TIM family of genes: regulation of the allograft response by TIM proteins”

NIH P01 AI 073748

Project Period: 04/01/08 – 03/31/13

Co-Investigator: Terry B. Strom

“Novel therapies for chronic renal allograft dysfunction in children”

NIH U01 AI77816

Project Period: 05/01/15-04/30/13

Principal Investigator: Terry Strom

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Activities

The focus of the highly interactive Strom, Turka, Robson, Li and Gao laboratories is immune tolerance. Using state-of the art molecular immunology as a tool, the long-term goal is to enable the development of new approaches and strategies for the induction of tolerance in transplantation and autoimmune diseases, thereby enabling patients to dispense with the need for long-term immunosuppressive drugs and their attendant complications. The approach we have taken is to utilize mouse models, often genetically manipulated mice developed by Dr. Gao, of these disorders to identify potential barriers to tolerance and explore ways to overcome them by creating, often times in Dr Strom's lab, novel therapies. Through collaboration with Dr. Koulmanda an adjunct member of the division interesting therapeutic ideas are tested in primate transplant models. We define the precise nature of immune tolerance and of immunoregulatory T cells at the molecular and cellular levels. Dr Li has identified novel T cell costimulatory pathways crucial to tolerance and rejection. Transplant tolerance is obtained when the functional supremacy of donor reactive immunoregulatory T cells is obtained and remains dominant following the cessation of immunosuppression. Even before Dr Turka's arrival, collaboration between the Turka, Strom and Li labs created the paradigm that transplant tolerance generally requires the wide-scale depletion of alloaggressive T cells. In the absence of such depletion the cadre of graft protective immunoregulatory T cells can not curtail rejection. Recently Dr Turka noted that unbiased deletion of all T cells actually can be a barrier to tolerance. These concepts have guided the development of new clinical trial world wide. A distinctive cell surface phenotype for mouse and human immunoregulatory T cells has been discerned in mice and present, in a variant form, in human regulatory T cells as a direct result of Dr Robson's interests. The molecular signature consists of two ectoenzymes that catalyze the formation of adenosine, a potent immunoregulatory substance.

Individual Accomplishments

Each of the Principal Investigators and several of their colleagues have been awarded new funding and each PI has delivered plenary session lectures at international meetings.

REPORT OF TEACHING

Educational Programs

Many former trainees of the faculty are now prominent academicians or hold senior positions in industry. The division holds weekly laboratory meetings, participates with other labs in a weekly journal club and holds a monthly science seminar. Drs. Strom and Turka are faculty member of Harvard's graduate program in Immunology. The Harvard Medical School Program in Immunology holds weekly seminars. Drs. Strom and Diane Mathis (Joslin, HMS) direct interlocking Juvenile Diabetes Research Foundation Centers. These Centers hold monthly seminars and a yearly retreat.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Gao W, Thompson L, Zhou Q, Putheti P, Fahmy TM, **Strom TB**, Metcalfe SM. Treg versus Th17 lymphocyte lineages are cross-regulated by LIF versus IL-6. *Cell Cycle* 2009;8:1444-50.

Gounaris E, Blatner NR, Dennis K, Magnusson F, Gurish MF, **Strom TB**, Beckhove P, Gounari F, Khazaie K. T-regulatory cells shift from a protective anti-inflammatory to a cancer-promoting proinflammatory phenotype in polyposis. *Cancer Res* 2009;69(13):5490-7.

Hastings WD, Anderson DE, Kassam N, Koguchi K, Greenfield EA, Kent SC, Zheng XX, **Strom TB**, Hafler DA, Kuchroo VK. TIM-3 is expressed on activated human CD4+ T cells and regulates Th1 and Th17 cytokines. *Eur J Immunol* 2009;39(9):2492-501.

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Mariat C, Degauque N, Balasubramanian S, Kenny J, DeKruyff RH, Umetsu DT, Kuchroo V, Zheng XX, **Strom TB**. Tim-1 signaling substitutes for conventional signal 1 and requires costimulation to induce T cell proliferation. *J Immunol* 2009;182(3):1379-85.

Zhou Q, Yan J, Putheti P, Wu Y, Kassam N, Enjoji K, Robson SC, **Strom TB**, Gao W. Isolated CD39 expression on CD4+ T cells denotes both regulatory and memory populations. *Am J Transplant* 2009;9:2303-11.

Original Articles (submitted or in press)

Bodonyi-Kovacs G, Putheti P, Marino M, Avihingsanon Y, Uknis ME, Monaco AP, **Strom TB**, Pavlakis M. Gene expression profiling of the donor kidney at the time of transplantation predicts clinical outcomes 2 years after transplantation. *Hum Immunol* 2009; in press.

Fan Z, Spencer JA, Lu Y, Pitsillides CM, Singh G, Kim P, Yun SH, Toxavidis VB, **Strom TB**, Lin CP, Koulmanda M. In vivo tracking of "color-coded" effector, natural and induced regulatory T cells in allograft response. *Nature Med* 2009; in press.

Kang HG, Lee JE, Yang SH, Lee SH, Gao W, **Strom TB**, Oh K, Lee DS, Kim YS. Donor-strain-derived immature dendritic cell pre-treatment induced hyporesponsiveness against allogeneic antigens. *Immunology* 2009; in press.

Putheti P, Awasthi A, Popoola J, Gao W, **Strom TB**. Human CD4 memory T cells can become CD4+IL-9+ T cells. *PLoS One* 2009; in press.

Reviews, Chapters and Editorials

Mariat C, Degauque N, **Strom TB**. TIM-1: a new player in transplant immunity. *Transplantation* 2009;87(9 Suppl):S84-6.

Strom TB, Koulmanda M. Recently discovered T cell subsets cannot keep their commitments. *J Am Soc Nephrol* 2009;20(8):1677-80.

RESEARCH SUMMARY

BASIC RESEARCH

My work to date illustrates an evolution of view from a gene-centric approach with studies on individual homeobox genes, to an organ/process-centric approach with studies concerning nephron formation.

In the laboratory of Dr. Steve Potter, I performed some of the earliest microarray studies in work done with kidney cell lines. These particular lines were derived from a transgenic mouse strain I created as a tool to study downstream targets of the homeobox transcription factor *Hoxa11*. This expertise led to my work in Dr. Andy McMahon's laboratory, where I established microarray studies in the lab and developed high-throughput *in situ* hybridization protocols for my studies on kidney development. I was also able to create several transgenic mouse strains in my work that proved invaluable in published studies on nephron induction, nephron patterning, and tubule repair. Further, my work here identified a population of nephron progenitors, the Six2⁺ cap mesenchyme, that were also shown to be self-renewing in collaboration with colleagues in the lab.

For the last four years I was the Project Leader within Dr. Andy McMahon's group for the GenitoUrinary Development Molecular Anatomy Project (GUDMAP). GUDMAP.org is an NIH funded consortium of laboratories working to create a molecular atlas of the mouse urinary tract system using microarray profiling and *in situ* hybridization, and made available to the whole community as a resource. The consortium is creating useful transgenic mouse strains for immediate distribution to the community as well. I have been involved in each component of this project from inception to the current form having served on the NIH steering committee for the initial RFA, coauthoring the grant from our group, and serving as Project Coordinator in Dr. McMahon's group. In this latter role, I hired, trained and managed several research technicians and was responsible for data interpretation, management, and submission to the website.



M. Todd Valerius, PhD

Joined BIDMC in August of 2009

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BASIC RESEARCH CONT'D

I have also remained a very active member of the consortium through continual interactions beyond the annual meetings and conference calls, and by presenting our work with GUDMAP at other conferences. The scientific relationships fostered from these activities has led to new collaborations and elevated the quality and visibility of my work. Aside from the scientific interests, this role has also given me valuable experience in hiring and training new scientists.

My current efforts involve building on the knowledge gained in GUDMAP and my other studies to further our understanding of the nephron progenitor population and nephron morphogenesis. Using microarray-profiling data I have been exploring genes expressed in the nephron progenitors and the surrounding cell populations, or progenitor niche, in an effort to identify the underlying genetic components in maintaining and supporting the progenitors. This work has identified several transcription factors and signaling molecules with distinct expression patterns that I am now investigating with functional studies such as gene knockout. Another thread of study is focused on the juxtaglomerular apparatus (JGA), the regulatory unit of the nephron. Here I am generating transgenic mouse strains that express reporters/recombinases in defined domains of the distal tubule and JGA for studying the cell lineages leading to these cell populations, and for manipulating gene function in these domains.

In addition, I have begun studies with Dr. Seth Karp to identify transcription factors and signaling pathways active during liver development in the mouse using the same high-throughput approaches I developed for GUDMAP. The goal here is to define a similar gene atlas focused on transcription factors and signaling pathways to define molecularly distinct domains in the liver.

LIST OF CURRENT FUNDING

"Cell interactions in development of the mammalian kidney"

NIH/NIDDK R37 DK054364

Project Period: 2004-2009

PI: Andrew McMahon, PhD

Co-Investigator: M. Todd Valerius, PhD

"Kidney Molecular Atlas Project (KMAP)"

NIH/NIDDK U01 DK070181

Project Period: 2005-2009

PI: Andrew McMahon, PhD

Co-Investigator: M. Todd Valerius, PhD

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress in the Past Year

In addition to my previously projects, I have a large number of ongoing unfunded projects that were begun in 2009. Please see the list below.

- Project Title: Cell interactions in nephron progenitor maintenance and differentiation.
Role: Principle Investigator
Purpose: We are using microarray analysis of the cell populations forming the nephron progenitor (stem cell) niche to identify and understand the signaling pathways that regulate the progenitors.
- Project Title: Patterning of the Loop-of-Henle during nephron tubulogenesis
Role: Principle Investigator
Purpose: We are determining the role of Beta-catenin dependent Wnt signaling in patterning and maturation of the Loop-of-Henle during kidney development.

- Project Title: Ectopic Notch signaling results in patterning defects in the developing nephron.
Role: Principle Investigator
Purpose: We have generated data that shows Notch signaling is sufficient to pattern nephron progenitors to form the most proximal nephron tubule structures at the expense of distal structures in forming nephrons.
- Project Title: Liver development gene expression screen
Role: Co-Investigator (with Dr. Seth Karp)
Purpose: We are investigating the detailed expression patterns of a set of 150 transcription factors and signaling molecules expressed during liver development.
- Project Title: Ox40 in T cell activation
Role: Collaborator
Purpose: I've be analyzing microarray data generated in Ox40 mutant T cells to help identify what downstream effects this signaling pathway has on T cell populations.
- Project Title: Tim1 conditional mutagenesis in T cells.
Role: Collaborator/Mentor
Purpose: I'm helping a postdoctoral fellow in designing and creating a Tim1 conditional mouse strain using BAC recombineering techniques.

Abstracts Presented at Local, National and International Meetings

Invited Presentations

"Cell interactions and patterning in nephron development". Lecture, Harvard Stem Cell Institute Kidney Disease Program Colloquium. Boston, MA. January 21, 2009.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Georgas K, Rumballe B, **Valerius MT**, Chiu HS, Thiagarajan RD, Lesieur E, Aronow BJ, Brunskill EW, Combes AN, Tang D, Taylor D, Grimmond S, Potter SS, McMahon AP, Little MH. Analysis of early nephron patterning reveals a role for distal RV proliferation in fusion to the ureteric tip via a cap mesenchyme-derived connecting segment. Dev Biol. 2009; 332(2):273-86.

RESEARCH SUMMARY

BASIC RESEARCH

Our group focuses on understanding the protective effects of heme oxygenase-1 (HO-1), its products, biliverdin/bilirubin, and carbon monoxide (CO) in both type 1 and type 2 diabetes.

We have previously demonstrated that bilirubin administration to the recipient induces tolerance towards islet cell transplants across a complete MHC mismatch in a mouse model. One of our major focuses in 2009 was to understand the molecular mechanisms of such protection. We found that bilirubin treatment of recipients improved function of islet allografts by suppressing expressions of pro-inflammatory and pro-apoptotic genes in those islets and by increasing Foxp3⁺ T regulatory cells (Tregs). Bilirubin treatment promoted *de novo* generation of Tregs in *Rag1*^{-/-} recipients. Tregs were both essential and sufficient for the tolerance induction of bilirubin given to recipients. We are currently studying the mechanisms of how bilirubin treatment leads to *de novo* generation of Treg cells.

Another focus of the lab is to study the protective effect of HO-1 and its products in type 2 diabetes. By using a type 2 diabetic mouse model, db/db mice, we observed that systemic induction of HO-1 rapidly reduces blood glucose levels in db/db mice with hyperglycemia in a dose-dependent manner. HO-1 promotes membrane transportation of GLUT4 in both muscle and adipose tissue. These studies strongly support our hypothesis that HO-1 expression promotes glucose metabolism by increasing insulin sensitivity and/or glucose uptake in skeletal muscle and adipose tissue. We are currently studying details of this novel effect of HO-1.

In addition, we are continuously exploring the mechanisms of how blocking danger signals (e.g. TLR4 and others) in islets/ β cells leads to better survival and function of islet allograft after transplantation.



Hongjun Wang, PhD

LIST OF CURRENT EMPLOYEES

Fredy Rocuts, MD
Xinyu Zhang
Yinan Yue

Research Fellow
Research Assistant
Summer student

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LIST OF CURRENT FUNDING

“The role of toll-like receptor 4 (TLR4) in islet transplantation”

JDRF (1-2007-629)

Funding period: 12/01/2007 - 11/30/2010

PI: Hongjun Wang

“PPAR γ activation protects islets from immune rejection”

JDRF (5-2008-692)

Funding period: 12/01/2008 – 11/30/2009

PI: Hongjun Wang

“Immunoisolation and Modulation of Islets with Nanoparticles”

JDRF (RFA 41-2009-760)

Funding period: 12/1/2009-11/30/2012

Role: Co-PI

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

“Suppression of toll-like receptors leads to survival of islet allografts after transplantation”

NIH, R01

Period: 2010-2015

PI: Hongjun Wang

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

In the year 2009, the lab had two manuscripts accepted for publication in peer-reviewed journals, one abstract received the Rachmiel Levine Award and one presented as a late breaking abstract at the American Transplantation Congress.

Abstracts Presented at Local, National and International Meetings

Rocuts, F, Zhang, X, **Wang H.** Carbon monoxide suppresses membrane expression of Toll-like receptor 4 via MD-2. Presented to the 9TH Annual Rachmiel Levine Diabetes Symposium, Anaheim, CA; March 2009.

Rocuts, F, Zhang, X, **Wang H.** CO suppresses membrane translocation of TLR4 through inhibiting its interaction with MD-2 which is essential for its glycosylation in β cells. Presented to the American Transplantation Congress, Boston, MA; June 2009.

Individual Accomplishments

- I received the 2009 Rachmiel Levine Scientific Achievement Award.
- I continue to be a reviewer for *Diabetes* and other related journals.
- I was appointed as a member of the Editor Board of *World Journal of Diabetes*.

REPORT OF TEACHING

Other Teaching Contributions

I have trained one student in the year 2009.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles (submitted or in press)

Rocuts, F, Zhang, X, **Wang H**. Carbon monoxide suppresses membrane expression of TLR4 via MD-2. J Immunology 2009; submitted.

Rocuts F, Zhang X, Yan J, Yue Y, Thomas M, Bach FH, Czismadia E, **Wang H**. Bilirubin promotes de novo generation of T regulatory cells. Cell Transplant 2009; in press.

Yan J, **Wang H**, Jain N, Toxavidis V, Tigges J, Yang H, Yue G, Gao W. Signal sequence is still required in genes downstream of “auto-cleaving” 2A peptide for secretory or membrane-anchored expression. Anal Biochem 2009; in press.

OTHER TRANSPLANTATION CONTRIBUTORS:

Anthony P. Monaco, MD

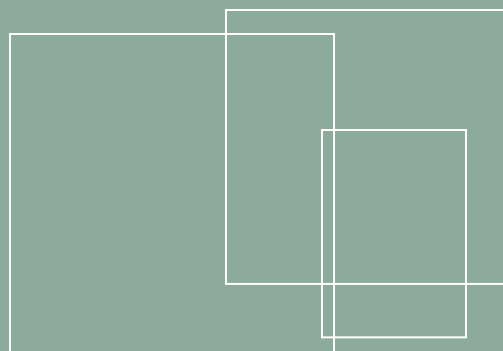
Peter Medawar Professor of Surgery

Keren Ladin, MSc

Research Associate in Surgery

Hongying Tang, MSc

Transplant IS Administrator



Anthony P. Monaco, MD

LIST OF CURRENT EMPLOYEES

Clare Sullivan	Administrative Assistant
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Keren Ladin, MSc

LIST OF CURRENT EMPLOYEES

Erica Langnas, BA	Research Assistant, Interview Coordinator
Helen Yang	Research Student
Jackie Hsieh	Research Student
Michelle Seslar	Research Student
Nicole St. Omer-Roy	Research Student
Rick McKellar	Research Student
Joseph Lopez, BA	HMS Summer Management Intern
Yves Chretien, BA	Consultant

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LIST OF CURRENT FUNDING

Keren Ladin

"Social networks and socialized risk: Understanding and mitigating disparities in renal transplantation."

Harvard Catalyst Pilot Grants Program

Project Period: 2009-2010

Principal Investigator: Douglas W. Hanto

Co-Principal Investigator: Keren Ladin

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Abstracts Presented at Local, National and International Meetings

Keren Ladin

Ladin K, Buyx A. Cross-national differences in compensation for organ donation: barriers and interventions to legislative process. Presented at the American Transplant Congress, May 2009.

Ladin K. Minding the gap: decomposing differences in utilization of health services between depressed and non-depressed elders in Europe. Presented at the 2009 Academy Health Annual Research Meeting. June 2009 .

Hongying Tang

Chudzinski RE, Khwaja K, Teune P, **Tang H**, Pavlakis M, Rogers C, Johnson S, Karp S, Hanto D, Mandelbrot D. Successful DCD kidney transplantation using early corticosteroid withdrawal. Presented at the American Transplant Congress, May 2009.

Abdul Q, Chudzinski RE, **Tang H**, Mandelbrot D, Wong M, Karp S, Johnson S, Hanto D, Pavlakis M. Infection incidence in pancreas after kidney transplantation compared to simultaneous kidney pancreas transplantation. Presented at the American Transplant Congress, May 2009.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Egbuna OI, Davis RB, Chudinski R, Pavlakis M, Rogers C, Molakatalla P, Johnson SR, Karp S, **Monaco AP**, **Tang H**, Hanto DW, Mandelbrot DA. Outcomes with conversion from calcineurin inhibitors to Sirolimus after renal transplantation in the context of steroid withdrawal or steroid continuation. Transplantation 2009; 88(5):684-92.

Goldfarb-Rumyantzev AS, Shihab F, Emerson L, Mineau G, Schafer C, **Tang H**, Hunter C, Naiman N, Smith L, Kerber R. A population-based assessment of the familial component of acute kidney allograft rejection. Nephrol Dial Transplant 2009;24(8):2575-83.

Ladin K, Rodrigue JR, Hanto DW. Framing disparities along the continuum of care from chronic kidney disease to transplantation: Barriers and interventions. Am J Transplant 2009; 9(4):669-74.

Original Articles (submitted or in press)

Ladin K, Daniels N, Kawachi I. Exploring the relationship between absolute and relative inequality and late-life depression: evidence from ten European countries. Gerontologist 2009; in press.

Ladin K, Hanto DW. Understanding disparities in transplantation: Do social networks provide the missing clue? Am J Transplant 2009; in press.

Reviews, Chapters and Editorials

Monaco AP. The role of mTOR inhibitors in the management of post-transplant malignancy. Transplantation 2009;87(2):157-63.

DIVISION OF UROLOGY

The Division of Urology has a wide-ranging research interest that incorporates both clinical and basic topics. The program touches on many aspects of this specialty including reproduction, stem cell biology, tumor markers, virology (AIDS), neurology and clinical outcomes analysis. The Urology laboratory community involves three PhD research scientists and several students from Harvard and MIT assigned to rotations thru our laboratories. Funding is continually growing and currently involves several NIH and DOD grants as well as private funding. Much of the clinical research is based on specialty clinics focusing on aspects of Neurourology, prostate cancer, renal cancer, and surgical education. Our Division is heavily involved in NIH outcomes research directed towards various quality of life issues and prostate cancer. Finally we have an active animal lab directed at various technical aspects of minimally invasive urologic surgery. The research work in Urology is presented at a wide range of meetings including the AUA, AACR, FASAB and NIH related meetings. In addition as noted in the following descriptions, the research work is published in a broad range of journals.

William DeWolf, MD
Chief, Division of Urology
Professor of Surgery, Harvard Medical School



UROLOGY DIVISION MEMBERS

Solomon Berg, MD

Assist Clinical Professor of Surgery (Emeritus)

Paul A. Church, MD

Assistant Clinical Professor of Surgery

Anurag (Andy) Das, MD

Assistant Professor of Surgery

William Connors, MD

Visiting Clinical Instructor of Surgery

DeWolf Lab Group

W. Mike Schopperle, PhD
Ignacio San Francisco, MD
Jung Min Lee, BS

Instructor in Surgery
Research Fellow in Surgery
Research Assistant

Robert C. Eyre, MD

Associate Professor of Surgery

Clifford Gluck, MD

Milton Hospital

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Gary Kearney, MD	Assistant Clinical Professor of Surgery
Michael Kearney, MD	Instructor in Surgery
Ann A. Kiessling, PhD	Associate Professor of Surgery
Stephen Lazarou, MD	Clinical Instructor in Surgery
Abraham Morgentaler, MD	Associate Clinical Professor of Surgery
Brian Saltzman, MD	Associate Clinical Professor of Surgery
Martin Sanda, MD	Associate Professor of Surgery
M. Simo Arredouani, PhD	Instructor in Surgery
Simpa Salami, MD, MPH	Research Fellow
Bin Lu, PhD	Research Fellow
Wen Yue, BS, MSci	Research Assistant II
Donna Cote, RN	Administrative Assistant
Andrew Wagner, MD	Assistant Professor of Surgery
Sarah Kim	Research Assistant

Clinical Fellows:

Michael Malone, MD	Clinical Fellow in Surgery
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RESEARCH SUMMARY

BASIC RESEARCH

My research interests span a broad range of disciplines that share the ultimate goal of identifying novel mechanisms of immune tolerance to prostate tumor antigens, and harnessing such mechanisms to break immune tolerance for immunotherapy of prostate cancer (PCa). I am using a variety of transgenic mice that spontaneously develop PCa and present a degree of tolerance to human antigens that can be manipulated through various interventions such as androgen ablation and manipulation of Tim1 receptor on T lymphocytes.

Another focus of my research is prostate cancer immunotherapy. I am trying to optimize strategies for inducing human HLA-restricted T cell responses to the prostate tumor antigens (e.g. ERG, SIM2 and other antigens) identified by unbiased, genome-wide array and proteomic studies of clinical prostate tumor samples and derived, well characterized representative cell lines. By a stepwise approach of screening epitope targets in HLA-A2.1 binding studies, immunization of human HLA-A2.1 transgenic mice to identify immunogenic peptides, and active and passive immunotherapy in mouse models (including HHD/TRAMP/Pb-ERG triple hybrid transgenic mouse) to determine which of these peptides provide the most suitable targets for effective, human HLA-restricted, anti-tumor immunity in vivo. Coupling the targeting of such novel TAA with modulation of Tim-1 or androgen pathways, to overcome T cell tolerance, is a rational avenue toward inducing effective, prostate cancer-specific immune responses. These studies are expected to lead to clinical trials of new strategies for prostate cancer immunotherapy. Finally, a part of my research is devoted to the molecular profiling of T lymphocyte subsets in the context of prostate cancer, with the goal of unraveling key molecules that drive immune tolerance to tumors.



Mohamed Simo Arredouani, PhD, MSc

LIST OF CURRENT EMPLOYEES

Laura Dunn, BS
Wen Yue, MS

Research Assistant
Senior Res. Associate

LIST OF CURRENT FUNDING

“Tumor-associated antigens and strategies for prostate cancer immunotherapy”

Prostate Cancer Foundation

Project Period: 9/1/2008 - 8/31/2011

Principal Investigator: Mohamed Simon Arredouani

“Targeting Tim-1 to Circumvent Immune Tolerance in Prostate Cancer”

Department of Defense, New Investigator Award (PC080363)

Project Period: 06/01/2009-05/31/2012

Principal Investigator: Mohamed Simon Arredouani

“Invariant NKT Cell Ligands for Prostate Cancer Vaccines”

Department of Defense, Laboratory-Clinical Translational Award (PC081107)

Project Period: 06/01/2009-05/31/2012

Principal Investigator: Steven Balk

Co-Investigator: Mohamed Simon Arredouani

“Targeting the ETS transcription factor ERG for prostate cancer immunotherapy”

Eleanor and Miles Shore Scholars in Medicine Fellowship, Harvard Medical School

Project Period: 09/01/2009-08/31/2010

Principal Investigator: Mohamed Simon Arredouani

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

We previously identified 3 ERG-derived and 5 SIM2-derived epitopes that proved to be immunogenic in A2.1 transgenic HHD mice. Cytotoxic lymphocytes elicited by these peptides are currently tested in an adoptive transfer/tumor xenograft mouse model where CTL are elicited in HHD mice, specifically expanded in vitro, and then adoptively transferred into immunodeficient SCID mice bearing human prostate tumors expressing HLA-A2.1 and the target antigen (PC3 for SIM2 and VCap for ERG).

After we showed that manipulating Tim-1 receptor using an agonistic monoclonal antibody was able to circumvent immune tolerance to prostatic Tag antigen and elevate specific CTL responses in the TRAMP mouse, similar findings were obtained using ERG and SIM2 as targets in HHD/ERG and HHD/TRAMP mouse models. ERG and SIM2-targeted immunotherapy is now being tested in tumor-bearing mice. Castration of mice prior to immunization proved to significantly enhance CTL responses to human PSA in a PSA/HLA-A2.1 double transgenic mouse model.

The mechanisms behind these observations are now being investigated through molecular profiling of prostate-draining lymph node T cells and Tregs from treated mice (Immunized WT and prostate tumor-bearing mice, combined with anti-Tim1 treatment or castration). Molecular profiling involves both genomic (gene expression + microRNA) and proteomic assessment of key components of T lymphocyte function.

We are pursuing the dissection of Treg gene expression profiles using Tregs and CD4 T cells from the TRAMP-GFP-Foxp3 hybrid and GFP-Foxp3 control mice. Analysis of gene expression array data in CD4 and Treg subsets from these two groups of mice points to profound dysregulations of key pathways in T cells and Tregs of prostate tumor bearing mice. Efforts are ongoing that aim at unraveling novel mechanisms that might be manipulated to strengthen CTL responses to prostate TAA. We anticipate that such novel strategies would replace lymphodepletion in PCa immunotherapy protocols and improve immunization outcome while preventing undesired collateral autoimmune responses.

Abstracts Presented at Local, National and International Meetings

M Simo Arredouani, Wen Yue, Terry B Strom, Martin G Sanda. Enhancing immune responses against prostate cancer self antigens by targeting Tim-1 receptor. Presented at the Prostate Cancer Foundation 16th Annual Scientific Retreat, Lake Tahoe, NV; September 2009.

Yue W, Strom TB, **Arredouani MS**. Targeting Tim-1 to circumvent immune tolerance to prostate tumor-associated antigens. Presented at the 1st International Conference on Immune Tolerance. Boston, MA; October, 2009.

Arredouani M.S., S. Tseng-Rogenski, B.K. Hollenbeck, D. Defeo-Jones, C. Hwang, M.G. Sanda. Androgen ablation augments cellular immune responses to PSA in a humanized PSA/HLA-A2.1 transgenic mouse model. Presented (as a poster) at the 24th Annual Meeting of the International Society for Biological Therapy of Cancer, National Harbor, MD; October, 2009.

Manoj Bhasin, Bin Lu, **M Simo Arredouani**. Human Prostate Cancer Transcriptome Reveals Distinct Signaling Pathway Dysregulations Associated With TMPRSS2:ERG Fusion. Presented (as a poster) at the Molecular Targets and Cancer Therapeutics Conference, Boston, MA; November, 2009.

Individual Accomplishments

- Active Memberships: International Society for Biological Therapy of Cancer
Clinical Immunology Society
- I joined the Communication Committee of the Clinical Immunology Society.
- I joined the Editorial Board of Clinical Immunology, and served as Ad Hoc reviewer for Cancer Immunology and Immunotherapy, BMC Medical Genomics, and Journal of Immunotherapy.
- I received two awards in 2009: 1) Top Performing Young Investigator award from the Prostate Cancer Foundation and 2) the Eleanor and Miles Shore Scholars in Medicine Award from Harvard Medical School.

Invited Presentations

"Novel Strategies For Prostate Cancer Immunotherapy". Beth Israel Deaconess Medical Center/Surgery: Principal Investigator Research Symposium, Boston, MA; November 2009.

"Targeting Prostate cancer Antigens and T Cells". Dana Farber Cancer Institute: Prostate SPORE Meeting, Boston, MA; November 2009.

REPORT OF TEACHING

Other Teaching Contributions

Tutor: MCM course, Harvard Medical School, September 2009
Responsibility: Run MCM tutorials for 1st year HMS students

Mentor: Osamede Obanor, a Medical Student from Boston University School of Medicine. DF/HCC CURE Program, June-August 2009. Project: "Identification of Potential Myosin VI-derived, HLA-A*0201-restricted, Immunogenic Epitopes for Prostate Cancer Immunotherapy"

BIBLIOGRAPHY (JANUARY-DECEMBER 2009)

Original Articles

Arredouani MS, Lu B, Bhasin M, Eljanne M, Yue W, Mosquera JM, Bubley GJ, Li V, Rubin MA, Libermann TA, Sanda MG. Identification of the transcription factor single-minded homologue 2 as a potential biomarker and immunotherapy target in prostate cancer. Clin Cancer Res 2009;15(18):5794-802.

Galicía G, Maes W, Verbinnen B, Kasran A, Bullens D, **Arredouani M**, Ceuppens JL. Haptoglobin deficiency facilitates the development of autoimmune inflammation. Eur J Immunol. 2009;39(12):3404-12.

Tseng-Rogenski SS, **Arredouani MS**, Escara-Wilke JF, Neeley YC, Imperiale MJ, Sanda MG. A safety-modified SV40 Tag developed for human cancer immunotherapy. Drug Des Devel Ther 2009;2:17-24.

Original Articles (submitted or in press)

Abdelkrima H, Domínguez-Bendala J, Wakeman J, **Arredouani MS**, Soria B. The immune boundaries for stem cell based therapies: problems and prospective solutions. J Cell Mol Med 2009; in press.

Reviews, Chapters and Editorials (submitted or in press)

Arredouani MS, Tseng-Rogenski SS, Hollenbeck BK, Escara-Wilke J, Leander KR, Defeo-Jones D, Hwang C, Sanda MG. Androgen ablation augments human HLA2.1-restricted T cell responses to PSA self antigen in transgenic mice. Prostate 2009; in press.

RESEARCH SUMMARY

BASIC RESEARCH

Our basic science research focuses on studying and characterizing unique and specific human cancer stem cell molecules with goals to further understand and define the molecular make-up of a human cancer stem cell, to determine the molecular differences between cancer stem cells and normal cells, and to identify potential cancer stem cell molecules that may be targets for novel treatments for human cancers. Our model to carry out these studies is embryonal carcinoma in the form of established human cancer stem cell lines derived from human germ cell tumors. Embryonal carcinoma cells are the malignant version of human embryonic stem cells derived from human embryos and embryonal carcinoma cells are true pluripotent cancer stem cells, which can be induced to differentiate into non-stem cell cancer cells. Thus, embryonal carcinoma is an excellent model for studying unique molecules expressed by human cancer stem cells and also to study their function as both cancer stem cells and their differentiated non stem-cell cancer cells.

Using this model, we have discovered a novel cancer stem cell marker in embryonal carcinoma called podocalyxin. Podocalyxin is a cell surface protein with very limited expression in human cells; it is expressed in subsets of blood cells and functions as a cell adhesion protein to allow blood cells to migrate into surrounding tissue (the spread of cancer within patients is thought to use similar mechanisms), and podocalyxin is expressed in kidney podocyte cells where it functions as a specific scaffolding protein to form large multi-protein complexes. Our identification of podocalyxin in human cancer stem cells was the first report of podocalyxin in either human cancer or human stem cells. Since this discovery, numerous laboratories have discovered podocalyxin in many human cancers including breast and prostate cancers. In fact, these studies have also shown that podocalyxin is a marker for an aggressive phenotypic behavior of cancer cells. Podocalyxin has also been identified as highly expressed in embryonic stem cells further confirming the close relationship of embryonal carcinoma with embryonic stem cells.



William C. DeWolf, MD
W. Mike Schopperle, PhD (above)

LIST OF CURRENT EMPLOYEES

Ignacio San Francisco, MD
Jung Min Lee

Research Fellow
Research Assistant

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Division of Urology

BASIC RESEARCH CONT'D

Our continued studies of podocalyxin have shown that it is the molecular carrier of the TRA antigens; TRA markers have been widely used for decades within the stem cell community to study human stem cells. The TRA markers have also been identified as potential blood markers for testis cancers. With the identification of podocalyxin as the carrier of the TRA molecules, studies can now be done to further the initial findings of the TRA antigens in human cancers and stem cells.

Our current studies on podocalyxin are now focused in two directions; the first direction is to determine the function of podocalyxin in human cancer stem cells by identifying other molecules in cancer stem cells that interact with podocalyxin. We have identified six true podocalyxin-interacting proteins including a glucose transporter – the molecules responsible for supplying energy (glucose) to all cells. We are now characterizing the glucose transporter-podocalyxin complex and we are excited at the prospect of identifying the first interaction between a glucose transporter and a cell adhesion protein. Indeed, in almost all human cancers, glucose transporters are highly over-expressed, but very little is known about the underlining molecular mechanisms that drive this process. The second direction with our studies of podocalyxin is more clinically oriented; we are exploring the expression of podocalyxin in human blood samples from patients with prostate and other cancers to determine the potential of using podocalyxin as a blood cancer marker.

CLINICAL RESEARCH

Clinical research is quite active and deals with diagnostic urologic oncology, sexual rehabilitation and qualitative analysis of urologic teaching. Our most active clinical research project is directed at the characterization of active surveillance as a management option for treatment of prostate cancer. Currently we have over 130 patients collected over 10 years and followed a strict active surveillance protocol refereed by a 20 core saturation biopsy technique performed every 12 - 18 months. We are currently gathering statistical data as to predictive indices characterizing these patients that progress vs those that do not progress. For example, those patients with a PSA density less than 0.085 seem to do well with a progression rate of only 20% over 8 years. We plan on summarizing that and other data this year now that we are in to our 10th year. We have presented preliminary data at several meetings and now plan on defining the data in manuscript form.

LIST OF CURRENT FUNDING

Intramural Funding
Urology Division
Beth Israel Deaconess Medical Center

APPLICATIONS SUBMITTED/PENDING APPROVAL

"Function of Podocalyxin in Human Cancer Stem Cells."
NIH (program # PA 06-282) R-21 Stem Cells and Cancer
Project Period: 07/01/2010-06/30/2012
PI: William Schopperle
Co-PI: William DeWolf

"Function of Podocalyxin in Cancer and Cancer Stem Cells."
American Cancer Society, Research Scholar Grant in Basic Research #RSG DDC-119636
Project Period: 07/01/2010-06/30/2013
PI: William Schopperle
Co-PI: William DeWolf

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

BASIC:

In our research studies we have confirmed that the stem cell/cancer cell adhesion protein podocalyxin forms a specific complex with the glucose 3-transporter in human cancer stem cells and have submitted a research paper entitled: "The Human Cancer/Stem Cell Marker Podocalyxin Interacts with the Glut-3 transporter in malignant pluripotent stem cells". Also, we have discovered a novel temperature dependent mechanism which regulates the differentiation of human cancer stem cells and are further studying this new regulation system.

CLINICAL:

Our Results Regarding Active Surveillance Were Presented at the New England AUA Meeting:

The study population consisted of 111 consecutive patients who were prospectively enrolled with low risk prostate cancer with intent to cure from January 2003 to January 2009 by one urologist (WCD). All patients were followed with 20-core saturation biopsy technique. The inclusion criteria were clinically localized cancer (T1c-T2), less than 3 positive cores, Gleason score 6 or less, and no more than 50% of core involved. The criteria for progression, and therefore treatment were: ≥ 3 positive cores, increase in grade (Gleason score ≥ 7) and \geq than 50% of any core involved with cancer. Patients were monitored with an office visit every 6 months and restaging 20-core saturation biopsy every 12-18 months. Definitive treatments as RRP or Radiotherapy were performed in patients who progressed.

From the 111 patients who fit the entering criteria, 3 withdrew the protocol before an endpoint was reached. Therefore 108 patients were analyzed in the final cohort. The mean age of the study group at the time of the first biopsy was 62 years. The median time of follow-up was 25 months. The median number of total biopsies was 2 (range, 1-5). Ninety five patients had at least one saturation re-biopsy. The progression rate was 26% (28/108). Fifty one patients (54%) had a negative first re-biopsy. Of the patients who progressed 54% did so due to an increased number of positive cores. Univariate analyses revealed PSA density, using cut point the median value 0.08 ng/ml/cc ($p=0.0048$), PSA velocity ($p=0.01$) and family history of prostate cancer ($p=0.01$) were predictors of progression. PIN and atypia were non predictors of progression. Most of the patients who progressed did so at second biopsy (17 patients). The median time to progression was 24 months. Of the patients who progressed 11 underwent RRP. Of those 10 patients (91%) had organ confined, low volume disease with negative margins, 4 had Gleason 3+4 and one patient had a T3b disease. Interestingly, 2 of 4 (50%) patients, who had Gleason 7 as criteria of progression on needle biopsies, had Gleason 6 on the final RP specimens.

In our study PSA density, PSA velocity and family history of prostate cancer are predictors of progression in univariate analysis. Most of the first re-biopsies (54%) had no cancer. In the group of patients with negative first re-biopsy there was still subsequent progression revealing a 30 months lead time bias as noted by Kaplan Meier curves. Of the patients who progressed and underwent RP, 91% had a final pathology with organ-confined and low volume disease. In our setting AS with delayed intervention appears to be a safe and viable option in selected men with low risk prostate cancer.

Individual Accomplishments

William DeWolf, MD

- AUA Program Committee for Basic Research: Prostate Cancer
- Member of Medical Advisory Board, Boston Prostate Cancer Walk
- Co-investigator, NIH CA 011391
- Member, Editorial and Advisory Board of Perspectives on Prostate Disease
- Editorial Board-Harvard Men's Health Watch
- Moderator Session on Prostate Cancer: Basic Research, National AUA Meeting, Chicago
- Editorial Board for European Urology
- Visiting Professor, Geisinger Clinic

Department of Surgery Annual Research Report 2009
Division of Urology

REPORT OF TEACHING

Undergraduate and Medical School Courses

William DeWolf, MD

Undergraduate Research Opportunities Program: This is an MIT-based teaching program in which 3-5 undergraduates rotate through our laboratory on 6-12 month basis science projects and gain experience in biological research. This is particularly important because it is the only undergraduate course with opportunity to view surgical operations as part of the curriculum. Additional medical school teaching includes SU518M.1 which is a general course in urologic science for medical students. The course includes a 1 month rotation on the urology service and involves clinical and didactic experience relating to urologic disease.

CME Courses

CME Course - Men's Health: Opening A New Frontier; course directors William DeWolf and Abraham Morgentaler, Saturday, May 16, 2009.

Other Teaching Contributions

Urologic Oncology Fellowship: Currently Dr. Ignacio San Francisco (Santiago, Chile) is spending 15 months with us completing work on our prostate cancer active surveillance program and other clinical projects.

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles (submitted or in press)

Schopperle W, Lee J, **DeWolf WC**. The human stem cell marker podocalyxin interacts with the glut-3 transporter in malignant pluripotent stem cells. Biochem Biophys Res Commun 2009; in press.

Reviews, Chapters and Editorials

DeWolf WC. (Editorial) Estimation and prediction of renal function in patients with renal tumor. J Urol 2009; 181:2460-2461.

Abstracts

Sanda M, Regan M, Dunn R, Kiebel A, Saigal C, Litwin M, Klein E, Pisters L, Wood D, Hollenbeck B, Dahl D, **DeWolf WC**, Hu J, Hembroff L, Wei J. Predicting erection recovery after prostatectomy: a multivariable nomogram from the prost QA Consortium. J Urol 2009;181:759A.

Williams S, Regan M, Wei J, Kerney M, **DeWolf WC**, Tang J, Buetti J, Genega, E, Eyre A, Sanda M. Discerning risk of clinically significant vs incident prostate cancer prior to biopsy: predictive model from a multi-center cohort. J Urol 2009;181:774A.

Yao D, **DeWolf WC**, Sanda M, Bloch N, Genega E, Barry A, Ngo L, Rofsky N. Increased positive yield of clinically significant prostate cancer with MRI prompted biopsies. J Urol 2009;181:782A.

RESEARCH SUMMARY

BASIC RESEARCH

The long-term goals of our research are to understand gene expression in male genitourinary tract tissues. 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. Male GU tract tissues involved in semen production are immune-privileged, creating an isolated sanctuary for HIV infection. Originally controversial, this concept is now broadly accepted, and the work was designated a Prize Paper study by the American Society for Reproductive Medicine.

The work in our group has lead to studies of the immune systems in the prostate, seminal vesicles and epididymis. Results suggest that the role of the prostate in immune-protection of spermatozoa contributes to the disease predisposition of the gland, 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. They thus may be life-long reservoirs of infection not penetrated by anti-retroviral drugs. Studies of bacteria in semen to determine if bacterial co-infection increases HIV in semen has revealed that the most prevalent species detected by PCR are difficult to culture organisms, particularly gram positive anaerobic cocci. Approximately 50% of semen specimens from non-HIV infected men contain greater than 20,000 organisms/ml. Work currently in progress indicates there is no correlation between the presence of HIV and the presence of bacteria in semen specimens.

More recent studies have extended the detection of bacteria to interstitial cystitis, a chronic, debilitating disease of unknown etiology for both men and women. Patients undergoing cystoscopy to diagnose/stage their disease may elect to submit a biopsy for bacterial assay. This approach may provide new information about treatment options.



Ann A. Kiessling, PhD (upper left)
Robert C. Eyre, MD (upper right)
Paul Church, MD (lower right)

LIST OF CURRENT EMPLOYEES

Anil Purohit	Medical Student
Richard Crowell, DVM	Volunteer

BASIC RESEARCH CONT'D

A few recent reports demonstrate that adult testis of mice and humans contain a population of stem cells that can be expanded as pluripotent stem cells in culture. Preliminary studies with male mice suggest that well-known methods of perturbing male germ cell populations may increase the number of stem cells that can be expanded in culture. A testis source of pluripotent stem cells holds great patient-specific therapeutic potential. We are initiating studies to derive testis stem cells from adult men.

Immunology of male GU tract tissues with emphasis on bacterial infection in the prostate, seminal vesicles, epididymis and bladder

Understanding immune control in these tissues will provide important insights into genitourinary tract pathologies, such as prostatitis, prostate cancer and interstitial cystitis. Several lines of evidence from our laboratory indicate that the prostate is immunosuppressed. This characteristic may play an important role in prostate diseases, such as prostatitis and prostate cancer. We have demonstrated that prostatitis may drive HIV disease by promoting the development of therapy resistance mutations. For these reasons, we have explored the bacterial species present in prostatic tissues using PCR amplification of bacterial ribosomal gene sequences. The work began with semen specimens from two cohorts of patients, one group undergoing fertility assessment, and another group undergoing vasectomy. Pre-and post-vasectomy specimens allowed the comparison of specimens with and without contribution from the epididymis. We have developed a reference library of bacterial DNA sequences amplifiable from laboratory reagents, a problem known to haunt this line of investigation. To date, we have amassed a total library of approximately 200 rDNA gene sequences which have been submitted to GenBank and recently published.

We have conducted whole human genome microarray analyses of RNAs in semen specimens from men with prostate cancer and prostatitis, biopsy proven, and are in the process of analyzing the data.

Pluripotent stem cells from adult testis

It had long been assumed that spermatogonia could give rise to cultured cell lines restricted to germ cell derivatives, and that such cells were most easily isolated from pre-pubertal testis. In early 2007, however, it was reported that pluripotent stem cell lines could be derived from adult mouse testis when provided with a specific complement of growth factors. This observation was repeated with human testis by a group of German investigators, and more recently by two teams in the U.S., the most recent of which reported 100% success in isolating stable lines of stem cells from testis specimens from men aged 40 to 60. Our previous experience perturbing testis populations with the alkylating agent, busulfan, suggested that the rebound from such treatment might further enrich adult mouse testis for stem cells, and we initiated a search for pluripotent stem cells in tissue sections, and in cultured cells from seminiferous tubules. If we can prove the principle in mouse testis, the approach might also be useful in human testis biopsies.

Genetic and phylogenetic analyses of HIV genes cloned from paired specimens of blood and semen contributed by study subjects in a longitudinal study

We have created a public database: www.lrb.med.harvard.edu in which we have compiled all the published HIV_{env} sequences from semen, including our own. We have included HIV_{env} sequences from paired blood specimens when available. This is the first and only public database of its kind and is providing background for understanding the most significant HIV host cells in semen producing organs, as well as for the design of vaccines targeting semen transmitted disease. To date we have sequenced and analyzed approximately 1350 clones of HIV genes, including Envelope, Protease and Reverse Transcriptase. The genetic analyses have illustrated unique clustering patterns of HIV quasispecies isolated from paired blood and semen specimens from long term study subjects. These findings support and extend the concept, proposed by this laboratory over 20 years ago, that semen producing organs are a sequestered focus of HIV infection, separate from blood. Importantly, several study subjects have demonstrated the appearance of therapy resistance-conferring mutations in semen before they appear in blood.

Phylogenetic analyses of HIV envelope genes have also revealed compartmentalization of syncytium-inducing virus species (utilize chemokine receptor CXCR4) and non-syncytium-inducing virus species (utilize chemokine receptor CCR5). This confirms and extends reports that HIV variants which utilize CCR5 receptors are the sexually transmitted virus species. As infection progresses, blood HIV variants mutate to express envelopes that preferentially bind to CXCR4 rather than CCR5. This switch in virus tropism is due to point mutations at one or two amino acid residues (S306R or E320K,R) in the V3 loop of HIV_{env}, and marks a turning point in disease progression due to increased levels of infection and loss of CD4⁺ lymphocytes. The switch in virus tropism was formerly attributed to a high error rate in the virus reverse transcriptase, but more recent studies have revealed that a family of deaminases, CEM15 (APOBEC3G) function as an innate cellular defense mechanism against retroviral infection. The logistics of archiving and analyzing the large data set of gene sequences have necessitated the development of a custom laboratory database in MySQL, used as the starting point for sequence analyses and evolution.

LIST OF CURRENT FUNDING

Urologic Research Fund

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Progress

We have nearly completed the studies of bacteria in semen from HIV infected men, which extends our previous comprehensive characterization of bacteria in semen. Results to date indicate there is no correlation between the presence of bacteria and the presence of HIV. There is also, surprisingly, no correlation between the presence of bacteria and elevations in white cells in semen specimens.

We have examined bladder biopsies from two patients with IC and found them to be bacteria negative. This work is ongoing.

The longitudinal phylogenetic analysis of HIV genes also continues. The results to date indicate that male GU tract organs are a clinically important reservoir of HIV disease in men. To establish tissue specific reservoirs of disease, we continue to apply for funds to support collaborative efforts with Southwest Biomedical Research Foundation to analyze tissue biopsies from HIV-infected chimpanzees.

Abstracts Presented at Local, National and International Meetings

Drakakis P, Loutradis D, **Kiessling AA**. Expression of HLA antigens in early cleaving human embryos. European Society for Reproductive Endocrinology, Amsterdam; June 2009.

Kiessling AA, Desmarais B, Loverde J, **Eyre RC**. Bacterial DNA and HIVgag in the semen of HIV infected men. Center for AIDS Research annual symposium, Harvard Medical School, Boston, MA; June, 2009.

Kiessling AA, Bletsa R, Desmarais B, Kallianidis D, Loutradis D. Comparison of cell cycle control in totipotent cells with pluripotency gene set. International Society for Stem Cell Research, Barcelona, Spain; July, 2009.

Kiapekou E, Desmarais B, Bletsa R, Loutradis D, **Kiessling A**. Pluripotent cells are under unique cell cycle control. American Society for Reproductive Medicine, Denver, Colorado; October, 2009.

Individual Accomplishments

Ann Kiessling

- Recipient of Jacob Heskel Gabbay award for Biotechnology and Medicine, Brandeis University, November, 2009.

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- Serves on the Research Standards Working Group for the California Institute for Regenerative Medicine, 2005-2011. Chairs the Pre-Clinical Research Standards Subcommittee and serves on the Peer Review committee for CIRM grant applications.
- Serves on the Stem Cell Advisory Committee for the State of Connecticut, and also serves on its Ethics Subcommittee. The duties of the Advisory Committee include review and priority assignment of stem cell grant applications to the State of Connecticut Stem Cell program.
- Appointed to the Harvard University Embryonic Stem Cell Research Oversight Committee by Vice Provost Steve Hyman. She also serves on the ESCROs of Children's Hospital and the Joslin Diabetes Center.
- Appointed a contributing editor to ChemTracts In Brief

Paul Church

- Gave multiple lectures to the medical students rotating through the Surgical Core Clerkship, Second Year and Third Year.

Robert C Eyre

- Appointed Chief of Urology, Beth Israel Deaconess-Needham, Needham, MA
- Best Doctors in America, 2009
- Chief of Urology, Faulkner Hospital, Boston, MA
- Gave multiple lectures to the medical students rotating through the Surgical Core Clerkship, Second Year and Third Year.

Invited Presentations

Ann Kiessling

"Update on stem cell science in Massachusetts". Massachusetts Biotechnology Council. Boston, MA. Feb, 2009.

"Policy Issues at the intersection of Reproductive Health and Research". California Institute for Regenerative Medicine legislative update. Sacramento, CA. Feb 2009.

"Unique cell cycle controls". University of Connecticut Stem Cell Institute. Farmington, CT. May, 2009.

"Strategies for Women's Career Success". University of Virginia. Charlottesville, VA. June, 2009.

"Stem Cell Therapies: How to Benefit from new NIH Rules and Funding". Thomson Webcast. August, 2009.

"Retroviruses, Reproduction and Regenerative Medicine". Gabbay Award, Brandeis University. Waltham, MA. November, 2009.

Robert C Eyre

"Management of urinary tract infections," Medical Grand Rounds, Beth Israel Deaconess Hospital-Needham. Needham, MA. February, 2009.

"Initial experience with the AdVance male urethral sling". Annual Meeting, New England Section, American Urological Association. Washington, DC. September 2009.

REPORT OF TEACHING

Graduate School and Graduate Medical Courses

Dr. Eyre

Director, Senior Surgical Residency Rotation, Faulkner Hospital

Drs. Church and Eyre

Surgical Core Clerkship Lecture Series, Second Year and Third Year, Harvard Medical School

BIBLIOGRAPHY (JANUARY – DECEMBER 2009)

Original Articles

Kiapekou E, Loutradis D, Mastorakos G, Bletsas R, Beretsos P, Zapanti E, Drakakis P, Antsaklis A, **Kiessling AA**. Effect of PRL on in vitro follicle growth, in vitro oocyte maturation, fertilization and early embryonic development in mice. *Cloning Stem Cells* 2009;11(2):293-300.

Kiessling AA, Bletsas R, Desmarais B, Mara C, Kallianidis K, Loutradis D. Evidence that human blastomere is under unique cell cycle control. *J Assist Reprod Genet* 2009;26(4):187-95.

RESEARCH SUMMARY

TRANSLATIONAL RESEARCH

The principal areas of research in the Sanda laboratory include 1) discovering and validating prostate cancer antigens and other biomarkers to improve prostate cancer detection and 2) evaluating prostate cancer antigens as targets for immunotherapy and biomarkers for cancer screening and severity assessment. Toward these goals Dr. Sanda serves as Chair of the Prostate and Genitourinary Cooperative Group of the National Cancer Institute Early Detection Research Network. He has led or co-led two large, multi-center studies of the EDRN and as PI of the Harvard-Michigan Prostate Biomarker Center Dr. Sanda has assembled a case-control cohort and biospecimen bank comprised of 2000 men at risk for prostate cancer. He is the co-Leader of the Prostate Program of Dana Farber Harvard Comprehensive Cancer Center.

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 leads a national study funded by NIH to compare effectiveness of robot-assisted laparoscopic and open prostatectomy.



Martin G. Sanda, MD

LIST OF CURRENT EMPLOYEES

Simo Arredouani, PhD	Instructor in Surgery
Simpa Salami, MD, MPH	Postdoctoral Fellow
Bin Lu, PhD	Postdoctoral Fellow
Kemi Williams, MD, MPH	Clinical Coordinator
Catrina Crociani, MPH	Clinical Coordinator
Donna Cote, LPN	Administrative Assist III
Wen Yue, BS, MSci	Senior Research Assoc
Laura Dunn, BA	Research Assistant I
Neha Mehta, BA	Research Assistant I

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LIST OF CURRENT FUNDING

“Harvard/Michigan prostate cancer biomarker clinical center”

National Institutes of Health, U01 CA011391-01

Project Period: 2005-2010

PI: Martin Sanda

“Effectiveness of Robotic Compared to Standard Prostatectomy for Prostate Ca”

National Institutes of Health, 1RC1EB011001-01

Project Period: 2009-2011

PI: Martin Sanda

“Effectiveness of Early Stage Prostate Cancer Treatment”

National Institutes of Health, 1RC1CA146596-01

Project Period: 2009-2011

PI: Martin Sanda (Multiple PI/PD Proposal together with P. Carroll, UCSF)

“SPORE in prostate cancer”

National Institutes of Health, P50 CA069568

Project Period: 2008-2013

Co-Investigator: Martin Sanda (Director, Career Development Award Core)

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Research Accomplishments and Presentations

In Basic Research, our lab collaborated with Towia Libermann, Glenn Bubley, and Steve Balk from Medicine at BIDMC in using the BIDMC prostatectomy tumor bank to identify prostate cancer antigens not expressed in normal tissue, which may serve as targets for prostate cancer detection and therapy. Dr. Simo Arredouani, a junior faculty member recruited to the Urology research team, is undertaking studies in collaboration with Terry Strom to explore avenues for breaking T cell tolerance to these human prostate cancer TAA's in transgenic mice to develop new strategies of prostate cancer.

In Translational Research, we completed the establishment of a Prostate Reference Set by the NCI-Early Detection Research Network. This resource is a prospectively collected cohort of serum and blood from over 1000 prostate cancer patients and non-cancer controls to be stored at NCI-Frederick for general availability to investigators poised to evaluate new prostate biomarkers via a blinded, rigorously defined blood sample set. I was appointed the Group Leader for the GU Collaborative Group of the EDRN, and in this capacity we are spearheading 2 national validation studies of new prostate cancer detection assays. I also served as the Director of the Career Development Program of the Dana Farber/Harvard Cancer Center SPORE in Prostate Cancer.

In Clinical Research, we expanded our follow-up and analysis of PROST-QA Consortium study of patient-reported prostate cancer outcomes to include a collaboration with the West coast consortium CaPSURE, and to initiate a new prospective cohort to compare open and robot-assisted laparoscopic prostatectomy. We have initiated collaborations with the Harvard School of Public Health Physician's Health Study and Health Professional's follow-up Study to evaluate outcomes of patients undergoing deferred management of prostate cancer. I continue to serve as the Urology co-Chair for the NCI-Radiation Therapy Oncology Group (RTOG) Trial 0232, for a phase III study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for patients with an intermediate risk for prostate cancer that has randomized over 500 patients nationwide.

Honors and Awards

Named to the registry of Best Doctors in Massachusetts, 2009-2010, representing 6 consecutive years in the Best Doctors registry.

REPORT OF TEACHING

Graduate School and Medical School Courses:

I mentored Konrad Szymanski, MD, MPH candidate in clinical research/MPH practicum (Validating the EPIC-26)

Co-mentored Norris Kamo (HMS –III) in a clinical research rotation (Measuring Cancer Care Satisfaction with a Web-based Instrument)

Co-mentored Simpa Salami, MD, MPH candidate in clinical research / MPH practicum (A Case-Control Cohort of Men Undergoing Prostate Biopsy)

Participated as a preceptor in the Physical Exam courses for HMS I and HMS II medical students.

Participated as educator in the Urology clerkship at HMS.

BIBLIOGRAPHY (JANUARY-DECEMBER 2009)

Original Articles

Arredouani MS, Lu B, Bhasin M, Eljanne M, Yue W, Mosquera JM, Bubley GJ, Li V, Rubin MA, Libermann TA, **Sanda MG**. Identification of the transcription factor single-minded homologue 2 as a potential biomarker and immunotherapy target in prostate cancer. Clin Cancer Res 2009;15(18):5794-802.

Eyre SJ, Ankerst DP, Wei JT, Nair PV, Regan MM, Bueti G, Tang J, Rubin MA, Kearney M, Thompson IM, **Sanda MG**. Validation in a multiple urology practice cohort of the prostate cancer prevention trial calculator for predicting prostate cancer detection. J Urol 2009;182(6):2653-8.

Lu B, Maqsoodi B, Yang W, McMaster GK, Perner S, Regan M, Bubley GJ, Balk SP, Rubin M, **Sanda MG**. Detection of TMPRSS2-ERG fusion gene expression in prostate cancer specimens by a novel assay using branched DNA. Urology 2009;74(5):1156-61.

Mosquera JM, Mehra R, Regan MM, Perner S, Genega MG, Bueti G, Shah RB, Gaston S, Tomlins SA, Wei JT, Kearney MC, Johnson LA, Tang JM, Chinnaiyan AM, Rubin MA,* **Sanda MG**.* Prevalence of TMPRSS2-ERG fusion prostate cancer among men undergoing prostate biopsy in the United States. Clin Cancer Res 2009;15(14):4706-11.

Shapple WV 3rd, Kenfield SA, Kasperzyk JL, Qiu W, Stampfer MJ, **Sanda MG**,* Chan JM*. A prospective study of determinants and outcomes of deferred treatment or watchful waiting among men with prostate cancer in a nationwide cohort. J Clin Oncol 2009;27(30):4980-5.

Tseng-Rogenski SS, Arredouani MS, Escara-Wilke JF, Neeley YC, Imperiale MJ, **Sanda MG**. A safety-modified SV40 Tag developed for human cancer immunotherapy. Drug Des Devel Ther 2009;2:17-24.

Tuck MK, Chan DW, Chia D, Godwin AK, Grizzle WE, Krueger KE, Rom W, **Sanda M**, Sorbara L, Stass S, Wang W, Brenner DE. Standard operating procedures for serum and plasma collection: early detection research network consensus statement standard operating procedure integration working group. J Proteome Res 2009;8(1):113-7.

Reviews, Chapters and Editorials

McDermott DW, **Sanda MG**. Health-related quality-of-life effects of watchful waiting re-evaluated in SPCG-4. Nat Clin Pract Urol 2009;6(3):124-5.

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Sanda MG. Live longer but not better ... yet. *Lancet Oncol.* 2009;10(4):313-4.

Sanda MG. Nerve sparing during radical prostatectomy is associated with better recovery of urinary continence. *Urology* 2009;73(6):1340-1; author reply 1341.

Clinical Communications

Sanda MG, Kaplan ID. A 64-year-old man with low-risk prostate cancer: review of prostate cancer treatment. *JAMA* 2009;301(20):2141-51.

DIVISION OF VASCULAR AND ENDOVASCULAR SURGERY

Frank Pomposelli, MD
Chief, Division of Vascular and Endovascular Surgery
Associate Professor of Surgery



VASCULAR AND ENDOVASCULAR DIVISION MEMBERS

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Maggie Chun

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Vascular Surgery Research Laboratory**

Instructor of Surgery
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Assistant Professor of Surgery
Instructor in Surgery
Harvard-Longwood Vascular T-32 Fellow
Harvard-Longwood Vascular T-32 Fellow
Research Fellow
Research Fellow
Research Fellow
Research Assistant II
Senior Research Associate

Allen Hamdan, MD

Associate Professor of Surgery

Marc Schermerhorn, MD

**Assistant Professor of Surgery
Section Chief, Endovascular Surgery
Outcomes Research**

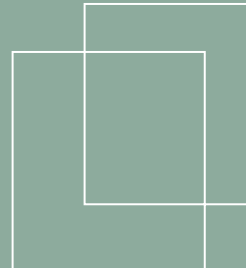
DIVISIONAL RESEARCH REPORT RESEARCH SUMMARY

BASIC RESEARCH

Vascular Surgery Research Laboratory

The Vascular Surgery Research Laboratory, directed by Dr. LoGerfo, has been extensively involved in four main areas of vascular biology research: 1) evaluating mechanisms responsible for prosthetic graft failure 2) prevention of intimal hyperplasia (IH) in vein grafts, 3) role of neuropeptides in diabetic wound healing and heart failure and, 4) developing novel biomaterial surfaces.

Anastomotic intimal hyperplasia (AIH) is the most common cause of delayed prosthetic arterial graft failure, and delayed failure of vein grafts. As graft healing occurs, genes are either up- or down-regulated as compared to a quiescent arterial wall. We study altered gene expression that results in endothelial cell activation as well as cellular proliferation, migration and extracellular matrix production by smooth muscle cells, leading to AIH. Differential gene expression is assessed using various techniques such as, microarray analysis, qPCR immunohistochemistry, and laser capture microdissection (LCM). We have now established proficiency with LCM, a tool designed to isolate homogeneous populations of cells for genetic analysis. This technique allows direct microscopic visualization and isolation of selected cell populations from frozen tissue sections and permits selection of cells within a chosen area of tissue. The significance and unique aspect of this work is that our group is the first to identify specific genes that are altered following prosthetic arterial grafting and vein grafting *in vivo* and to examine their role in the cellular environment using various *in vitro* cell culture assays. This information is now being used to identify targets for RNA interference-mediated gene silencing. We have established our ability to silence RNA in cell culture and in the vein graft wall and are working to develop systems for RNA silencing that will be practical for intraoperative use.



Frank W. LoGerfo, MD (upper left)

Christiane Ferran, MD, PhD (upper right)

Marc Schermerhorn, MD (lower right)

LIST OF CURRENT EMPLOYEES

Vascular Surgery Research Laboratory

Frank W. LoGerfo, MD

Mauricio A. Contreras, MD	Instructor in Surgery
Leena Pradhan, PhD	Instructor in Surgery
Asma Ejaz, PhD	Research Fellow
Zhen Huang, MD	T-32 Training Fellow
Shunsuke Yoshida, MD	T-32 Training Fellow
Lindestey Korepta	Visiting Fellow, MSU
Monica Jain	Undergraduate Student
Elizabeth Alden Landis	Undergraduate Student
Maggie Chun	Undergraduate Student

Immunobiology Research Laboratory

Christiane Ferran, MD, PhD

Elzbieta Kaczmarek, PhD	Assist. Professor of Surgery
Clayton Peterson, MD	T-32 Training Fellow
Scott Damrauer, MD	T-32 Training Fellow
Cleide Da Silva, PhD	Instructor in Surgery
Peter Studer MD	Research Fellow
Sanah Essayagh, PhD	Research Fellow
Renata Guedes, PhD	Research Fellow
Eva Czismadia, MS	Sr. Research Assoc.
Viktorya Marusyk, BS	Research Assistant II

BASIC RESEARCH CONT'D

For the neuropeptide-diabetic wound healing research, we have developed different *in vivo* and *in vitro* models. Both the *in vivo* and *in vitro* projects are conducted by Dr. Leena Pradhan who is an instructor in my laboratory and for the *in vivo* project we collaborate with Dr. Aristidis Veves in the Division of Podiatry. Peripheral neuropathy and peripheral vascular disease are the major contributors to diabetic foot ulcers and their failure to heal. Therefore, it is important to assess the individual and combined role of neuropathy and vascular disease and their intricate interplay that leads to DFU. To achieve this goal we have successfully developed an *in vivo* diabetic rabbit model of ischemic and neuroischemic wound healing. The results of the *in vivo* studies are highly promising implicating a role for neuroinflammation in abnormal diabetic wound healing. We have used this rabbit model to test therapeutic molecules from different companies. In addition we are also using rat model of wound healing to assess new therapies. Angiogenesis is an important phase of wound healing and dermal microvascular endothelial cells are central to achieving a successful closure of the wound. Our *in vitro* studies using dermal vascular endothelial cells are specifically designed to monitor the role of neuropeptides in angiogenesis in a hyperglycemic environment.



Leena Pradhan, PhD

In addition to investigating the role of neuropeptides in wound healing, we are also investigating their role in diabetic heart failure. Heart failure (HF) is a major cause of mortality in the United States, affecting nearly 5 million Americans and causing 300,000 deaths annually. Approximately 15 to 25% of patients with HF are diabetics and it has been suggested that diabetes may play an important role in the pathogenesis, prognosis, and response to treatment of HF. Advanced HF is related to marked insulin resistance. Coronary artery disease and cardiomyopathy are major causes of HF in diabetics. In addition, diabetes is known to cause both peripheral and autonomic neuropathy. The goal of this project is to investigate the role of SP, NPY and Calcitonin Gene Related Peptide (CGRP) in diabetic heart failure. As described above it is known that levels of these neuropeptides are reduced in diabetes.

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* and tested *in vivo*, as described in our Phase I and Phase II STTR proposals, a novel small-diameter nanofibrous polyurethane vascular graft via electrospinning technology. We have completed Phase I of our Novel Bioactive Conduit for Assist Devices, and are now initiating our Phase II *in vivo* animal (canine) studies. 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, and a SBIR Phase II grant application for *in vivo* testing has been submitted.

Immunobiology Research Laboratory

The Immunobiology Research Laboratory, directed by Dr. Ferran, has research interests in the field of vascular and transplantation Immunobiology. Seventy percent of her time effort is devoted to Research and the other thirty per cent for teaching and administrative tasks. Dr. Ferran's major research interests are in the field of vascular biology, micro and macrovascular complications of diabetes, liver and β -cell regeneration, solid organ and islet transplantation and autoimmune diabetes. More specifically, the work in her laboratory is focused on the understanding of the function(s) of the cytoprotective genes A20, Bcl-2, Bcl-x_L and A1 in different cell types, their relationship to the pathophysiology of diseases and their potential therapeutic use in vascular diseases, organ transplantation, diabetes and liver resection and transplantation among other diseases. This interest is based on

our original finding that these genes serve a broad cytoprotective function in endothelial cells (EC). Expression of A20, A1, Bcl-2 and Bcl-x_L in endothelial cells not only protects the cells from apoptosis but also serve a broad anti-inflammatory purpose, which defines their homeostatic potential.

We have now expanded the work to other cell types and made additional critical observations. First that A20 retains in β -cells its anti-apoptotic and anti-inflammatory potential and thus is an ideal candidate to genetically engineer islet grafts for the treatment of diabetes. Second that A20 serves an anti-atherogenic function in smooth muscle cells (SMC) via inhibition of cell proliferation and induction of apoptosis of neointimal SMC. This translates into prevention but also regression of lesions of neointimal hyperplasia following balloon angioplasty of rat carotid arteries and protection from transplant arteriosclerosis (TA), thanks to an additional modulation of the immune response, skewing it towards an immunomodulatory and away from a pathogenic phenotype. Accordingly, A20 over-expression protected aortic allografts from TA in a fully mismatched mouse aorta to carotid transplant model (manuscript submitted). This is the first report proving a cause-effect relationship between over-expression of A20 in EC/SMC and protection from TA. Extensive analysis of these *in vivo* results and of gene expression microarrays from A20-over-expressing and A20-silenced human coronary artery SMC has identified novel targets of A20 in EC/SMC that help to explain this positive outcome (Fig. 1). Over-expression of A20 in EC and SMC transforms the molecular signature of the vessel wall to change its response to injury. This modifies the microenvironment of the graft, reducing pro-inflammatory mediators and rechanneling the bi-directional cross talk between the allograft and the immune system to protect from TA. The first part of this work pertaining to intimal hyperplasia post-balloon angioplasty has been published in *FASEB J* and is in press in *Atherosclerosis*. The second part is being finalized for submission to *Circulation Research*. This work will be presented at the American Transplant Congress 2010, and has received a Young Investigator Award from the ATC.

Interestingly, we have also unraveled that high glucose/hyperglycemia regulate A20 levels that are decreased in diabetic patients and animals. A20's decrease is due to unique post-translational modifications (PTM). In response to high glucose, A20 is O-glycosylated, subsequently ubiquitinated and degraded in the proteasome. Loss of this important atheroprotective mechanism is part of the molecular basis for the increased risk of atherosclerosis in diabetes. This work was recently submitted for publication to PLOS one.

In addition, A20 demonstrates a potent anti-angiogenic function in retinal endothelial cells. Here again, diabetes-related degradation of A20 would significantly contribute and aggravate heightened angiogenesis in diabetic retinopathy. We are mapping and mutating the glycosylation sites within A20. Glycosylation resistant A20 should be able to sustain the insults of high glucose as to provide adequate atheroprotective and anti-angiogenic effects to protect from macro and microvascular complications of diabetes. Finally, A20 deficiency as in heterozygote mice seems to protect from the development of aortic abdominal aneurysms (AAA), likely by modulating the differentiation status of smooth muscle cells, through modulation of microRNA patterns. This work is being finalized for publication.

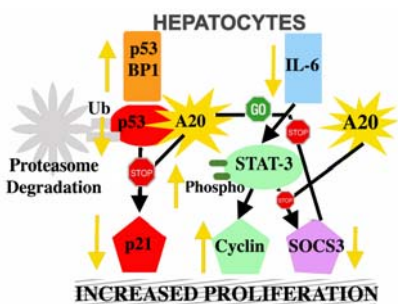


Fig 1: Two major targets for the proliferative function of A20 in hepatocytes: the CDKI p21^{waf1} and the IL-6/STAT3 axis. Yellow arrows indicate the impact (increase or decrease) of A20 on the given targets.

As for the ongoing liver regeneration and response to injury, we have recently shown that A20 protects mice from lethality in models of acute toxic hepatitis, lethal radical hepatectomy, and prolonged warm ischemic time by promoting hepatocyte survival, protecting them from necrosis through a PPAR α -dependent mechanism, containing inflammation and unexpectedly promoting their proliferation by shutting down the cell cycle inhibitor: p21^{waf1} and also promoting IL-6 proliferative signals by shutting down SOCS-3. This latter work is being finalized for publication (Fig. 2). Interestingly, we have also unraveled in loss-of-function experiments, using A20 heterozygote mice (A20 +/-), that partial loss of A20 significantly delays liver regeneration, increasing lethality following 2/3 partial hepatectomy. In that A20 (*tfaip3*) gene polymorphisms have been identified as susceptibility loci for several inflammatory and autoimmune diseases, we were interested to see whether these polymorphisms could also affect the rate of liver regeneration in recipients of living donor liver transplants. Accordingly, we have engaged in a collaboration with Dr.

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Elizabeth Pomfret at the Lahey Clinic to study that and have submitted a grant proposal to the NIH/NIDDK in that regard. Funding of this proposal is pending.

Additionally, we have recently discovered that Hepatocyte Growth Factor upregulates A20 in renal proximal tubular epithelial cells and endothelial cells by engaging the non-canonical form of NF- κ B without promoting any inflammation. These results could be particularly important for the design of preventive or pre-conditioning regimen that would limit inflammation in many disease processes including prior to major vascular interventions and organ transplantation. This work is being finalized for publication and has been already presented at National and International Meetings. We hope that data obtained in experimental models will set the basis for the therapeutic use of these proteins in clinical settings.

We are also working on defining at the molecular level the intracellular targets that account for the function(s) of these proteins, and on establishing a structure/function analysis to map the domains associated with their different functions. As part of this work we discovered, in collaboration with Dr. Pope from Northwestern University in Chicago that A20 interrupts caspase-independent cell death in macrophages and in collaboration with Dr. Roya Khosravi-Far from the BIDMC, that A20 was involved in the resistance of cancers to TRAIL. These findings were respectively accepted for publication in the Apoptosis Journal and submitted for publication. It is our hope that defining specific domains and targets responsible for the function(s) of these genes may allow the development of peptide-based therapies and drug-design strategies.

The personnel effort is equally divided between the clinically oriented projects and the basic science projects. Two post-doctoral research fellows, one research associate, two T32 residents in Surgery, an Instructor, an Assistant Professor and a visiting Surgery fellow from Switzerland are currently working in the laboratory. I provide direct supervision of all the projects in my laboratory as well as for the T32 trainees in Vascular Surgery who are in Dr. Legerfo's laboratory, given my role as a co-director of this training grant. This includes informal teaching sessions, technical help, experimental design, literature search and manuscript writing. All of which is part of my teaching responsibilities.

Since Dr. Kaczmarek (Assistant Professor of Surgery) has joined our group, an additional line of investigation was initiated in the laboratory, mainly focusing on the induction of A20 and other protective genes such as A1 by extracellular nucleotides. Extracellular nucleotides play a significant biological role in many tissues and cell types, as signaling molecules that regulate cellular function under both normal and pathophysiological conditions. They are released in tissue fluids and plasma in response to different cellular stimuli and as result of tissue damage and cell death. Extracellular nucleotides exert their biological action via specific purinergic P2 receptors that are classified into two main groups: P2X, ligand-gated ion channels and P2Y, G protein-coupled receptors. Recently, Dr. Kaczmarek and colleagues has demonstrated that P2 receptors activate endothelial nitric oxide synthase (eNOS) in endothelial cells through a novel PKC δ -dependent pathway that could be used therapeutically to circumvent the defect in eNOS associated with EC dysfunction in diabetes.

Relevant to our line of research, Dr. Kaczmarek has shown that P2 receptor signaling upregulates expression of the two anti-apoptotic "cytoprotective" genes, A20 and A1 in human endothelial cells. In addition, extracellular nucleotides activate endothelial nitric oxide synthase (eNOS), even under high glucose levels. These two observations indicate that P2 receptors may be targets for management of EC dysfunction, and possibly diabetic complications. Treatment with extracellular nucleotides may thus represent an alternative therapeutic avenue to increase expression of A20 that could be much easier to implement than gene therapy.

Recent effort in the laboratory is geared towards expanding collaborations across discipline boundaries with the hope of delineating common patterns of responses to injury in different cell types, organ systems and diseases that would help restore homeostasis to the system. This endeavor is centered around A20/tnf α 3 that has been the subject of intense research in our laboratory for over 10 years. As part of these collaborations we have now engaged a collaboration with Dr. Atul Malhotra MD, Associate professor of Medicine at Harvard Medical School, a member of the Pulmonary Division at the Brigham and Women's Hospital in Boston and Director of the Sleep Apnea Laboratory, to study the effect of sleep apnea in affecting vascular homeostasis and predisposing to vascular disease, including atherosclerosis, again with a particular emphasis on A20 and P2 receptors.

CLINICAL RESEARCH

Vascular Surgery Outcomes Research Group

The Division of Vascular and Endovascular Surgery now has an active interest in outcomes research on a national level as well as at the local level here at BIDMC. Dr. Schermerhorn directs the Vascular Surgery Outcomes Research Group, whose main interest is to compare outcomes after open surgery and endovascular surgery for a variety of vascular diseases. We have access to national data from the Nationwide Inpatient Sample (a 20% sample of all non-federal hospital admissions). This administrative database allows us to evaluate in-hospital outcomes after open vascular surgical or endovascular procedures in large cohorts of patients, representative of the entire nation, as well as allowing estimates of national rates of various vascular interventions (open and endovascular) over time. We have also recently purchased data from statewide databases that also include procedures performed without an admission to the hospital that may be missed by other administrative databases with only inpatient admissions.

Since BIDMC is a participating hospital for data collection, we have access to the American College of Surgeons National Surgical Quality Improvement Program data. This data consists of detailed and surgery-specific preoperative, intraoperative, and 30-day postoperative information with a specific risk adjustment variable for mortality and morbidity. Open surgical vascular operations as well as major endovascular operations such as AAA repair, TAA/A repair, and ruptured aneurysm repair are collected in this database and thus we can perform detailed evaluations of surgical outcomes as well as comparative analysis between open and endovascular procedures.

We also have our own database in the Division with all vascular procedures captured prospectively. This allows tailored evaluation of comorbidities and various outcomes with physician chart review and angiographic review. This allows appropriate risk adjustment for various factors associated with choice of a given treatment strategy.

Working with Bruce Landon, MD from the School of Health Policy at HMS we have developed collaboration with the Centers for Medicare and Medicaid Services and have access to data from all Medicare patients. Through this database we have access not only to in-hospital outcomes from Part A files, but with access to Part B files we can adjust for pre-existing conditions based on diagnoses made prior to the index admission. The use of part B files also allows the extra specificity and accuracy from CPT codes submitted by the treating physician, rather than ICD-9 codes submitted by the hospital coders. We also have unique identifiers allowing us to track long term readmission, re-intervention, and survival of patients after open or endovascular treatment. Collaboration with James O'Malley from the School of Health Policy at HMS allows us to perform detailed statistical analyses, including propensity score matching of patients undergoing open or endovascular surgery.

LIST OF CURRENT FUNDING

“Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery”

NIH/NHLBI R01 HL086741-04

Project period: 01/01/2007-12/31/2011

PI: Frank W. LoGerfo

Co-Investigator: Christiane C. Ferran

“Mechanisms of prosthetic arterial graft failure”

NIH/NHLBI, R01 HL21796-25

Project period: 12/01/2009 -11/30/2014

PI: Frank W. LoGerfo

Co-Investigator: Christiane C. Ferran

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“Harvard-Longwood Research Training in Vascular Surgery”

NIH/NHLBI, 5-T32-HL007734-16

07/01/1997 – 06/30/2014

Director: Frank W. LoGerfo

Co-Director: Christiane C. Ferran

“William J. von Liebig Research and Research Training in Vascular Surgery”

William J. von Liebig Foundation

Project Period: 2001 – 2011

PI: Frank W. LoGerfo

“Impaired wound healing in diabetic foot ulceration”

NIH/NIDDK 1R01DK076937-01

Project Period: 01/01/2007-12/31/2011

PI: Aristidis Veves

Co-Investigators: Frank W. LoGerfo and Leena Pradhan

“The effect of diabetes, neuropathy and arterial disease in lower extremity energy”

NIH/NIDDK, 1R21DK82987-01A1

Project Period: 09/1/2009 - 08/31/2011

PI: Aristidis Veves

Co-Investigator: Frank W. LoGerfo

“A novel bioactive conduit for assist devices”

NIH/NHLBI SBIR Phase II Contract (Phaneuf, M)

Project Period: 06/01/2009 - 05/31/2011

PI: Mauricio A. Contreras

Co-Investigator: Frank W. LoGerfo

“A nanofibrous bioactive prosthetic sewing cuff”

NIH/NHLBI, SBIR 1 R41 HL095189-01A2

Project Period: 08/01/2009 - 07/31/2011

PI: Mauricio A. Contreras

Co-Investigator: Frank W. LoGerfo

“Localized gene delivery from implantable arterial devices”

NIH/NHLBI, NSF STTR Phase II 0923674

Project Period: 08/01/2009 - 07/31/2011

Co-PI's: Mauricio A. Contreras and Matthew Phaneuf

Co-Investigator: Frank W. LoGerfo

“Improved liver function and regeneration with A20”

NIH NIDDK DK063275-06

Project Period: 01/01/2003-05/31/2014

PI: Christiane C. Ferran

“Vascular remodeling in transplant arteriosclerosis”

NIH HL080130A1-03

Project Period: 06/15/2006-05/31/2010

PI: Christiane C. Ferran

“The therapeutic potential of A20 in diabetic retinopathy”
Juvenile Diabetes Research Foundation grant JDRF#1-2007-567
Project Period: 09/01/2007-08/31/2010
PI: Christiane C. Ferran

“Harvard Longwood Medical Area Training in Transplantation”
National Institutes of Health Grant T32 AI070085
Project period: 08/01/2007-07/31/2011
Faculty: Christiane Ferran
Director: John Iacomini (BWH)

APPLICATIONS SUBMITTED AND PENDING REVIEW/FUNDING

“Role of neuropeptides in diabetic foot problems”
NIH/NIDDK 1R01NS066205-01
Project Period: 07/01/2010 - 06/30/2015
Co-PI's: Frank W. LoGerfo and Aris Veves
Co-Investigators: Leena Pradhan and Christiane C. Ferran
Received Priority Score of 19 (2nd percentile)
Pending Council Review

“Living donor liver transplantation: Diagnostic markers of liver regeneration to predict outcomes”
NIH NIDDK RFA DK-09-003
Project Period: 2010-2015
Principal Investigator: Elizabeth Pomfret MD/PhD, Lahey Clinic
Subcontract and project Leader at BIDMC: Christiane C. Ferran

RESEARCH ACCOMPLISHMENTS IN THE PAST YEAR

Basic Research Progress

Vascular Biology Research Laboratory

Mechanisms of Bypass Graft Failure: Intimal hyperplasia (IH) is the pathologic process of vessel wall thickening and lumen narrowing that occurs in blood vessels in response to injury. This process remains the most common cause of delayed bypass graft failure, a consequence of focal gene expression. As graft healing occurs, genes are either up or down-regulated compared to a quiescent arterial or venous wall. Our hypothesis is that altered gene expression results in cellular proliferation, migration, and extracellular matrix production by smooth muscle cells leading to IH.

Vein Bypass Graft Failure: Canine femoral artery interposition bypass using reversed autologous cephalic vein grafts were harvested, along with contralateral cephalic vein controls, after 1, 7 and 30 days (n=3 for each time point). RNA was purified from laser capture microdissection (LCM)-isolated ECs and SMCs, converted to cDNA, and prepared for Affymetrix Canine2.0 GeneChip hybridization. Isolate purities were quantified via qRT-PCR (EC markers: CD31, eNOS, vWF; SMC markers: alpha-actin 2, SMC-MHCII). Average isolate purities were 34-90% for ECs and 79-100% for SMCs.

Gene expression was considered significantly up- (UR) or down-regulated (DR) if the graft genes had ≥ 2.0 average fold change versus control and an absolute lower confidence bound of ≥ 2.0 . Human genes were matched using BLAST PERL scripts. Principal component and clustering analyses showed unique clustering of graft versus control ECs and SMCs, demonstrating the reproducibility of the results. Comparing grafts versus controls (Table 1), at 1 day: 2101 differentially expressed genes in ECs, 1753 in SMCs; UR: ECs 1112, SMCs 729, 322 in common; DR: ECs 989, SMCs 1024, 444 in common; 7-days: 1667 differentially expressed genes in ECs, 1679 in SMCs; UR: ECs 1174, SMCs 1164, 568 in common; DR: ECs 493, SMCs 515, 199 in common; 30-

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days: 494 differentially expressed genes in ECs, 334 in SMCs; UR: ECs 403, SMCs 270, 88 in common; DR: ECs 91, SMCs 64, 8 in common. At 1 day, there were 2101 and 1753 differentially expressed genes in ECs and SMCs, respectively, and the total differentially expressed genes markedly decreased over time, with less than 25% of the initial total genes remaining by 30 days.

1-day gene ontology (GO) analysis exhibited predominant gene functions in protein binding (ECs and SMCs), inflammatory processes (ECs), cell motility (SMCs) and plasma membrane (ECs) and extracellular matrix (SMCs) localizations. 7-days GO analysis demonstrated similar EC characteristics but SMC gene functions shifted to enzymatic activities, extracellular structure organization, cell cycle regulation and localizations to the endoplasmic reticulum and cytoplasm. 30-days GO analysis showed a shift in EC gene functions to growth factor binding, extracellular structure organization and cell cycle regulation, while SMCs remained fairly similar.

Distinct temporal gene expression patterns were present for cytokines (large early up-regulation that greatly diminished over time), collagen (increasingly up-regulated at 7- and 30-days) and other extracellular matrix-modulating genes. Immunohistochemical (IHC) analysis of the cytokines IL6 and IL8 (both markedly up-regulated in vein graft ECs and SMCs versus controls at 1 day with subsequently diminished expression over time) has confirmed this temporal expression pattern at the protein level. IHC analysis for other markedly UR or DR gene-products are ongoing, namely for TFPI-2, NRG-1, BCL2-A1, and ITIH1 (please see below for discussion on these genes of interest). Verification of the microarray data will also entail qRT-PCR analysis of these genes.

Given the substantial number of differentially expressed genes at the 1-day time point, we have performed two additional time points at 2 and 12 hours in order to elucidate the gene expression patterns prior 24 hours. The surgical technique for these additional time points was modified to minimize the number of animals used. We initially isolated one cephalic vein for the 2-hour bypass and used only a portion of the contralateral cephalic vein to serve as control tissue for 2 hours while the remainder of the contralateral cephalic vein was used for the 12-hour bypass. During the harvesting of the 12-hour time point, we needed to isolate a saphenous vein, which served as control tissue. The isolation of ECs and SMCs via LCM is in progress. These samples will be subjected to the same analysis methods (i.e. Microarrays, IHC, and qRT-PCR) as the prior three time points.

From these data, we have begun to focus on specific genes of interest (Table 2). Of the maximally up-regulated genes seen in both ECs and SMCs, when comparing control versus bypass graft, were those involved in inflammation, namely tissue factor pathway inhibitor 2 (TFPI-2), neuregulin-1 (NRG-1) and IL-8. IL-8 was not surprising given that the inflammatory cascades are set off post-bypass. The most down-regulated gene was inter-alpha-inhibitor.

TFPI-2 is a Kunitz-type serine proteinase inhibitor that is involved in numerous physiologic processes including blood coagulation, complement fixation, fibrinolysis, and ECM remodeling which, in turn, plays an important role in cell migration and angiogenesis (Chand, et al. *Thromb Haemost* 2005, 94: 1122-30). This is of particular interest given that neointimal formation requires SMC migration and proliferation.

NRG-1 is also associated with numerous physiological roles including neurological development and more recently and more relevant to our study, inhibition of SMC proliferation and attenuation of neointimal formation in rats following vascular injury (Clement, et al. *J Vasc Res* 2007, 44: 303-312). However, the exact mechanism(s) by which these effects occur are still unknown.

On the other end of the spectrum, the gene for inter-alpha (globulin) inhibitor H1 (ITIH1) was the most down-regulated in both ECs and SMCs when comparing control versus bypass graft samples. ITIH1 is a serine protease inhibitor, whose exact physiologic function is still unclear. However, it has been implicated as an anti-inflammatory agent (Wisniewski HG et al, *J Immunol*. 1996 Feb 15;156(4):1609-15). Therefore, one can postulate a protective role against inflammation and neointimal formation for I-alpha-I.

Another gene of particular interest was BCL2-related A1 (Bfl-1/A1), which was up-regulated only in SMCs at the 1-day time point. It is part of Bcl-2 family of anti-apoptotic genes and localizes to mitochondria and is expressed in multiple tissues (e.g. various cancer cells, spleen, lymph nodes, peripheral blood leukocytes, bone marrow) (Zong WX et al, *Genes Dev*. 1999 Feb 15;13(4):382-7). It suppresses p53-induced apoptosis, inhibits TNF- α induced apoptosis and is a direct transcriptional target for NF- κ B in B lymphocytes (Sakuma H et al, *Am J Physiol Cell Physiol* 283:422-428, 2002). siRNA down-regulation of Bfl-1/A1 allowed for increased apoptosis of virulent M. tuberculosis infected lymphocytes (Dhiman R et al, *Biochim Biophys Acta*. 2008 Apr; 1780(4):733-42). Given

this gene's function and its up-regulation only in SMCs at the 1-day time provides an opportunity to potentially regulate SMC proliferation without altering EC function early post-bypass.

	Total Genes		EC Genes Only		SMC Genes Only		Common EC & SMC Genes	
	EC	SMC	UR	DR	UR	DR	UR	DR
1 day	2101	1753	1112	989	729	1024	322	444
7 days	1667	1679	1174	493	1164	515	568	199
30 days	494	334	403	91	270	64	88	8

Table 1: Comparing grafts versus controls, total number of differentially expressed genes (absolute fold change and lower confidence bound of greater than or equal to 2) in ECs and SMCs for 1, 7 and 30 days (UR=up-regulated, DR=down-regulated)

Gene Name	Gene Symbol	24-hour FC in Graft vs. Control		7-Days FC in Graft vs. Control		30-Days FC in Graft vs. Control	
		ECs	SMCs	ECs	SMCs	ECs	SMCs
inter-alpha (globulin) inhibitor H1	ITIH1	-109.7	-127.4	-7.96	-22.75	0	0
interleukin 8	IL-8	504.83	395.08	27.55	55.35	0	0
interleukin 6 (interferon, beta 2)	IL6	22.72	566.25	10.43	23.96	0	0
tissue factor pathway inhibitor 2	TFPI2	212.4	625.94	274.25	185.94	96.48	45.99
neuregulin 1	NRG1	169.2	82.84	18.05	19.22	0	0
Bcl-2-related protein A1 (BFL-1 protein)	BCL2A1	0	110.47	0	0	0	0
myristoylated alanine-rich C kinase substrate	MARCKS*	23.26*	9.54*	57.49*	50.41*	23.53*	4.14*

Table 2: Expression levels for genes of interest at 1, 7 and 30 days. FC= Fold Change. ND=not detected by applied criteria. *MARCKS gene was not included on canine microarray; results shown are from qRT-PCR.

RNA Interference for the Prevention of IH in Vein Grafts: IH 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 IH, 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 IH. **It is our hypothesis that silencing of genes upregulated by injury to the vein wall will diminish IH.** Furthermore, gene silencing can be accomplished within the constraints of operating room conditions. We have demonstrated the ability to identify candidate genes associated with IH 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 IH in vein grafts in vivo. We are performing

studies in human tissue and canine models as well as in vitro using human smooth muscle cells and human coronary artery endothelial cells. 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. In 2006, the work of Dr. Thomas Monahan characterized the contributions of two novel target genes identified by our lab, Cadherin 11 (CDH11) and the myristoylated alanine-rich C kinase substrate (MARCKS), to the pathologic in vitro phenotypes associated with IH and identified both as promising targets for therapeutic gene silencing in vein grafts. Currently, Lindsey Korepta is investigating the signaling mechanisms of MARCKS in both ECs and SMCs and its contribution to IH by using siRNA. Lindsey has demonstrated that MARCKS silencing preferentially up-regulates p27^{kip1} in proliferating human SMCs and ECs and that there is a negative correlation between MARCKS and p27^{kip1} protein expression in SMCs. P27^{kip1} is a cyclin dependent kinase inhibitor that negatively regulates SMC migration, proliferation and promotes a quiescent differentiated SMC phenotype *in vitro* and *in vivo*. By suppressing cell proliferation and migration, p27^{kip1}, has been shown to protect against atherosclerosis and re-stenosis. In addition, we are also investigating expression of MAP kinases such as ERK1/2, JNK and p38 in ECs and SMCs treated with MARCKS siRNA.

These studies have been presented at numerous national and international conferences including, American College of Surgeons, Society of University Surgeons, Society of Vascular Surgeons and New England Society of Vascular Surgeons.

Prosthetic Bypass Graft Failure: We successfully renewed this long-standing NIH-R01 grant for years 25-30. This is a proposal to create a biologically active prosthetic arterial graft incorporating gene silencing to an antithrombotic and pro-angiogenic surface. The research team is unique in its cohesiveness and breadth of expertise including textiles, polymers, cell biology, molecular biology, and surgery, all with an established focus on vascular grafts.

This project builds on our long-standing work where we have 1) characterized the lesion of anastomotic neointimal hyperplasia (AIH) downstream of the prosthetic graft, 2) established the role of blood flow-surface interaction in AIH pathogenesis, 3) applied biologic modification to the graft surface by incorporating antithrombotic (rHirudin) and endothelial cell growth factor (VEGF) to delay thrombus formation and improve endothelialization, and 4) determined the unique gene signature associated with AIH development, including identification of high profile pathogenic targets.

The goals of this project are to 1) Validate the involvement of MARCKS, CDH11, and Thrombospondin2 (TSP2) in the pathogenesis of AIH, by means of in vitro loss-of-function studies in endothelial and smooth muscle cells using siRNA, 2) Create a bioactive electrospun nanofibrous graft material and determine optimal physical properties that it requires for effective siRNA delivery to the vasculature under pulsatile flow and operating room conditions and, 3) implant the graft prototype in a large canine animal model, after preliminary testing in a rat model, and determine sequentially its potential to deliver siRNA, effectively induce gene silencing and positively impact the development of AIH lesions, including graft healing and patency.

This is a stepwise study bringing to bear a unique and appropriately broad range of expertise on the effective application of gene silencing to improve the outcome of prosthetic arterial grafts. The information will also be of interest in the larger use of materials to deliver siRNA for therapeutic purposes.

A Nanofiber Biocomposite Small Diameter Graft: The specific aim of this study was to assess blood permeation, graft patency and healing of our novel nanofibrous biocomposite vascular graft (ESDC-rHir-VEGF) using a canine arterial grafting model. ESDC-rHir-VEGF grafts were synthesized using electro-spinning methodology. The structural component of these novel grafts was Polyester, which is utilized in items ranging from clothing to medical implants. Polyester has been utilized in vascular grafts for more than 48 years. This material has established mechanical and physical properties as well as long-term biocompatibility once implanted. Polyester also has excellent handling characteristics. It can be formed into various constructs and can undergo some degree of surface modification, if necessary. Thus, these properties render polyester a strong and durable attractive material that could be used as the main structural component of the graft wall.

For the bioactive components of our graft we chose the following: 1) Antithrombin Component: Thrombin is a pivotal enzyme in the blood coagulation cascade that is primarily responsible for cleavage of fibrinogen to fibrin .

During clot lysis, enzymatically-active thrombin is released rendering the vessel susceptible to prompt re-thrombosis. Even within a clot, thrombin also functions as a smooth muscle cell mitogen, is chemotactic for monocytes and neutrophils and an aggregator of lymphocytes. Thus, thrombin that goes unregulated within a clot or pseudointima is an important trigger of cellular infiltration and uncontrolled SMC proliferation. Recombinant Hirudin (rHir) is the most potent direct inhibitor of thrombin, inhibiting the enzymatic, chemotactic, and mitogenic properties of thrombin. Additionally, rHir also inhibits clot bound thrombin. In previous studies, localized release of rHir from novel small-diameter nanofibrous vascular grafts were evaluated and did not result in any complications with suture line hemostasis or subsequent healing, even in the presence of systemic heparinization. The rationale for this self-sealing process is two fold. Firstly, the nanofibrous matrix comprising the wall wraps around the puncture sites, thereby preventing bleeding. Secondly, rHir is released at low but biologically effective concentrations, such that, thrombus formation is affected locally without systemic effects. For example, clinical dosing of rHir is 0.4mg/kg (IV), which equates to 27.2mg for a 150 pound patient. Localized rHir release from the nanofibrous graft would be approximately 0.00016mg/cm². While significantly lower than the systemic dosage

(factors in rHir loss due to renal clearance and tissue absorption), this release amount equates to a sustained, localized biological activity of 3 antithrombin units (ATU)/cm² at the highest release periods from the graft surface. Thus, slow and sustained release of rHir from our prosthetic graft surface provides an attractive strategy to prevent surface thrombus while promoting cellular healing. Our specific aim with these prosthetic grafts was to prevent surface thrombus formation and subsequent thrombo-embolic events by inhibiting the enzymatic, chemotactic and mitogenic properties of thrombin via localized release of rHir from the nanofibrous surface. 2) EC mitogenic

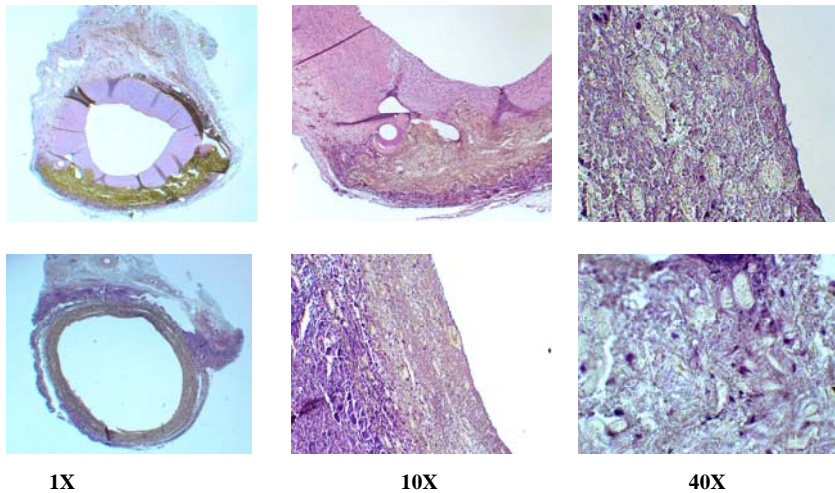


Fig 2: 4mm Bio-Spun Vascular Graft / Hirudin & VEGF / 30 days Anastomosis (CCA & Prosthetic Graft) H&E

Component: VEGF, a 38kDa homodimeric glycoprotein, has been shown to be an EC-specific mitogen and vasopermeability factor. VEGF is produced by many different cell types both in tissue culture and in vivo. VEGF binds to specific membrane receptors on ECs i.e VEGF-Receptors 1 and 2. VEGF-R2 is the predominant receptor that mediates the EC mitogenic effects of VEGF. In that timely re-endothelialization of the PAG is a critical means of preventing thrombogenic events as well as neointima formation, incorporating angiogenic factors such as VEGF into the graft matrix is highly desirable.

Direct incorporation of these biologically-active agents into the nanofibrous polyester fibers holds several key advantages over other methodologies in that: 1) the active agent incorporates into the nanofibrous material without molecular modification, 2) the amount of active agent can be adjusted within the bulk polymer, 3) no cross linking agents are needed, avoiding concerns over drug carrier toxicity, biocompatibility, and mutagenicity, 4) low temperatures are used during the fiber formation, which helps maintain the biologic activity of the active agent, and 5) active agent elution is controlled and sustained as shown in our preliminary studies.

Using our canine model (previously described) our prosthetic grafts (n=3) were implanted and harvested at different time intervals (7,14 and 30 days). At the anastomosis, both grafts healed from cellular proliferation and migration from the adjacent native carotid artery, as expected. However, it is interesting that within the woven polyester (control) fibers there was less cellular penetration, particularly when compared to the nanofibrous BioSpun-Vascular Grafts. The size and distribution of the nanofibers conferred to the prosthetic vascular graft through electrospinning seemed to provide a more suitable environment for cells to adhere, migrate and proliferate, structurally almost resembling extracellular matrix. One of the most striking findings through our histological analysis, however, occurred when the midportion of each graft was assessed. Unlike the sections

taken from the anastomotic interface, the typical mid-section of prosthetic grafts lack the initial cellular source (i.e. SMCs, ECs) provided by the adjacent artery. Thus, recruitment and sustainability of SMCs and ECs would be dependent on sufficient blood supply in the initial phase after implantation, particularly in the midportion of the graft wall, where insufficient vascularization can lead to improper cellular integration or even cell death. The architecture and design of the BioSpun-Vascular Grafts had a profound effect on the rate of vascularization after surgical implantation and was a critical determinant of blood-vessel ingrowth. It is important to note that these significant and essential changes in vascularization of the matrix of the graft wall did not occur in woven polyester grafts (Control).

The luminal surface of the BioSpun-Vascular Grafts was equally surprising in that a different cellular healing pattern emerged as compared to the woven polyester grafts. There was a cellular monolayer observed on the electrospun grafts resembling ECs. In contrast, woven polyester grafts had no cellular monolayer on their luminal surface. Instead, there was deposition of fibrin, platelets and red blood cells. These results are exciting because one of the current limitations of tissue engineering of vascular graft designs is the inability to provide sufficient blood supply into the graft wall. Most tissues in the body rely on blood vessels to supply the individual cells with nutrients and oxygen. For a tissue to grow beyond a distance of 100-200nm (the diffusion limit of oxygen), new blood-vessel formation is required, which is also true for tissue-engineered constructs. BioSpun-Vascular Grafts were shown to be a superior construct where vascularization could be achieved.

Our research will continue on the graft design to find ways to regulate SMC proliferation, so that anastomotic intimal hyperplasia does not become the contributing factor to secondary graft failure. The incorporation of rHir in to the graft construct made a significant contribution in preventing early graft failure due to acute thrombosis. A new methodology that we will be pursuing is RNAi-mediated gene therapy via siRNA transfection, for it has gained attention as a promising new therapy, yet remains untested as a tool for engineering vascular grafts. Multiple attributes of the RNAi pathway suggest that siRNAs are the ideal candidates for vascular graft gene therapy. siRNAs can be designed to target virtually any gene in the genome, thereby making every transcriptional unit a potential therapeutic target. The duration of action of RNAi closely matches the hypothesized window of genetic alteration responsible for the development of AIH. While the RISC complex is catalytic and can degrade multiple copies of mRNA, the effect of siRNA in cells is limited to 1-4 weeks, resulting from siRNA degradation and the dilution of siRNA molecules between daughter cells after cell division. The duration of action of siRNA is related in part to the proliferative activity of the transfected cell. Within this temporal limitation RNAi is a highly promising system for blocking a discrete genetic signaling event, and appears to be a normal cellular mechanism. These research results and our new vascular bio-engineered graft designed made possible for us to be the recipients of a high funding (competitive continuation) score of our RO1 "Mechanisms of prosthetic arterial graft failure" NIH grant that will give us the opportunity to pursue this research further for the next 5 years.

Development of Infection-Resistant Suture Materials: The specific aim of this study is to assess infection-resistant nylon, silk and Dacron (polyester) sutures *in vivo* using a rabbit wound infection model. Experimental parameters such as bacterial colonization of the wound, wound healing and physical properties of the suture post-explantation will be examined.

Our experiments have succeeded in: 1) Applying antibiotics to our suture materials: Polyester sutures (size 0) were either hydrolyzed (HYD) or EDA-treated (EDA). Surfaces were then subjected to either Methylene Blue (MB; carboxylic acid group determination) or Acid Red 1 (AR1; amine group determination). HYD sutures, which have carboxylic acid groups, had significant MB uptake whereas EDA, nylon and silk sutures, which have both functional groups, had significant uptake of both dyes. In contrast, untreated polyester had no uptake of either dye. Polyester suture surfaces (unmodified, HYD or EDA) as well as the nylon and silk sutures were then dyed with the Cipro, Linezolid and Doxycycline. 2) We have characterized the physical properties and evaluated the fiber microscopy of our suture materials: The physical properties of untreated, antibiotic-dipped (no heating/autoclaving) and antibiotic-dyed (heating and autoclaving) polyester, silk and nylon sutures were determined. There was no significant difference in strength between the untreated and antibiotic-dyed sutures. Fiber microscopy in conjunction fluorescence was also performed on the untreated and Cipro-dyed polyester sutures, which showed Cipro presence on the surface of the dyed polyester suture. 3) We have determined antibiotic release and antimicrobial activity (in vitro). Untreated, antibiotic-dipped and antibiotic-dyed polyester, nylon and silk underwent a stringent wash regiment for various time periods. Wash solutions were changed at each time period and read on a UV/VIS spectrophotometer. Segments (1cm length) were removed at each time

period and embedded into *S. aureus*-streaked agar plates in order to determine antimicrobial activity. To date, all segments have undergone washing. The acute time periods for each material have been assessed for antimicrobial activity. Antibiotic release has been rapid in the dipped samples whereas the dyed samples have released antibiotic slowly. As projected, spectroscopy detection of Cipro would be limited to the early time periods due the sensitivity of the assay. Thus, all samples will be tested for antimicrobial activity. Dyed segments also showed greater antimicrobial activity as compared to untreated/antibiotic-dipped controls.

4) We have completed our in vivo experiments in the rabbit model (previously described). At the time of sacrifice, animals were anesthetized and then euthanized. Each suture-tissue site was then blindly graded by a single observer. Suture specimens as well as the surrounding skin were then excised. A section of each explanted suture was placed into 10% buffered formalin for histological evaluation. The remainder of each segment was stored in a sterile 15ml Falcon tube and was used for physical and biological evaluation.

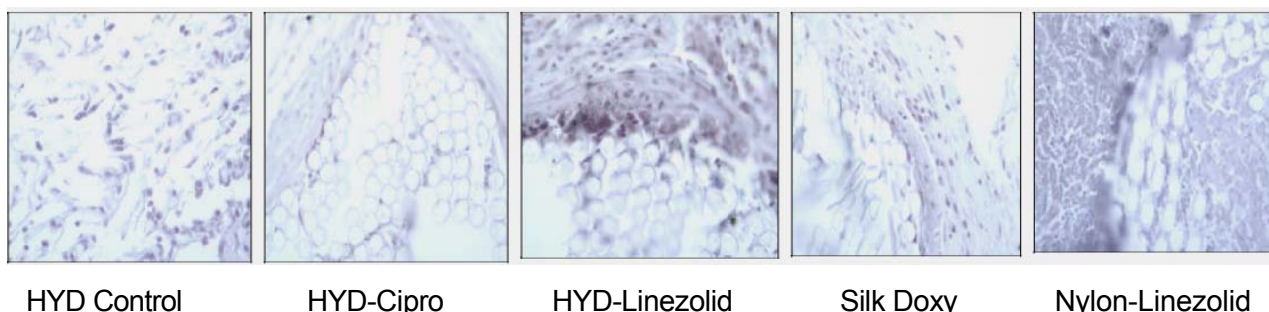


Fig 3: Histological analysis of hydrolyzed sutures for healing/infection resistance

Evaluation of explanted sutures for healing/infection-resistance and strength using physical testing and Histological Techniques, Respectively: Two centimeters of each explanted suture was placed into 70% ethanol for 24 hours followed by a distilled water wash for 1 hour. Segments were then oven-dried at 40°C overnight. Segments were then weighed and evaluated for tensile strength. All PET sutures as well as nylon sutures did not have any strength loss as compared to their respective unimplanted controls. Two sutures, silk and Vicryl Plus, which are both biodegradable, had strength loss after implantation for 7 days.

Microbiological Assessment: Explanted segments (1cm length; n = 2 segments/explanted suture) were evaluated for remaining antimicrobial activity as well as bacterial contamination (culture positive). One segment was embedded into *S. aureus*-streaked agar plates for 24 hours at 37°C with humidity in order to determine if any residual antimicrobial activity was remaining after implantation. Due to the extreme bacterial challenge that each suture was exposed to, there was no residual antimicrobial activity by any of the explanted suture materials as indicated by no zone of inhibition for any of the suture materials. The other explanted segment was embedded into agar plates (without bacteria) and placed in a humidified incubator at 37°C for 24 hours in order to determine if the explanted sutures had bacterial contamination. Segments deemed contaminated if bacterial growth was evident on or around the suture. Summarizing this data revealed that the antibacterial suture Vicryl Plus had over a 60% infection rate. EDA, HYD, Silk and Nylon control suture materials had greater than a 70% infection rate. In contrast, Cipro, Linezolid and Doxycycline-dyed suture materials had lower infection-rates. The results of the PET sutures were not conclusive; the PET controls had a low infection rate, comparable to PET dyed with Cipro. PET dyed with Linezolid did not prevent infections.

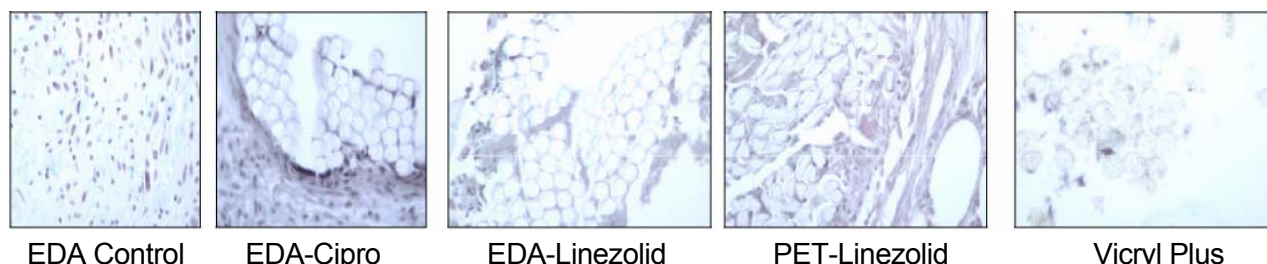


Fig 4: Histological analysis of EDA-treated sutures for healing/infection resistance

Histological Analysis: Specimens, which were placed in 10% buffered formalin for 24 hours, were dehydrated through graded alcohol solutions, and embedded in paraffin for microtome sectioning (6 μ m) perpendicular to the axis of the skin sample (Figure 5-8). Histological sections were deparaffinized and stained with hematoxylin and eosin (H&E). A series of pictures under different magnifications (ranging from 1X to 40X) were taken to show the whole tissue sample, skin, underlying adipose tissue and suture sample. Increasing magnification permitted assessment of the suture fibers in cross-section as well as the healing response generated to these four different sutures (untreated polyester, Cipro-dyed polyester, untreated nylon and Cipro-dyed nylon). **Gram Staining:** To better identify *Staphylococcus aureus* (SA) present in our histology sections, we decided to use a specific staining method for gram positive bacteria (Twort's Gram Stain; PolyScientific). This procedure would permit a clear distinction between the bacteria and any other cell type by improving color contrast and allow for a more accurate identification as well as quantitative analysis of our samples. Each slide was assigned a number so that the count of SA would be performed without any bias or knowledge of the suture type or treatment. Specimens were observed using light microscopy and a total spot count of the same area (1 mm² grid) for each different slide was determined (n = 3-4 sections/suture treatment). The following images (40 X) depict the different type of sutures and the presence or absence of SA bacteria.

Silk-Doxy and Nylon-Linezolid had the lowest SA counts as compared to the total group. This finding was comparable to the backplating results which showed no bacterial growth after explantation. Additionally, HYD sutures treated with Cipro or Linezolid also had significantly less bacterial growth as compared to HYD controls as well as when compared to the Vicryl Plus antibacterial suture. EDA with Cipro had significantly lower gram positive counts as compared to the EDA control and EDA-Linezolid sutures. However, these counts were higher than the HYD materials treated in a similar fashion. Backplating of the EDA-Cipro and EDA-Linezolid sutures did not indicate bacterial presence, indicating a disconnect between the EDA count and backplating results.

The average cost to treat nosocomial infections per incident is projected to be \$2,300. Surgical wound infections result in an annual cost to the healthcare system of greater than \$5 billion. Thus, a significant market exists for application of our technology in order to prevent wound infection. This technology can be applied to other medical devices such as vascular grafts, carotid patch material and wound dressings, etc. Our long-term goal (Phase III) will be to utilize the results from the Phase II *in animal vivo* studies in order to apply to the FDA for 510K approval, a pathway recently pursued by Ethicon for their biodegradable polyglactin 910 suture containing the biocidal agent Triclosan (VICRYL*Plus). After 510K approval, clinical trials would follow.

Development of a Biologically-Active Prosthetic Graft: We have completed our goal for this Phase I STTR grant, which was to develop *in vitro* a novel polyester vascular graft with a bioactive surface. Polyester graft material was chemically-modified in order to provide surface functional groups that would serve as "anchor" sites for protein attachment. The physical and chemical properties of the bifunctionalized polyester have been characterized. Activated protein C (APC), a natural potent anticoagulant that exists in an inactive form on the surface of endothelial cells was covalently bound to functional groups on the modified polyester surface, with binding optimized. Biologic activity of surface bound APC was determined using chromogenic and canine whole blood assays. Biostability of surface immobilized APC under simulated arterial flow conditions has been determined. Lastly, the effect of immobilized APC on graft endothelialization was evaluated by *in vitro* endothelial cell seeding and cell viability/proliferation assays.

For our Phase II submission (funding pending) we will use these data to propose that covalent immobilization of APC onto a polyester vascular graft surface will prevent surface thrombin formation via renewably inactivating FVa and FVIIIa and by anti-platelet activation; promote adherence to the graft of endothelial cell protein C receptor (EPCR) positive cells circulating in the blood through a highly specific, high affinity ligand-receptor binding reaction and signal graft-adherent cells or cells from adjacent endothelium to proliferate and migrate onto the graft surface.

Abnormal wound healing is a major complication of both type I and type II diabetes and is the most frequent cause of non-traumatic lower limb amputation. Wound healing requires the orchestrated integration of complex biological and molecular events. Inflammation, proliferation and migration of cells followed by angiogenesis and re-epithelization are essential phases of wound healing. Recently, dysregulation of neuropeptides, such as Substance P (SP) and Neuropeptide Y (NPY), secreted from peripheral nerves have been implicated in abnormal wound healing. The link between wound healing and the nervous system is clinically apparent as peripheral neuropathy is reported in 30-50% of diabetic patients and is the most common and sensitive predictor of foot ulceration. Furthermore, molecular studies have shown SP and NPY levels are reduced in diabetic patients. Receptors for SP are found on relevant wound healing cells including monocytes, mast cells, endothelial cells (ECs) and keratinocytes. SP is known to evoke an acute inflammatory response, consistent with the inflammatory phase of wound healing. It also has a proliferative effect on ECs, an important step in angiogenesis. Thus, SP affects numerous phases of wound healing and any dysfunction in the production, release or signaling of SP could impair wound healing. NPY has a similar proliferative effect on ECs, and NPY receptor null mice demonstrate impaired wound healing. Although SP and NPY production and metabolism appear to play a role in diabetic wound healing, the exact molecular and cellular mechanisms underlying these complex interactions remain elusive. Our hypothesis is that inadequate levels of neuropeptides such as SP and NPY and/or dysregulation in their signaling pathways lead to abnormal wound healing in diabetes.

In Vivo Model: Both peripheral vascular disease and peripheral neuropathy are major contributors to diabetic foot ulcers hence we have developed 3 different models that will mimic these 2 processes and thus will help understand the complex pathology underlying non-healing ulcers in diabetic patients. The surgeries for the 3 different models are performed in one of the ears of the rabbits whereas the other ear serves as a sham control. Following surgery, skin punch biopsy wounds are made in the rabbit ears and wound healing is monitored. At the end of the study period of 10 days post-surgery, molecular analysis is performed on the wounds.

The 3 different rabbit models of diabetic wound healing:

1. Ischemic Model: The central and the rostral arteries of the ear are ligated.
2. Denervation Model: The central and the rostral nerves of the ear are severed.
3. Neuroischemic Model: The central and rostral arteries of the ear are ligated and the central and rostral nerves of the ear are severed.

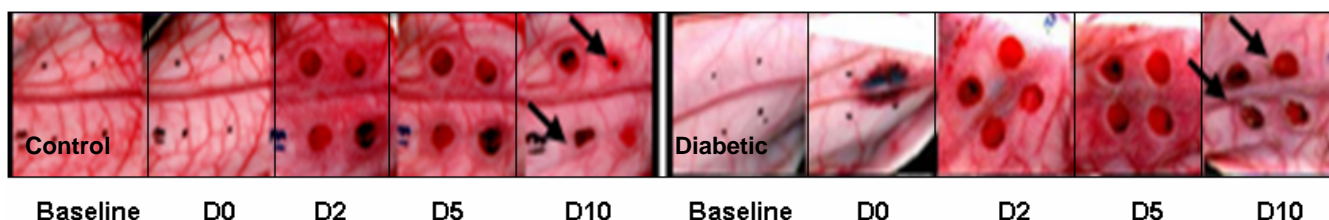


Fig 5: Representative pictures of progression of wound healing in control (non-diabetic) and diabetic rabbits over 10 day period

Our findings suggest that compared to control rabbits, diabetic rabbits have a chronic baseline increase in inflammatory cytokines, IL-6 and IL-8 and a decrease in neuropeptides SP and NPY. In the control rabbits sham ears heal faster than ischemic ears. Compared to sham ears, ischemic wounds heal significantly slowly in both diabetic and control rabbits. Sham wounds heal significantly slower in diabetic rabbits compared to controls. Upon injury, compared to control rabbits, diabetic rabbits fail to achieve an acute inflammatory response that probably hinders wound healing in both ischemic and sham ears. This work was presented at the American Diabetes Association 69th Scientific sessions in New Orleans, LA in 2009.

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We received NIH/NIDDK funding for a SBIR grant in conjunction with Lynntech Inc. This project involved use of Nitric Oxide (NO) releasing gel in the diabetic wound bed. We have also collaborated with Ikaria Inc. to test their therapeutic agent, a hydrogen sulfide donor, in a rat model of wound healing.

In Vitro Model: Since angiogenesis is an important phase of wound healing, and diabetes is known to impair angiogenesis, the goal of the *in vitro* studies is to investigate the effects of hyperglycemia on endothelial cells.

The *in vitro* studies are conducted in Human Dermal Microvascular Endothelial Cells (DMVECs). DMVECs were treated with different concentration of glucose in the absence or presence of SP, NPY and inflammatory cytokines IL-6 and IL-8. Our data so far suggest that high glucose blunts DMVEC proliferation and angiogenic tube formation where as co-exposure to NPY, SP, IL-8 and IL-6 ameliorates the inhibitory effects of high glucose. Both NPY and SP did not affect the expression of classical pro-angiogenic receptors. Protein expression of neither VEGF receptor, KDR nor PDGF receptor, PDGF-BB was modulated by NPY and SP. Studies are also being performed using siRNA to further delineate the signaling pathways in the neuropeptide-cytokine axis.

Role of Neuropeptides in Diabetic Heart Failure: Our hypothesis is that deficiency in vasoactive neuropeptides such as SP, NPY and CGRP in diabetes can contribute to heart failure. This new project is being conducted by our postdoctoral fellow, Dr. Asma Ejaz under the supervision of Dr. Pradhan in collaboration with Dr. Frank Sellke and Dr. Cesario Bianchi. Our goal is to measure the levels of SP, NPY and CGRP and their receptors from the tissues (atrial muscle and saphenous vein) obtained from non-diabetic and diabetic patients undergoing coronary artery bypass surgery (CABG) and investigate the downstream signaling effectors in each of these neuropeptides.

Immunobiology Research Center

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 diabetes mellitus. This work has set the basis for a 3 years funding from the Juvenile Diabetes Research Foundation grant aimed at evaluating the role of A20 upon diabetic retinopathy. In addition, we have requested a year of funding from the JDRF to map the residues that are glycosylated within the A20 protein with the hope of mutating them and generating a mutant that can be longer affected by high glucose and hyperglycemia.

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 has served as a basis to 2 grant proposals. Both were successful in securing funding. The first grant received funding from the Roche Organ Transplant Research Foundation for one year. The second grant received funding as an RO1 from the National Institutes of Health (started June 15 2006), and we have recently applied for a competing renewal of this grant. This later work has also been submitted in a proposal to the NIH loan repayment program (LRP) that was successfully awarded to Mark D. M. Fisher MD.

We have expanded our research interest thanks to Dr. Elzbieta Kaczmarek who joined our laboratory in July of last year. Dr. Kaczmarek, an expert in P2 receptor signaling has recently demonstrated that P2 receptor signaling upregulate expression of A20 and A1 in human endothelial cells (EC). In addition, extracellular nucleotides activate endothelial nitric oxide synthase (eNOS), even under high glucose levels. These two observations indicate that P2 receptors may be targets for management of EC dysfunction, and possibly diabetic complications. The molecular mechanisms of these purinergic regulations of A20 expression and eNOS activity are under investigation, including in the context of sleep apnea. Two grants to the AHA and the NIH based on this work were submitted and results are pending.

We have also expanded our work on the effect of A20 upon liver regeneration and demonstrated that this gene has the unique capacity to promote liver regeneration via decreasing the expression of the cell cycle brake p21^{waf1}. This data has been published in Hepatology. New stimulating data generated, implicating an effect of A20

on the Cyclin Dependent Kinase p21waf1 and PPAR α , were solid leads that constituted the basis for the competitive renewal of this grant that received a priority score of 113 (0.9%) and a secure funding for 5 more years, in addition to 1-year bridge funding that was secured by the NIH for this grant in order to avoid any gap in the work.

Clinical Research Progress

Outcomes Research

AAA Repair: With access to the Medicare database, we have analyzed outcomes after open and endovascular repair of abdominal aortic aneurysms in the Medicare population. Our work has confirmed the perioperative benefit seen in recent randomized trials and demonstrated that these results may be generalized to the entire Medicare population. Additionally, we are the first to demonstrate that laparotomy related problems such as bowel obstruction or abdominal wall hernia require frequent intervention after open surgery, matching the need for aneurysm related reintervention after endovascular repair.

This year Dr Giles published our analysis of predictors of perioperative mortality after open and endovascular aneurysm repair and derived a mortality risk prediction model for clinical use. She presented this risk stratification model at the New England Vascular Society annual meeting and published it in the Journal of Vascular Surgery (JVS).

Dr Giles and I also presented 2 papers at this years Society for Vascular Surgery meeting using this database. We analyzed 30 day mortality after re-interventions and re-admissions after open and endovascular aneurysm repair. We showed that overall reinterventions are more common after endovascular repair. However, while rupture and conversion to open repair are more common after endovascular repair, these events are rare compared to the more common minor endovascular re-interventions after endovascular repair which are associated with a relatively smaller operative mortality. These are balanced in part by an increase in laparotomy related re-admissions and re-interventions after open repair with a higher 30 day mortality. This increase in re-interventions likely contributes in part to the late convergence of survival curves after endovascular and open AAA repair. We also showed age related trends in overall AAA related mortality with those <75 showing a decrease in elective AAA repair and at the same time a decrease in rupture rate. However, in those >75 there was an increase in elective repair rate and a reduction in rupture rate that was greater than that seen in the younger age group. We hypothesize that the overall incidence of AAA may be decreasing and that an increase in elective repair in the elderly likely related to the use of endovascular repair has caused this greater reduction in elderly ruptures. With the same database, Dr Giles presented data at the annual meeting of the Society for Clinical Vascular Surgery demonstrating the differences between in-hospital mortality, 30 day mortality, and the combined 30 day and in-hospital mortality. Administrative databases often have access to only in-hospital data which may bias in favor of endovascular repair given the shorter length of stay. We found that the absolute difference in mortality remained constant with each definition. However, the relative benefit of EVAR is overestimated when using odds ratios or relative risk with in-hospital mortality. We also showed that the period of increased risk of death after EVAR and open repair persists for at least 4 months. We also evaluated the volume outcome effect at the hospital level or EVAR and open AAA repair and I presented this at the New England Vascular meeting. We found that while there is a relatively low volume threshold above which centers demonstrate adequate outcomes with EVAR, there is a continued improvement in outcome with increasing volume of open AAA repair such that the busiest centers have the best results. This may impact referral patterns and supports the concept of regionalization for open AAA repair.

Using the NIS database, we demonstrated a reduction in overall AAA related deaths after the introduction of EVAR. Dr Giles presented this at the SVS and it was published in JVS.

Using the NIS database, we demonstrated a significant survival benefit with EVAR for ruptured AAA that Dr Giles presented at SVS and published in Journal of Endovascular Therapy. Using the NSQIP database we adjusted for preoperative hemodynamic status and again found a significant benefit with EVAR for ruptured AAA. Dr Giles presented this at the International Congress on Endovascular Interventions, and published it in the Journal of Endovascular Therapy.

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Using the NIS database, Michelle Martin demonstrated the increased mortality with renal or mesenteric revascularization on mortality with open AAA repair in the United States, which she presented at the Peripheral Vascular Society and published in the Annals of Vascular Surgery.

We analyzed the impact of obesity on mortality and complications with open and endovascular AAA repair using the NSQIP database. Dr Giles presented this at the Clinical Vascular Society and will submit the manuscript to JVS.

Dr Schermerhorn published a review of AAA management in the Journal of the American Medical Association and was subsequently asked to join the editorial board of the JAMA clinical crossroads.

Lower Extremity Revascularization: Dr Simosa published our local analysis of factors that predict durable success with vein graft angioplasty for lower extremity bypass grafts, presented at the Clinical Vascular Society and published in JVS. We used the NIS database to compare outcomes of surgical revision versus angioplasty for failing lower extremity bypass grafts, Dr Hsu presented this at the Clinical Vascular Society. Dr Martin is will further analyze our local database with patient level data to compare PTA to surgical revision of bypass grafts. Dr Simosa also used our local database to evaluate outcomes in patients with failed lower extremity bypass grafts who underwent subsequent revascularization with angioplasty/stenting, presented at the New England Vascular Society and published in JVS.

We also used the NSQIP database to analyze the impact of obesity on mortality and wound infection after lower extremity bypass, which Dr Giles presented at the Peripheral Vascular Society and published in Annals of Vascular Surgery.

Carotid Revascularization: Using the NIS, we analyzed national outcomes of carotid endarterectomy versus stenting taking into account that stent patients are more likely to meet CMS defined high risk criteria. We noted increased stroke and death with stenting despite controlling for high risk characteristics including concurrent coronary artery bypass grafting and percutaneous coronary interventions. Dr Giles presented this at the New England Vascular Annual Meeting.

With the Society for Vascular Surgery outcomes group, Dr Schermerhorn found increased stroke and death rates for carotid stenting versus endarterectomy as it is being practiced currently in centers enrolled in this large national registry, presented at the SVS and published in JVS.

Mesenteric Ischemia: We demonstrated the increasing role of angioplasty and stenting for treatment of both chronic and acute mesenteric ischemia in the United States with the NIS database. We also showed the decreased mortality with angioplasty/stenting compared to surgical revascularization. This was presented at the New England Vascular Society meeting and published in JVS.

Upcoming projects: We have submitted 7 abstracts to the 2010 SVS annual meeting. These include an update of EVAR vs. open AAA repair demonstrating the continued expansion of EVAR for elective AAA to >70% of repair. Additionally, there has been a dramatic decline in the number of open AAA repairs nationally, which combined with our prior volume outcome analysis may increase the push toward regionalization and have implications on resident training and attending experience. We also evaluate the use of percutaneous EVAR both with our local dataset as well as NSQIP. Similarly, we use both the NIS as well as our own data to compare outcomes of lower extremity interventions for claudication. We show a dramatic national increase in percutaneous interventions for claudication with associated increase in national charges. We also analyze the use of thoracic EVAR for aortic transection using the NIS database. We evaluated the institution of a protocol for rapid evaluation and EVAR when possible for ruptured AAA at BIDMC with a reduction in mortality. Dr Schermerhorn will moderate a special session at this meeting entitled: Methods of Comparative Effectiveness – Outcomes Research at the SVS meeting.

Future research projects include an analysis of prior operations that may be associated with subsequent bowel obstruction or abdominal wall hernia. After this we will analyze their impact on the choice of EVAR vs. open repair as well as long term outcomes of laparotomy related complications of open AAA repair vs. EVAR.

Individual Accomplishments

Christiane Ferran

- Reviewer for the American Transplant Congress 2009 Boston.
- Reviewer for the Wiener Wissenschafts Forschungs und Technologiefonds, Vienna Austria.
- Member of the Scientific Advisory Committee for the Roche Organ Transplant Research Foundation (ROTRF).
- Reviewer for the NIH-NHLBI/NIAID Scientific Review Group ZRG1 2009/05 Immunology IMM-G(02) Special Emphasis Panel. Immunology: Member Conflicts and Special Grant Applications (February 17th-18th, 2009).
- Member of the A2ALL (Adult to adult liver transplantation) Consortium and Steering Committee, NIDDK, NIH. Co-chair of the subcommittee on Liver Regeneration (2009).
- Reviewer for Several peer review highly ranked journals including:
Blood, Journal of Clinical Investigation, Circulation
Atherosclerosis Thrombosis and Vascular Biology
Transplantation, American Journal of Transplantation
American Journal of Kidney Diseases, Nephrology Dialysis and Transplantation
Kidney International, Oncogene, American J. of Rheumatology, Diabetes
- Named Chair of the subcommittee for Junior Faculty at the CVBR. Responsible for mentoring Junior Investigators for their career development and for securing grant funding. Indeed and after becoming more tightly associated with the Center for Vascular Biology Research (CVBR) at the Beth Israel Deaconess Medical Center, I have recently agreed to head the Subcommittee for Junior Investigators at this CVBR. This Subcommittee includes as members Drs. William Aird (Director of the CVBR and Chief of the Division of Vascular and Molecular Medicine), Dr. Peter Oettgen (Cardiology) and Dr. Donald Senger (Pathology). This major endeavor involves meeting with over 12 Junior Faculty members affiliated to the Departments of Surgery, Medicine, Pathology and Emergency Medicine. These interactions happen on a regular basis and are aimed to help them prioritize their work and focus their science, guide them in approaching different funding agencies, provide help in terms of grantsmanship and in editing their proposals or seeking help from the most appropriate senior colleagues of the Center to do so. Approximately 10% of my time has been devoted to this work that I consider to be a critical part of my teaching and mentoring responsibilities. I have extended this endeavor, although not in an official manner, to other Junior Faculty members from the Department of Surgery. Dr. C. Peterson, Fellow in the laboratory received the American Transplant Congress Young Investigator
- Award for his work on A20 and prevention of transplant arteriosclerosis.

Kristina Giles

- Finalist in Karmody Competition, Society of Clinical Vascular Surgery Annual Meeting 3/2009.
- Third Place - Endovascular Research Forum, International Congress on Endovascular Interventions XXII 2/2009

Abstracts Presented at Local, National and International Meetings

Siracuse JJ, da Silva CG, Damrauer SM, Fisher MD, Studer P, Skroch M, Choi LY, Csizmadia E, Kaczmarek E, Daniel S, Ferran C. A20's Opposite Effect on CD40. Expression in Endothelial Cells and Smooth Muscle Cells Underscores its Atheroprotective Potential. Accepted for oral presentation at the 2009 SVS Research Initiatives in Vascular Disease Conference, Washington, D.C; April 2009.

Da Silva CG, Skroch M, Studer P, Damrauer SM, Siracuse JJ, Maccariello E, Kaczmarek E and Ferran C. The pro-proliferative effects of A20 map to the 7-Zinc finger domain: A means to define small peptides with therapeutic potential. Presented at the American Transplant Congress, Boston, USA; May 2009.

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Daniel S, Kaczmarek E, Choi L, Fisher MD, Siracuse JJ, Csizmadai E, Damrauer SM, Studer P, da Silva CG, Ferran C. A20 increases the expression of endothelial and inducible nitric oxide synthases in endothelial and smooth muscle cells to protect from transplant arteriosclerosis. Presented at the American Transplant Congress, Boston, USA; May 2009.

Siracuse JJ, da Silva CG, Damrauer SM, Fisher MD, Studer P, Skroch M, Choi LY, Csizmadia E, Kaczmarek E, Daniel S, Ferran C. Opposite effects of A20 upon CD40 expression in EC and SMC: Implication in A20's protective effect against transplant associated vasculopathy. Accepted for poster presentation at the American Transplant Congress, Boston, USA; May 2009.

Leena Pradhan, Szuhuei Wu, Patrick Guthrie, Michelle Martin, Sarada Kuchibhotla, Junaid Malek, Nicholas Andersen, Frank LoGerfo, Aristidis Veves. Neuropathic and Ischemic In Vivo Models of Diabetic Wound Healing. Presented at the American Diabetes Association, 69th Annual Scientific Sessions, New Orleans, LA; June, 2009.

Zhen S Huang, Junaid Y Malek, Manoj Bhasin, Mauricio A Contreras, and Frank W LoGerfo. Differential Gene Expression in Vein Graft Endothelial and Smooth Muscle Cells Using Laser Capture Microdissection. Podium presentation at the American College of Surgeons 95th Clinical Congress, Chicago, IL; October 2009.

Huang ZS, Malek JY, Bhasin M, Contreras MA, LoGerfo FW. Selective Isolation of Vein Graft Endothelial and Smooth Muscle Cells Using Laser Capture Microdissection for Microarray Gene Analysis. Presented at the North American Vascular Biology (NAVBO at Experimental Biology), New Orleans, LA; 2009.

Giles KA, Wyers M, Hamdan A, Pomposelli F, Schermerhorn ML. The Impact of Obesity on Perioperative Outcomes of Open and Endovascular Abdominal Aortic Aneurysm Repair from the National Surgical Quality Improvement Program. Manuscript in submission to J Vasc Surg. Presented at the Society for Clinical Vascular Surgery 37th Annual Symposium 2009, Ft. Lauderdale, FL; 2009.

Hsu R, Jhaveri A, Hamdan A, Pomposelli F, Wyers M, Giles K, Schermerhorn M. National Outcomes of Endovascular and Open Reinterventions of Lower Extremity Bypass Graft Repair. Manuscript in preparation. Presented at the Society for Clinical Vascular Surgery 37th Annual Symposium 2009, Ft. Lauderdale, FL; 2009.

Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Landon BE, Cotterill P, O'Malley AJ, Pomposelli FB. Discrepancies in perioperative mortality definitions after open and endovascular aortic aneurysm repair: evaluation in United States Medicare beneficiaries. Manuscript in preparation. Poster presentation at the Society for Clinical Vascular Surgery 37th Annual Symposium 2009, Presenter KA Giles. Finalist in Karmody Competition. Ft. Lauderdale, FL; 2009.

Giles KA, Hamdan A, Pomposelli F, Wyers M, Schermerhorn ML. Body Mass Index: Surgical Site Infections and Mortality After Lower Extremity Bypass from the National Surgical Quality Improvement Program 2005-2007. Ann Vasc Surg. Presented at the Peripheral Vascular Surgery Society, 19th Annual Winter Meeting 2009, Steamboat Springs, CO; 2009.

Martin M, Giles KA, Pomposelli FB, Hamdan AD, Wyers M, Schermerhorn ML. National outcomes after open repair of abdominal aortic aneurysm with visceral or renal bypass. Manuscript in submission to Ann Vasc Surg. Presented at the Peripheral Vascular Surgery Society, 19th Annual Winter Meeting 2009, Steamboat Springs, CO; 2009.

Invited Presentations

Frank LoGerfo

"Hoof and Heart Disease in Diabetes". Grand Rounds, Department of Surgery, Mt. Sinai Medical Center. New York, NY. November 11, 2009.

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"Pathophysiology of Foot Ulcers in Diabetes". Grand Rounds, Department of Surgery, BIDMC. Boston, MA. November 26, 2009.

Christiane Ferran

"The Roadmap to a successful scientific collaboration". Beth Israel Deaconess Medical Center, Harvard Medical School, Center for Faculty Development Women's Subcommittee, Workshop. Boston, MA. February 23, 2009.

"A20 in the liver: A Greek tale of Survival and Regeneration". Surgical Grand Rounds, New England Medical Center, Tufts Medical School. Boston, MA. November 19, 2009.

"A20 in the liver: A Greek tale of Survival and Regeneration". Transplant Institute Seminars, Beth Israel Deaconess Medical Center, Harvard Medical School. Boston, MA. November 10, 2009.

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).

Ferran C, Inventor; No assignee. Use of Pro-apoptotic factors in treatment of atherosclerosis. US serial no 09/765,519. January 19, 2001.

Ferran C, Co-Inventor: Measurement of protective genes in allograft rejection, Patent number: US 6,900,015 B2. May 31, 2005.

Method for Making Infection-Resistant Fabricated Textile Articles for Biomedical Applications (09,876,604).

Monahan TS, Andersen ND, and LoGerfo FW. Methods of inhibiting vascular smooth muscle cell migration and proliferation. Docket Number 1440.2045-002. February 9, 2006.

Patent Disclosures (submitted)

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).

REPORT OF TEACHING

Undergraduate Courses

Frank W. LoGerfo

Course Director: HMS SU526M.128: This is a Vascular Surgery elective for HMS and other 4th year medical students. 3 students this year for 4 weeks each were enrolled in this course.

Tutorial for HMS 3 students during their surgical clerkship. Four students, 1 hour per week.

Lectures to Primary Clinical Elective students: Four per year.

William J. von Liebig Research Training in Vascular Surgery
Program Director: Frank W. LoGerfo, MD

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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, IH, prosthetic/host interactions and thrombosis. Trainees pursue a program of intense research activity. Students carry out their research projects under the guidance of a faculty advisor, selected from renowned vascular researchers based at Harvard Medical School hospitals (Beth Israel Deaconess Medical Center and Brigham and Women's Hospital).

For summer of 2009, six students were enrolled in the program.

Mentors

Frank W. LoGerfo, MD

Students

Frank Bauer

University of Rochester School of Medicine and Dentistry
Stents

Monica Jain

Boston University School of Medicine
Nerve Fiber Density and Diabetic Wound Healing

Arthelma Cheneé Tyson

University of Rochester School of Medicine and Dentistry
Confirmation of temporal cytokine gene expression patterns in canine vein bypass grafts

Christiane Ferran, MD, PhD

Anish Geevarghese

Boston University School of Medicine
The Effects of A20 on the Global Gene Expression Profile of Smooth Muscle Cells

Bruce Furie, MD

Department of Medicine
Beth Israel Deaconess Medical Center
Professor of Medicine
Harvard Medical School

Samuel Chen

University of California-Irvine
Origin of Tissue Factor in the Laser Injury Model of Thrombosis: The Role of Subendothelial Smooth Muscle

Richard N. Mitchell, MD, PhD

Department of Pathology
Brigham and Women's Hospital
Associate Professor of Pathology
Harvard Medical School

Alejandro Torres-Hernandez

Drexel University College of Medicine
Developing An In Vitro Model: siRNA Directed Against Mig and Itac In Endothelial Cells

Jim Lederer, MD

Department of Surgery
Brigham and Women's Hospital
Associate Professor of Surgery
Harvard Medical School

Kimberly Hoang

Ohio State University College of Medicine
Phenotypic Influences of Radiation and Combined Injury on the Immune System

In addition, we had a visiting student for the summer, Atish Chopra who is a medical student at Royal College of Surgeons, Ireland. His project was titled: *Transfection of Human Vein Bypass Grafts With Small Interfering RNAs Under Operative Conditions*

Vascular Surgery Research Laboratory Students: Mentor: Frank W. LoGerfo, MD

Lindsey Korepta has completed her second year in medical school at Michigan State University, School of Medicine. Lindsey, a former William J. von Liebig summer research fellow in our lab has taken a year off from her medical school to continue work on this project under the guidance of Leena Pradhan.

Project: "MARCKS RNAi in endothelial and smooth muscle cells".

Monica Jain is a second year medical student at Boston University School of Medicine. Under the guidance of Leena Pradhan, Monica has continued to work part-time in the lab on this project.

Project: "Role of neuropeptides and inflammatory cytokines in diabetic wound healing" (*In vitro* model).

Elizabeth Alden Landis is a senior in college at Boston University. Alden works on the same project as Lindsey and assists her mainly in the Q-RT-PCR and western blot analysis studies.

Project: "MARCKS RNAi in endothelial and smooth muscle cells".

Immunobiology Research Center: Mentor: Christiane Ferran, MD, PhD

2004-2009. Lecturer at the Vascular Biology Course for undergraduate summer students Topic: The Vascular Response to Injury.

All benefited from bench top teaching as well as didactic teaching sessions, including the vascular Biology Summer Course held at the CVBR.

Anish Gheevarghese, Medical Student, BU medical School, recipient of the Von Liebig Fellowship.

Karine El Feghali, Medical Student, American University of Beirut, Lebanon.

Augusto Saboia, Medical Student, University Christus, Fortaleza, Brasil.

Livia Mara Almeida Silveira, Medical Student, University Christus, Fortaleza, Brasil.

Vascular Outcomes: Mentor: Marc Schermerhorn, MD

Premal Trivedi: Premal is a 2nd year medical student at Georgetown University who spent the summer analyzing outcomes of percutaneous access vs cutdown for EVAR as well as stent grafting versus open repair for aortic transaction using NSQIP and the NIS database. He has submitted 2 abstracts to the SVS and has gained knowledge of biostatistics and the use of large databases for clinical research.

Graduate School and Graduate Medical Courses

Frank W. LoGerfo, MD:

NIH T-32 Training Program

Harvard-Longwood Research Training Program in Vascular Surgery (T32): Director: Frank W. LoGerfo, MD

This training program is designed to provide two years of intense basic research training in vascular surgery for academic clinicians. The training program in its sixteenth year, addresses the absence of adequate research training for vascular surgeons as it applies to specific areas of clinical disease. Trainees pursue a program of research activity supplemented with course work in research design, ethics, statistics and evaluation of published research in the areas of molecular and cell biology, biomechanics, coagulation and thrombosis and angiogenesis. Clinically relevant problems such as atherogenesis, IH, prosthetic/host interactions and thrombosis will be the main focus of these research projects. Trainees carry out their research projects under the guidance of a faculty advisor selected from 20 renowned vascular researchers based at four Harvard Medical School hospitals (Beth Israel Deaconess Medical Center, Brigham and Women's, Children's Hospital (Boston) and Joslin Diabetes Institute) and the Massachusetts Institute of Technology. Upon completion of the program, trainees are capable of independent research and possess the scientific and research background needed to obtain peer-reviewed grants. Selection of trainees is based on candidate's demonstrated ability and career choice of academic practice. Applicants are resident physicians who have completed either 2/3 years of clinical 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.

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Trainee

Third Year (recruited July 2007)

Scott Damrauer, MD

Second Year (recruited July 2008)

Zhen Huang, MD

Michael Robich, MD

First Year (recruited July 2009)

Nathan Araonson

Antonia Henry

Binh Nguyen

Clayton Peterson,

Shunsuke Yoshida

General Surgery Training Program

Massachusetts General Hospital

Beth Israel Deaconess Medical Center

Beth Israel Deaconess Medical Center

University of Southern California, LA, CA

Brigham and Womens Hospital

UT, Galveston, TX

Beth Israel Deaconess Medical Center

East Carolina, NC

Four trainees graduated from the program in summer of 2009:

Kristina Giles, MD

Eric Griffiths, MD

Michelle Martin, MD

Jeffrey Siracuse, MD

Vascular Surgery Research Laboratory Fellows: Mentor: Frank W. LoGerfo, MD

Asma Ejaz, PhD was recruited from Tufts University. Her project is to investigate the role of neuropeptides in diabetic heart failure.

Zhen Huang, MD is a second year T32 Fellow who has completed his PGY2 in the General Surgery Residency, program at BIDMC. His project is to assess the contribution of gene expression of specific cell populations (namely vascular smooth muscle cells and endothelial cells) to the phenotypic transformation of endothelial and vascular smooth muscle cells and ultimately to the pathologic process of IH.

Shunsuke Yoshida, MD is a first year T32 fellow who has completed his PGY2 in the General Surgery Residency program at East Carolina Medical Center, NC. Specifically, Shun is pursuing the disease process of IH (IH) in prosthetic bypass grafts, more specifically the signaling mechanisms of TSP2.

Immunobiology Research Center: Mentor: Christiane Ferran, MD, PhD

Weekly teaching sessions for the 2 surgical residents in addition to informal bench based teaching.

Elizabeth Macariello, MD. Visiting Scholar, BIDMC.

Clayton Peterson, MD. Surgical Resident, BIDMC.

Scott Damrauer, MD. Surgical Resident, Massachusetts General Hospital

Cleide Gonçalves Da Silva, PhD. Instructor, BIDMC

Sanah Essayagh, PhD. Post-doctoral Fellow, BIDMC.

Renata Guedes, PhD. Post-doctoral Fellow, BIDMC

Peter Studer, MD. Post-doctoral Fellow, University of Bern, Switzerland

Viktoriya Marusyk, BS. BIDMC

Vascular Surgery Outcomes Research Fellows: Mentor: Dr. Marc Schermerhorn, MD

Kristina Giles, MD: Kristina entered her second year of outcomes research and was very productive speaking 6 times at national meetings - SVS twice, the Clinical Vascular Society twice, the PVSS, the ICEI (winning a resident research award), 2 regional meetings – NESVS twice (once winning the Deterling award). She has had multiple research publications and review chapters. Her focus has been use of large databases to analyze comparative outcomes of endovascular versus surgical treatment for AAA, lower extremity arterial disease and carotid revascularization.

Teviah Sachs, MD: Teviah has begun his year of outcomes research and will present at the Southern Vascular meeting in Feb 2010 and has submitted 2 abstracts to the SVS. He is continuing to analyze comparative effectiveness of endovascular versus open surgical treatment of vascular disease using large databases, including Medicare, NIS, NSQIP, state databases from HCUP. He will also obtain a Masters in Public Health from Harvard School of Public Health.

Vascular Residents:

Hector Simosa MD: Hector completed his clinical vascular surgery fellowship and published 2 papers analyzing our treatment of failing and failed lower extremity bypass grafts with percutaneous interventions.

Michelle Martin MD: Michelle worked with me on 2 clinical outcomes projects. In the first she demonstrated the increased mortality associated with visceral or renal bypass with open AAA repair in the United States. In the other she is comparing open surgical revision to angioplasty for vein graft stenosis in patients at BIDMC.

Richard Hsu MD: Richard is completing his vascular fellowship at BIDMC and has presented our analysis of national data comparing angioplasty to surgical revision for failing bypass grafts.

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