

2012-2013



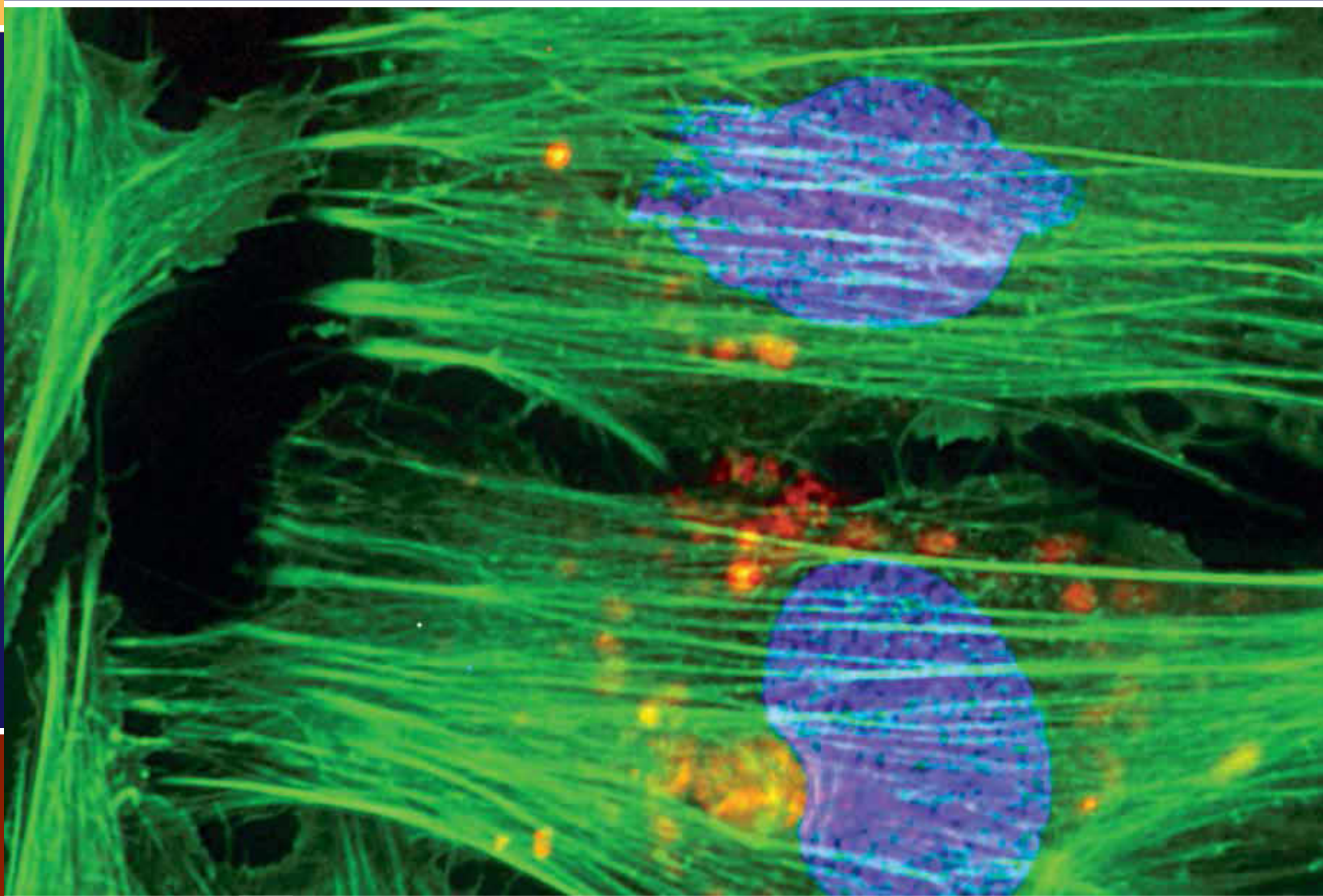
Beth Israel Deaconess
Medical Center



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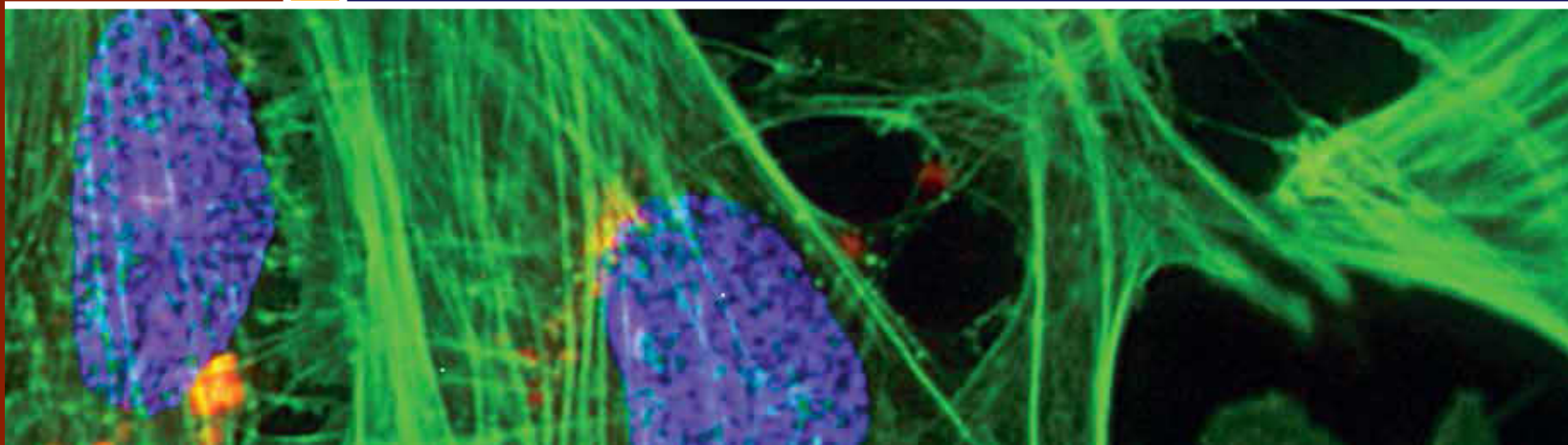
SURGERY RESEARCH REPORT

Department of Surgery | Beth Israel Deaconess Medical Center



Roberta and Stephen R. Weiner Department of Surgery

SURGERY RESEARCH REPORT



◀ Cover image: Mitochondrial uptake in heart cells. This micrograph shows rat cardiomyocyte cultures that were treated with fluorescently-labeled mitochondria isolated from the liver of another animal. These mitochondria were added to the cultured heart cells for eight hours and appear red. The cells were then stained for their cytoskeleton (green) and for their nuclei (blue).

Experiments by Department of Surgery researcher James McCully, PhD (page 50), and his collaborator Douglas Cowan, PhD, Boston Children's Hospital, have shown that injection of autologous mitochondria in the heart decreases the extent of damage and improves the function of this vital organ in a model of myocardial infarction.

The full version of this image, provided courtesy of Drs. McCully and Cowan, was one of 10 winning entries in the 2013 BioART contest sponsored by the Federation of American Societies for Experimental Biology (FASEB).

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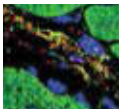
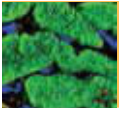


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From the Chairman



Innovation derives from being empathetic with the world around us: To place ourselves within the lives of others — our patients and their families; our colleagues and collaborators in the provision of care; and our students and trainees to whom we entrust the future. It means seeing through the eyes of those around us, being dissatisfied with the status quo, and feeling indignant when we recognize the gaps in what we can achieve. This issue of our Surgery Research Report celebrates the tradition of clinical innovation carried on by the Department of Surgery at Beth Israel Deaconess Medical Center since its inception as the Fifth (Harvard) Surgical Service 150 years ago.

Innovation and discovery occur at the interface of disciplines — where diverse viewpoints interact, problems are examined through prisms that reflect different perspectives, and ideas from highly disparate fields intermix. This is what germinates new solutions to intractable clinical problems.

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

We foster and celebrate these qualities because imaginative and inventive surgeons and investigators, students, residents, and fellows who are given the opportunity to work in diverse collaborations and teams have always been central to the creation of new pathways leading to therapeutic breakthroughs.

It is the inspiration and ingenuity of our academic community that contribute to the arena of ideas, which has always distinguished surgery at Beth Israel Deaconess Medical Center and Harvard medicine.

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

As you will read in this report, our department has a robust research enterprise with nearly \$16.4 million dollars in funding as well as some 590 publications generated by our faculty and students. The impressive work within our department continues to attract the brightest young women and men, who perform cutting-edge science that crosses boundaries.

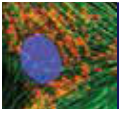
The individuals whose research is highlighted in this report represent the very best of our department and the medical center. One and all, they are dedicated to fulfilling our mission — of serving our communities, improving health through innovation and discovery, and preparing future leaders in American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

Elliot L. Chaikof, MD, PhD
Johnson and Johnson Professor of Surgery
Chairman, Department of Surgery
Surgeon-in-Chief



We need approaches to the solutions that aren't just arithmetic and additive, but are in some sense logarithmic. This will require us to reach across historic boundaries and unlock the potential of collaboration."

—Jeffrey S. Flier, MD, Dean of the Faculty of Medicine, Harvard University



Introduction

In addition to delivering outstanding patient care, research (basic, clinical, and translational) constitutes one of the cornerstones and missions of the Department of Surgery. Research programs in Surgery at Beth Israel Deaconess Medical Center (BIDMC) include cancer biology, inflammation, development, vascular biology, cardiothoracic research, transplantation-immunology, obesity-nutrition-metabolism, wound healing, epithelial and endothelial biology, bioengineering, and clinical outcomes.

The Office for Surgical Research provides an administrative infrastructure to facilitate research in the Department of Surgery. The Office for Surgical Research is headed by Per-Olof Hasselgren, MD, PhD, Vice Chairman for Research in Surgery at Beth Israel Deaconess Medical Center and the George H.A. Clowes Jr. Professor of Surgery at Harvard Medical School. Susan J. Hagen, PhD, who is Associate Vice Chair for Research in Surgery and Associate Professor of Surgery at Harvard Medical School, assists with the management of the Office for Surgical Research. In 2012, activities were supported by two administrative assistants.

The Office for Surgical Research has the following responsibilities:

- Pre-award review and approval of all grant submissions in the Department of Surgery. This includes assisting in the process of the submission of grant applications (collaborative or T32 grant applications) and interaction with the BIDMC Office of Sponsored Programs
- Management of research space, including laboratory and office space. Specifically 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 BIDMC
- Organizing research seminars and other departmental research functions
- Tracking academic benchmarks in the Department of Surgery (grant submissions, grant funding, publications, etc.) and contributing to the preparation of an annual or semi-annual Surgery Research Report
- Organizing laboratory and shared equipment maintenance and telecommunications
- Supporting and mentoring junior faculty in the establishment of research laboratories
- Interacting with and providing information to surgical residents who plan to spend time in the research laboratory
- Obtaining visas for foreign scholars in research and preparing applications for Harvard Medical School appointments for research fellows and instructors in surgery research
- Making recommendations concerning research faculty appointments and reappointments in Surgery (working with the Department of Surgery Appointment, Reappointment, and Promotion Committee)
- Assisting the Chairman of Surgery with the development of existing and new research areas within the department, including both short- and long-term strategic planning and recruitment

Research Faculty

All divisions in Surgery have at least one active research program. In 2012 and 2013, research in the department was conducted by many faculty, post-doctoral research fellows, research assistants, surgical residents, nurse educators/practitioners, and many undergraduate, graduate, and medical students. Numerous research coordinators, administrative assistants, and administrative coordinators provide important administrative support for research efforts in the department.

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.

Surgery investigators also received prestigious awards in 2012-2013 including, among many other others:

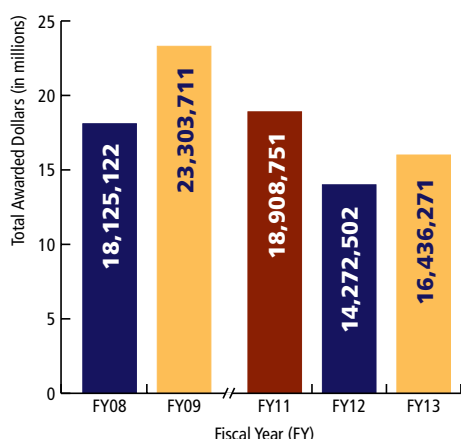
- SAGES Recognition of Excellence Award (Daniel Jones, MD)
- 2012 (Vitaliy Poylin, MD) and 2013 (Barbara Wegiel, PhD) Eleanor and Miles Shore Fellowship from Harvard Medical School

- Master of the American Board of Obesity Recognition Award (George Blackburn, MD, PhD)
- Robert Stone Award for Excellence in Teaching (Mark Callery, MD)
- National Endowment for Plastic Surgery Award from the Plastic Surgery Foundation (Samuel Lin, MD)
- First Prize Video award at the 2012 World Congress of Endourology (Andrew Wagner, MD)
- Winner in the 2013 FASEB BioART contest (James McCully, PhD)

Surgery faculty continued to travel and lecture worldwide. Their contributions included an address to the National Academies (Daniel Jones, MD); prestigious invited professorships, such as the Lister Centennial Invited Professorship in Scotland (Mark Callery, MD); and invited speaking engagements at international meetings in Hawaii (Susan Hagen, PhD), China (Jin-Rong Zhou, PhD), Brazil and France (Leo Otterbein, PhD), Austria (Wolfgang Junger, PhD), and the United Kingdom (Barbara Wegiel, PhD).

Research faculty in the Department of Surgery also participated in teaching endeavors. These included acting as mentors in the: NIH in-service teacher program, MIT Bioengineering Undergraduate Research Program, Biomedical Science Careers Program, Project Success and other minority research programs, Undergraduate Research Opportunities Program, and the Research Science Institute Summer Research Program. The Vascular and Endovascular Surgery Division remains actively involved in the William J. von Leibig Research Training Program for both medical and post-doctoral students. Several Surgery research faculty teach at Harvard Medical School in the Body, Cell Biology, Pharmacology, and GI Pathophysiology courses, and most of the surgeons in the Department participate in the surgical clerkships.

Research Funding



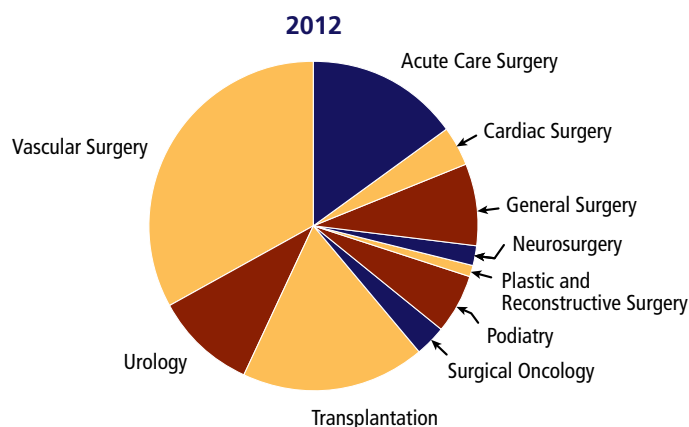
▲ Figure 1: Total (direct and indirect, federal and non-federal) awarded funds during the 5-year period 2008-2013 (no data was collected in 2010).

All research—both basic and clinical—in the Department of Surgery is supported by external funding, with more than two-thirds of this funding in the form of NIH grants.

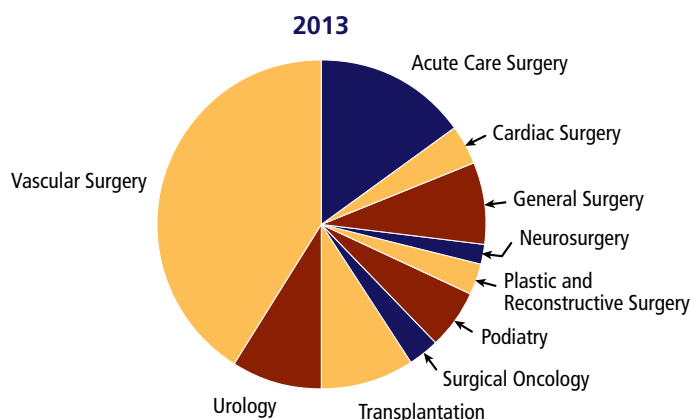
In fiscal years (FY) 2012-2013, Surgery held numerous NIH investigator-initiated grants (R01, R21, U01, R41, and RC1); T32 training grants; numerous non-federal and industry-partnered grants, one Department of Defense grant, and one F32 training grant, for a total of more than \$16 million dollars in total awarded grant funding (Figure 1).

It should be noted that in FY 2012, Surgery funding levels dropped concomitant to the considerable budget restraints imposed on the NIH, with many meritorious grant applications not meeting the pay line. Despite the challenges of obtaining NIH funding, numerous new awards were obtained in 2013, including a new T32 training grant, which resulted in a 12.4% increase in grant funding when compared to FY 2012 (Figure 1).

The distribution of external funding among the divisions in the Department of Surgery for FY12 and FY 2013 is illustrated in Figure 2 a and b. Most notable is the growth of research funding in Vascular and Endovascular Surgery, which now comprises more than 40% of total funding in the Department of Surgery. While funding for research in the divisions of Transplantation, General Surgery, and Urology declined in FY 2013, there was a marked growth in funding for research in Plastic and Reconstructive Surgery and Podiatry.



▲ Figure 2a: Total (federal and non-federal) funding in 2012 by division.



▲ Figure 2b: Total (federal and non-federal) funding in 2013 by division.

Pre-submission Review Program for Grant Applicants

Basic science, clinical, and translational researchers in the Department of Surgery are competing for extramural funds at a time when federal funding for new scientific discoveries is very limited. In 2012, the Department of Surgery implemented a pre-submission review program designed to give faculty and trainees a competitive edge when submitting grant applications. Under this program, faculty and trainees who are planning to submit a research grant may request a pre-submission review of their draft application.

The intent of this pre-submission grant application review program is to provide critical and timely feedback to the applicant so the grant application can be revised and strengthened prior to formal submission to the grant agency. This program is modeled after several successful pre-submission review programs at other top medical centers and universities throughout the country.

The program is coordinated by James Rodrigue, PhD, who identifies and solicits reviews from paid consultants who are experienced funded researchers with considerable expertise in the content area of the application. Also, consultants typically are current or former Study Section members who can provide an “insider’s” perspective on the review process.

T32 Training Grants

In 2012, the Department of Surgery continued its longstanding NIH Training Grant in Vascular Surgery Research (PI: Frank LoGerfo, MD). Investigators in Surgery also actively participated in a GI Surgery Research Training Grant, which is a joint training grant among the three Harvard Medical School teaching hospitals led by Richard Hodin, MD, (PI) at Massachusetts General Hospital, with Per-Olof Hasselgren, MD, PhD, as a member of the executive committee. In July 2013, a new departmentally-initiated T32 training grant, submitted in 2012, was awarded (PIs: Wolfgang Junger, PhD, and Carl Hauser, MD) in the area of trauma and inflammation.

Surgical Residents, Post-doctoral Fellows, and Research

Clinical Scholarship Program

Launched in 2011, the Clinical Scholarship Program pairs first-year categorical General Surgery residents with a faculty research mentor. Mentors guide the residents throughout the year as they acquire the requisite skills to develop and implement a clinical research or scholarly project. Residents are given one month of protected time, in the spring/summer, to complete their project.

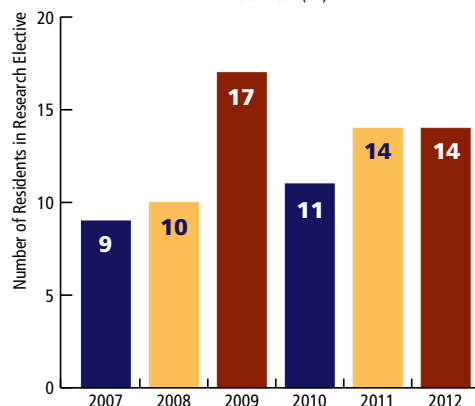
Directed by James Rodrigue, PhD, Marc Schermerhorn, MD, and Jennifer Tseng, MD, MPH, the Clinical Scholarship Program has several core objectives: to provide residents with a robust foundation for scholarship early in their training, increase their academic productivity, and enhance their opportunities to compete for outstanding fellowships and extramural research funding. The program also provides faculty with a wonderful opportunity to develop a research mentorship relationship with a resident and to work collaboratively on research with clear clinical implications. By providing this experience early in the training program, the department provides a supportive environment in which to nurture and facilitate residents’ interest in scholarship, clinical research, and an academic career.

Within the structure of the Clinical Scholarship Program, residents meet regularly with research mentor(s), participate in the Surgical Outcomes Analysis & Research (SOAR) meetings, receive informal and formal feedback from faculty on project proposals, and are provided with readings. They also attend presentations on core topics such as clinical study design, biostatistics, communicating about research, ethics and regulatory issues, and grant writing.

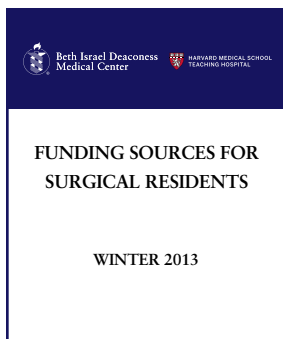
Residents are expected to prepare, submit, and present their research at the annual Harvard Medical School Surgery Research Day, as well as submit abstracts for presentations at conferences, and manuscripts for publication in peer-reviewed scientific journals.

Residents Research Rotation

Over the past few years, approximately 10 residents per year elected to spend time in a basic or clinical research laboratory as part of their surgical training. In 2012, however, 14 residents elected to do research (Figure 3). The residents performed research in basic science laboratories doing bench research or conducted clinical outcomes research. The current policy is to have residents dedicate time to research after their third or fourth clinical years.



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



▲ Figure 4: “Funding Sources for Surgical Residents” aids in finding grant funding for surgical research training.

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

An important aspect of a resident’s 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, the NIH, and the American College of Surgeons. These applications are usually written with and supported by the resident’s research mentor. If the applications are not funded, training grants in the department or other funds from the individual laboratories frequently provide support. Only rarely does a resident have to rely on departmental financial support for his or her time in the laboratory. To assist residents in obtaining funding, the Office for Surgical Research provides a 65-page booklet entitled “Funding Sources for Surgical Residents,” which describes various funding sources, deadlines, financial support available, and application forms. This booklet is updated annually. It is also available electronically at: bidmc.org/surgery.

Research Abstract Competition for Surgical Trainees

The annual Research Abstract Competition was held again in 2012 to coincide with the George H. A. Clowes Visiting Professor event in the Department of Surgery. The competition was open to all research trainees in the Department of Surgery, including post-doctoral research fellows (residents on a research rotation or post-doctoral trainees), and graduate and undergraduate students working in research labs in the Department of Surgery. The winners of this competition (in basic science and clinical research categories) received a cash prize.

The abstracts submitted in 2012 were truly outstanding. Peer-review grading by faculty of the Department of Surgery identified six basic science and four clinical abstracts as semi-finalists for the competition, which were presented to a judging panel that included the Clowes Visiting Professor, Alexander W. Clowes, MD.

The semi-finalists in 2012 were:

Basic Science

- **Wande Pratt, MD**
“Effective Intraluminal Delivery of TSP-2 siRNA to Reduce Intimal Hyperplasia in a Rat Model”
Mentor: Frank LoGerfo, MD
- **Alessandra Mele, MD***
“Transdifferentiation of Liver Cells into Insulin Producing Cells by A20 Overexpression Causes Diabetes Regression in Streptozotocin Treated Mice”
Mentor: Christiane Ferran, MD, PhD
- **Denis Gilmore, MD**
“Cytoreductive Surgery and Intraoperative Administration of Paclitaxel-loaded Expansile Nanoparticles Delay Tumor Recurrence in Ovarian Carcinoma”
Mentor: Yolanda Colson, MD, PhD (Boston Children’s Hospital)
- **Matheus Correa-Costa, BS**
“Carbon Monoxide Requires Ectonucleotidase CD39 to Protect Against Renal Ischemia Reperfusion Injury”
Mentor: Leo Otterbein, PhD
- **Antonio Lassaletta, MD**
“Ethanol Promotes Arteriogenesis and Restores Perfusion to Chronically Ischemic Myocardium”
Mentor: Frank Sellke, MD (Brown University and Rhode Island Hospital)
- **Gab S. Kim, PhD**
“Activation of Sphingosine-1-Phosphate Receptor 1 Provides Neuroprotection after Ischemic Brain Injury in a Brain Derived Neurotrophic Factor (BDNF)-Dependent Way”
Mentor: Teresa Sanchez, PhD

Clinical Research

- **Ahmed M.S. Ibrahim, MD**
“Use of the NSQIP Database for Comparison of Complication Rates in Tissue Expander/Implant Based Breast Reconstructions With and Without the Use of Acellular Dermal Matrix”
Mentor: Samuel Lin, MD
- **Yoshihiro Yonekawa, MD**
“Efficacy of Aflibercept for Refractory or Recurrent Neovascular Age-Related Macular Degeneration”
Mentor: Jorge Arroyo, MD
- **Erica M. Fallon, MD***
“Neonates with Short Bowel Syndrome: An Optimistic Future for Parenteral Nutrition Independence”
Mentor: Mark Puder, MD, PhD (Boston Children’s Hospital)
- **Charity C. Glass, MD**
“Readmission Following Pancreatectomy: What Can We Do Better?”
Mentors: Mark Callery, MD, and Tara Kent, MD

* First place prizes:

Basic Science: **Alessandra Mele, MD**
Clinical Research: **Erica M. Fallon, MD**

Surgical Outcomes Analysis & Research (SOAR)

Led by James Rodrigue, PhD, Director of the Center for Transplant Outcomes and Quality Improvement; Marc Schermerhorn, MD, Chief of Vascular and Endovascular Surgery; and Jennifer Tseng, MD, MPH, Chief of Surgical Oncology, SOAR is a rich resource for members of the Department of Surgery who are involved in or contemplating clinical research of any type for outcomes studies or comparative-effectiveness investigations.



The mission of SOAR is to help further increase the academic productivity of the department by offering access to a wide range of previously hard to find or non-existent resources and expertise in one location. The goal is to examine quality, delivery, and financing of care in order to have an immediate impact on patient care and system improvements. SOAR utilizes national health services and administrative databases, as well as prospective institutional tissue-linked databases, to investigate and address factors contributing to disease outcomes and healthcare disparities.

Affinity Research Collaboratives (ARCs)

The Department of Surgery, in collaboration with BIDMC Research and Academic Affairs, completed the first year of a new grant program—the Affinity Research Collaborative (ARC) program, which is aimed at promoting interdisciplinary bench-to-bedside research in the department. ARC's ultimate goal is to foster the development of translational programs and centers of excellence investigating innovative solutions to unmet clinical needs. This program was developed by Christiane Ferran, MD, PhD, assisted by Susan Hagen, PhD, Associate Vice Chair for Surgical Research, and more recently by Leo Otterbein, PhD.

Progress reports from funded ARC projects in year one were extremely promising. This was gauged by cohesiveness of the groups, an impressive roster of speakers, and widely attended seminars by faculty at BIDMC from all departments and even across institutions (listed in the "Seminars" section, following).

Other results included a number of collaborative publications and abstract presentations, as well as successful funding that included a new T32 training grant awarded to Wolfgang Junger, PhD, a faculty member of the "Activation of Innate Immunity by Surgery and Injury" ARC (Carl Hauser, MD, Director). Additionally, another new T32 training grant application, led by Aristidis Veves, MD, Co-director of the "Neuropeptides in Wound Healing, Health, and Disease" ARC, was favorably received. Other collaborative grant applications are either submitted or are pending review.

After a very successful first year, in which four out of 11 projects were funded, the Department of Surgery launched a second round of funding for year 2012-2013. Six projects across multiple disciplines were submitted, including three that were competitive renewals from programs funded in 2011, in addition to three new projects.

As in the past year, an ARC director had to be a full-time member of the Department of Surgery, and the project had to involve four to five investigators across disciplines, including at least two investigators from the Department of Surgery. Successful applicants were awarded funds to nucleate the group, support seminars and group meetings, foster collaborative projects, and provide funding.

Year-two successful ARC programs include three ARCs headed by senior faculty and two ARCs led by junior Department of Surgery faculty, as listed below:

Competitively Renewed ARC Programs

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

Frank LoGerfo, MD, and Aristidis Veves, MD: "Neuropeptides in Wound Healing, Health, and Disease"

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

New ARC Programs in 2012-2013

Teresa Sanchez, PhD: "Development of Novel Therapeutic and Diagnostic Approaches for Stroke"

Leo Otterbein, PhD, and Barbara Wegiel, PhD: "Cancer and Metabolism"

Surgery Seminars

Surgical Horizons

The 2012-2013 Surgical Horizons Seminar Series had outstanding seminars by young emerging leaders, as well as senior leaders, from both surgical and non-surgical disciplines, including those who work in the engineering, physical, and social sciences whose endeavors promise to dramatically alter the landscape of care for the surgical patient.

The Surgical Horizons Seminars include refreshments and a lecture from the invited speaker. External speakers are invited to dinner with a small group of faculty and residents. Drs. DaRosa and Zwolak were welcomed as visiting professors with daylong resident, faculty, and staff engagements. The speakers in this series for 2012-2013 were:

September 10, 2012	Terry B. Strom, MD Professor of Medicine and Surgery, Harvard Medical School Co-Director, Transplant Institute, BIDMC "Taming Inflammation to Create Immune Tolerance"
October 15, 2012	David J. Mooney, PhD Robert P. Pinkas Family Professor of Bioengineering, Harvard School of Engineering and Applied Sciences Core Faculty Member, Wyss Institute for Biologically Inspired Engineering, Harvard University "Cell Instructive Polymers for Regeneration and Immunotherapy"
November 12, 2012	Mark W. Grinstaff, PhD Professor of Biomedical Engineering, Boston University Professor of Chemistry, Boston University College of Engineering Distinguished Faculty Fellow "Expansile Nanoparticles for the Treatment of Lung Cancer and Mesothelioma"
November 29, 2012	Debra A. DaRosa, PhD Professor of Surgery and Vice Chair of Education, Department of Surgery Northwestern University, Feinberg School of Medicine "Ultimate Multi-Tasking: Teaching and Assessing in the OR"
January 14, 2013	Monica Bertagnolli, PhD Professor of Surgery, Harvard Medical School Chief, Division of Surgical Oncology, Brigham and Women's Hospital Group Chair, Alliance for Clinical Trials in Oncology "Surgical Contributions to the National Cancer Clinical Trials Network"
February 11, 2013	Victor R. Ambros, PhD Silverman Professor of Natural Sciences, Program of Molecular Medicine University of Massachusetts Medical School "MicroRNA: From Worms to Humans"
March 11, 2013	Robert Zwolak, MD Professor of Surgery, Dartmouth-Hitchcock Medical Center Chief of Surgery, White River Junction VA Medical Center "Medicare Physician Payment Reform: Do RVUs Still Have Value, and is the SGR Sustainable?"
April 8, 2013	Stephen F. Badylak, DVM, MD, PhD Professor of Surgery, University of Pittsburgh Deputy Director, McGowan Institute for Regenerative Medicine (MIRM) "Clinical Translation of a Biologic Scaffold Approach to Regenerative Medicine"
April 22, 2013	Sarah Thayer, MD, PhD Associate Professor of Surgery, Harvard Medical School Director, Pancreas Biology Laboratory, Massachusetts General Hospital "Pancreatic Cancer: Approaches to Future Therapies"

May 13, 2013	C. Keith Ozaki, MD Associate Professor of Surgery, Harvard Medical School Associate Surgeon, Brigham and Women's Hospital "Adipose Biology and the Surgical Horizon"
June 10, 2013	Richard A. Hodin, MD Professor of Surgery, Harvard Medical School Chief, Endocrine Surgery, Massachusetts General Hospital Surgical Director, MGH Center for Inflammatory Bowel Disease "IAP—A Key Enzyme at the Host-Microbial Interface"
September 30, 2013	K. Dane Wittrup, PhD Carbon P. Dubbs Professor of Chemical Engineering and Bioengineering, Associate Director of Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology "Invoking Synergistic Cooperation Between Innate and Adaptive Immunity with Immunotherapy"

ARC Seminar Series

MUSCLE WASTING

Director: Per-Olof Hasselgren, MD, PhD

February 21, 2012	Alfred L. Goldberg, PhD Professor of Cell Biology, Harvard Medical School "New Insights into the Mechanisms of Muscle Atrophy and Cachexia"
March 20, 2012	Bruce Spiegelman, PhD Stanley J. Korsmeyer Professor of Cell Biology and Medicine, Dana-Farber Cancer Institute and Harvard Medical School "Irisin—A Novel Myokine that Links the Benefits of Exercise with Metabolic Disease"
April 17, 2012	David Glass, MD Executive Director, Muscle Diseases Novartis Institute for Biomedical Research "Signaling Pathways that Mediate Skeletal Muscle Size and Function"
June 12, 2012	Denis Guttridge, PhD Associate Professor, Ohio State University College of Medicine "Muscling in on NF- κ B Signaling in Metabolism and Cancer"
July 17, 2012	Zoltan Arany, MD, PhD Assistant Professor of Medicine, Harvard Medical School Cardiovascular Institute, BIDMC "From PGC-1 α and Angiogenesis to New Insights on Peripartum Cardiomyopathy"
September 14, 2012	Muscle Wasting Symposium
September 18, 2012	Lars Larsson, MD, PhD Professor and Chair, Department of Clinical Neurophysiology, Uppsala University Hospital, Sweden "Effects of Aging on Muscle Function: Underlying Mechanisms at the Motor Unit, Muscle Cell, and Motor Protein Levels"
October 16, 2012	Paul Greenhaff, PhD Professor of Muscle Metabolism, University of Nottingham School of Biomedical Sciences, Nottingham, UK "Regulation of Muscle Fuel Metabolism and Mass Under Non-Inflammatory and Inflammatory Conditions"

ACTIVATION OF INNATE IMMUNITY BY SURGERY AND INJURY
Director: Carl Hauser, MD

February 24, 2012	Diane Mathis, PhD Professor of Microbiology and Immunobiology, Head of the Division of Immunology, Department of Microbiology and Immunobiology, Harvard Medical School "Control of Metabolic Indices by Adipose-Tissue-Resident Regulatory T Cells"
June 4, 2012	Daniel Remick, MD Professor and Chair, Department of Pathology and Laboratory Medicine, Boston University School of Medicine "Adenosine Improves Macrophage Function to Improve Sepsis Survival"
October 31, 2012	Polly Matzinger, PhD Chief, T-Cell Tolerance and Memory Section, Laboratory of Cellular and Molecular Immunology, National Institute of Allergy and Infectious Disease, National Institutes of Health "Are Surgeons Dangerous?"
November 30, 2012	Brahm H. Segal, MD Professor of Medicine, University at Buffalo School of Medicine Chief, Infectious Diseases, Professor of Oncology, Member, Dept. of Immunology, Roswell Park Cancer Institute "Roles of NADPH Oxidase in Infection, Inflammation, and Injury"
December 17, 2012	Joost J. Oppenheim, MD Chief, Laboratory of Molecular Immunoregulation, Frederick National Laboratory for Cancer Research, National Cancer Institute "Proinflammatory Alarmins Promote Host Defense"
January 24, 2013	Alfred Ayala, PhD Professor of Surgery (Research), Division of Surgical Research, Lifespan-RI Hospital/Alpert School of Medicine at Brown University "Pathological Processes in Shock/Sepsis-Induced Acute Lung Injury: From Cell Death to Programmed Cell Death Receptor-1"
May 9, 2013	Robert Weinberg, PhD Professor of Biology, Massachusetts Institute of Technology Member, Whitehead Institute "Stromal Activation, the Epithelial-mesenchymal Transition, and Malignant Progression"
July 9, 2013	Tanya N. Mayadas, PhD Professor of Pathology, Harvard Medical School Center for Excellence in Vascular Biology, Brigham and Women's Hospital "Neutrophil Recruitment in Immune Complex-Mediated Diseases"
September 12, 2013	Lyle L. Moldawer, PhD Professor of Surgery and Vice Chair for Research University of Florida College of Medicine "Sepsis as a Myelodysplastic Disease"

**ACTIVATION AND INHIBITION OF NEUROMUSCULAR SYSTEMS USING MEMS
(MICROELECTROMECHANICAL SYSTEMS) TECHNOLOGY: THE NEXT STEP**

Director: Samuel Lin, MD

April 24, 2012	Ron L. Alterman, MD Chief of Neurosurgery, BIDMC Professor of Surgery, Harvard Medical School "Deep Brain Stimulation: State of the Art"
May 15, 2012	Jit Muthuswamy, PhD Associate Professor of Bioengineering, Arizona State University "Neural Interfaces for Next Generation Prostheses"
June 5, 2012	Joseph Rosen, MD Professor of Surgery, Dartmouth-Hitchcock Medical Center Adjunct Professor of Engineering and Senior Lecturer, Thayer School of Engineering at Dartmouth "The New Face of War Injuries in the 21st Century-Adapting the Plastic Surgery Reconstructive Ladder"
June 19, 2012	Tessa Gordon, PhD Neuroscientist, HSC Research Institute, University of Toronto "Strategies to Promote Functional Recovery After Peripheral Nerve Injury and Surgical Repair"
July 17, 2012	Dominique M. Durand, PhD Professor in Biomedical Engineering Director, Newual Engineering Center Case Western Reserve University "Interfacing with Peripheral Nervous System"
August 7, 2012	John Rogers, PhD Lee J. Flory Founder Chair in Engineering Innovation Professor of Materials Science and Engineering, Professor of Chemistry, University of Illinois at Urbana-Champaign "Soft, Tissue-like Semiconductor Devices for Clinical Applications"
October 23, 2012	Clifford Woolf, MD, PhD Professor of Neurology and Neurobiology Director, F.M. Kirby Neurobiology Center, Boston Children's Hospital "Strategies for Promoting Neural Regeneration"
December 18, 2012	Stephen J. Schiff, MD, PhD Brush Chair Professor of Engineering Professor of Neurosurgery, Engineering Science and Mechanics, and Physics, Director of the Center for Neural Engineering, Pennsylvania State University "Towards Model-Based Control of Neural Systems"
June 14, 2013	Kevin J. Otto, PhD Associate Professor, Department of Biological Sciences Weldon School of Biomedical Engineering, Purdue University "Microstimulation of Sensory Cortices and Mitigation of Degradation in Neural-Tissue Interfacial Quality"
June 28, 2013	Marc AM Mureau, MD, PhD Assistant Professor and Head, Oncologic Reconstructive Surgery Department of Plastic and Reconstructive Surgery Erasmus MC, University Medical Center, Rotterdam, the Netherlands "Principles and Outcomes of Aesthetic Facial Reconstruction after Excision of Skin Malignancies"

- August 16, 2013 Buddy D. Ratner, PhD
Michael L. and Myrna Darland Endowed Chair in Technology
Commercialization, Professor, Departments of Bioengineering and Chemical Engineering,
University of Washington, Seattle, WA
"Healing, Regeneration, and Tissue Engineering: Ideas Intersect"
- September 24, 2013 Paul C. Cederna, MD, FACS
Robert Oneal Professor of Plastic Surgery and Professor,
Department of Biomedical Engineering, Chief, Section of Plastic Surgery
University of Michigan Health System, Ann Arbor, MI
"Development of a Biosynthetic Regenerative Peripheral Nerve Interface for High Fidelity Prosthetic Control"

METABOLISM AND CANCER

Directors: Leo E. Otterbein, PhD, and Barbara Wegiel, PhD

- February 6, 2013 Daniel B. Costa, MD, PhD
Assistant Professor of Medicine, Harvard Medical School
Division of Hematology/Oncology, BIDMC
Dana-Farber/Harvard Cancer Center Lung Cancer Co-Leader
"Managing Non-Small-Cell Lung Cancer (NSCLC) in the Clinic: Insights into Standard Practices, Clinical Trials, and Personalized Therapies"
- March 6, 2013 Chunkong Barden Chan, PhD
Instructor of Medicine, Harvard Medical School
Division of Nephrology, BIDMC
"Regulation of Cancer Growth by Metabolites in the Pentose Phosphate Pathway"
- March 25, 2013 Jozef Dulak, PhD, DSc
Professor and Head, Department of Medical Biotechnology
Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland
"From Stem Cells to Cancer: Cross-talk of miRNAs with Antioxidant Genes"
- April 3, 2013 Susan J. Hagen, PhD
Associate Professor of Surgery, Harvard Medical School
Associate Vice-Chair for Research, Department of Surgery, BIDMC
"An Overview of Gastric Cancer: Mucosal Pathogenesis that is an Infection-Mediated Process"
- April 17, 2013 Costas A. Lyssiotis, PhD
Damon Runyon Postdoctoral Fellow, Harvard Medical School
Department of Medicine, Signal Transduction, BIDMC
"Metabolic Addictions in Pancreatic Cancer"
- May 1, 2013 John G. Clohessy, PhD
Instructor in Medicine, Harvard Medical School
Director, Preclinical Murine Pharmacogenetics Facility
Department of Medicine, Division of Genetics
BIDMC, Dana Farber/Harvard Cancer Center
"Testing of Novel Therapeutics in Mouse Models of Human Cancer"
- May 3, 2013 Karl-Heinz Wagner, PhD
Professor, University of Vienna, Austria
"Lifestyle Changes as an Important Tool for Improving DNA Damage and Oxidative Stress"
- June 11, 2013 Keisuke Ito, MD, PhD
Assistant Professor of Cell Biology and Director
Scientific Resources, Ruth L. and David S. Gottesman Institute for Stem and Regenerative Medicine Research,
Albert Einstein College of Medicine
"A PLM-PPAR α Pathway for Fatty Acid Oxidation Regulates Hematopoietic Stem Cell Maintenance"

- June 26, 2013 Shaoyong Chen, PhD
Assistant Professor of Medicine
Division of Hematology and Oncology, BIDMC
"Functional Divergence and Convergence of the Multifaceted Androgen Receptor: Implications in Prostate Cancer"
- September 11, 2013 Lijun Sun, PhD
Director, Center for Drug Discovery and Translational Research
Department of Surgery, BIDMC
"Mitochondrial Energetics-ROS Inducers as Anti-Cancer Agents"
- September 18, 2013 Nika Danial, PhD
Associate Professor of Cell Biology, Department of Cell Biology, Dana-Farber Cancer Institute and Harvard Medical School
"Integration of Mitochondrial Fuel Utilization Pathways and Cellular Stress Responses"

THERAPEUTIC AND DIAGNOSTIC APPROACHES FOR STROKE

Director: Teresa Sanchez, PhD

- July 29, 2013 Louise D. McCullough, MD, PhD
Professor of Neurology and Neuroscience, Director of Stroke Research and Education, University of Connecticut School of Medicine
Attending Vascular Neurologist, Hartford Hospital Stroke Center
"Social Isolation and Stroke"

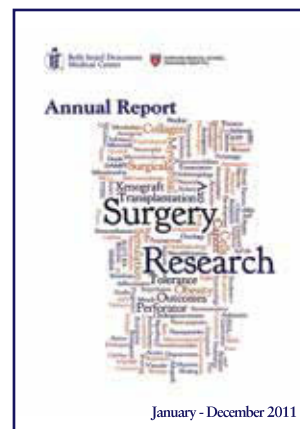
NEUROPEPTIDES IN HEALTH AND DISEASE

Directors: Aristidis Veves, MD, and Frank W. LoGerfo, MD

- April 27, 2012 Ioannis Yannas, PhD
Professor of Mechanical and Biological Engineering, Massachusetts Institute of Technology
"Organ Regeneration: The Mechanism of Scaffold Activity"
- July 12, 2012 Paula Hammond, PhD
David H. Koch Professor in Engineering, Department of Chemical Engineering
Massachusetts Institute of Technology
"Layer-by-Layer Approaches to Wound Healing and Remediation From Surfaces"
- November 2, 2012 Marjana Tomic-Canic, PhD
Professor of Dermatology, University of Miami Miller Medical School
"Applied Basic Science: Understanding Cutaneous Wound Healing and its Inhibition"
- November 9, 2012 Mark Yorek, PhD
Professor of Medicine, University of Iowa
Associate Chief of Staff Research, Iowa City Veterans Affairs Medical Center
"New Advances in the Study of Diabetic Neuropathy"
- May 10, 2013 Bruce N. Cronstein, MD
Paul R. Esserman Professor of Medicine
Director, Clinical and Translational Science Institute
Langone Medical Center, New York University
"Adenosine Receptors and Outrageous Fortune: Those Slings and Arrows Leave their Marks"
- May 31, 2013 Leslie I. Gold, PhD
Associate Professor of Medicine and Pathology
Division of Translational Medicine, NYU School of Medicine
"Calreticulin: A New Therapeutic Approach to Improve Impaired Diabetic Wound Healing"
- June 10, 2013 Omaida C. Velázquez, MD
Vice-Chair of Research and Professor of Surgery, University of Miami, Miller School of Medicine
"Cells and Signals Involved in Blood Vessel Homeostasis, Tissue Repair, and Vascular Disease"

Annual Research Reports

The Surgical Research Office continues to highlight progress in research by producing an annual research report for the Department of Surgery. The previous report was published in 2011. The 2011 Annual Report for Surgery Research, this report, and reports from 2000-2011 can be found at: [bidmc.org/surgery \(research\)](http://bidmc.org/surgery (research)).



Appointments, Reappointments, and Promotions Committee

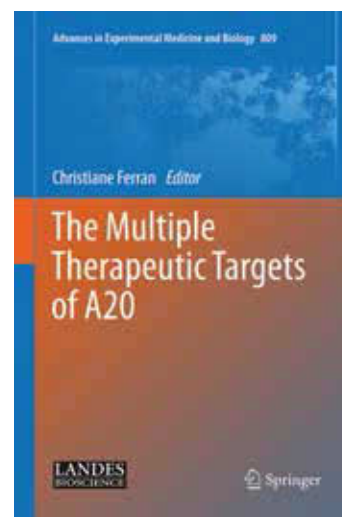
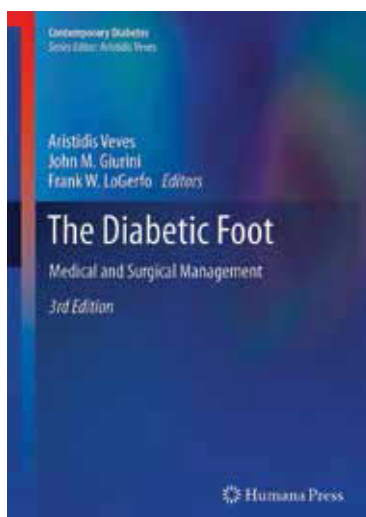
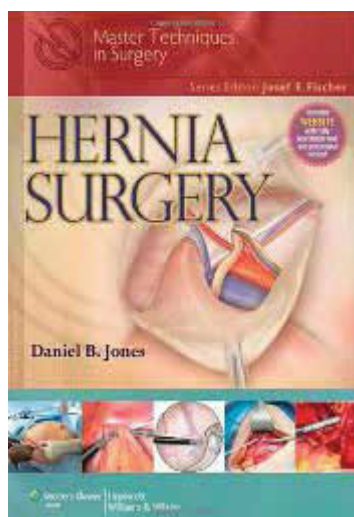
Surgical Research is involved in the Appointments, Reappointments, and Promotion Committee, which was formed in 2003 to assist the Chairman. The purpose of this committee, which meets monthly, is to review the credentials of faculty members who are being considered for reappointment or promotion at Harvard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

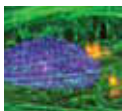
Research Facilities and Space

In 2012, research in the Department of Surgery occupied approximately 26,037 square feet of space, including wet labs, special purpose rooms (cold rooms, tissue culture rooms, and shared equipment rooms), and office space. Although the greatest number of research faculty and staff in Surgery are located on the eighth floor of the Dana/Research West building on the East Campus, Surgery also has research space in several other locations. These spaces include the Center for Life Sciences (CLS), Slosberg-Landy, Research North, and Stoneman. Clinical research space is located in the Palmer, Feldberg, Lowry, Deaconess, Farr, and Shapiro buildings. The overall dollar density in 2012 for research space in the Department of Surgery was approximately \$220 per square foot.

Tracking Academic Performance

In addition to a strong performance in obtaining external research grant funding (Figure 1, page 6), publications are an additional benchmark of the academic performance in Surgery. There were a considerable number of published original articles and in press articles in 2012 and 2013, many of which were in high-impact journals such as *PNAS*, *Nature*, *PLoS One*, *Journal of Immunology*, *Gastroenterology*, *JAMA*, *Biochemical Journal*, etc. In addition, there were eight books/textbooks and series editorships in 2012-2013, and one in-press book (below right, which was published in January 2014). These books (left to right, below) were edited by Daniel B. Jones, MD; Aristidis Veves, MD, John M. Giurini, DPM, and Frank W. LoGerfo, MD; and Christiane Ferran, MD, PhD. On the following pages is the integrated bibliography for 2012-2013; BIDMC faculty and trainees in Surgery are highlighted in bold.





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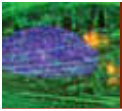
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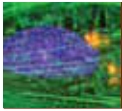
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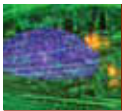
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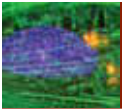
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VASCULAR AND ENDOVASCULAR SURGERY

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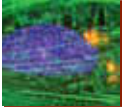
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Carl J. Hauser, MD

Lecturer on Surgery
Trauma Medical Director
Interim Chief, Acute Care Surgery, Trauma, and Surgical Critical Care

Research Group

Christopher Barrett, MD
Arthur Celestin, MD
Elzbieta Kaczmarek, PhD
Haipeng Li, MD
Nicola Sandler, MD

Research Focus

The major research focus of my research is clinical inflammation biology. My lab is especially interested in the role of cellular Damage molecules, or “damage-associated molecular patterns” (DAMPs, aka “alarmins”) in inflammation. Our laboratory is a world leader in investigating the role of intracellular DAMPs derived from mitochondria. Our original work on this subject was published in *Nature* (March 4, 2010) and was widely cited as a groundbreaking conceptual advance in sepsis and inflammation research.

The known mitochondrial DAMPs include mitochondrial DNA, formyl peptides, some of the mitochondrial lipids, and other peptides that we are currently delineating. Mitochondrial DNA is a potent activator of toll-like receptors (TLRs), especially TLR-9. Signaling downstream from this receptor may be critical in the suppression of immune function after injury. Formyl peptides (FPs) are potent chemo attractants. They are also critically important activators of immune responses to damaged tissue, including wound debridement and the initiation of healing. On the other hand, however, these molecules may compete for the immune system’s “attention” in systemically injured patients. Thus also the innate response to FPs released by injury may render the host susceptible to infection.

Our current work centers on molecular aspects of this dichotomy between the necessity of inflammation after injury and the susceptibility to infection it incurs. Molecular aspects of these problems that we study (and which participants can become expert in) include neutrophil signaling, chemokine biology (especially intracellular calcium flux signaling), the regulation of endothelial permeability in SIRS, and most recently the study of neutrophil extracellular traps (“NETs”). Current investigations and collaborations with external organizations include studies investigating formyl peptide DAMPs in the plasma of trauma and septic patients as well as patients with cancer. We are also studying small peptides that inhibit the formyl peptide receptor family. Current collaborations within the institution include work with my longtime colleague Kiyoshi Itagaki, PhD, and the labs of Leo Otterbein, PhD, and Wolfgang Junger, PhD.

Based upon this work, we received a Department of Defense grant three years ago and were subsequently awarded an NIGMS R01 grant based upon it. We have begun to work with bioengineers to create “PCR-on-a-chip” assays to discriminate sepsis from SIRS based on this model, and were awarded a CIMIT grant to further that translational collaboration. We believe the central mechanisms we have discovered are a solid basis for large-scale collaborative research and have been begun work on a P50 Research Center Grant proposal. We have just submitted our first multi-PI grant with Leo Otterbein, PhD, and plan to extend this into a P50 Center Grant in collaboration with three other inflammation laboratories (James Lederer, PhD, Wolfgang Junger, PhD, and Michael Yaffe, MD, PhD) — all powerhouses on the Longwood campus.

Accomplishments 2012-2013

- Appointed Acting Chief of the Division of Acute Care Surgery, Trauma, and Surgical Critical Care, BIDMC
- Appointed Medical Director of Trauma Services, BIDMC
- Served as Secretary of the Western Trauma Association
- Elected to membership in the American Surgical Association
- Made ad hoc reviewer for *Science*
- Mentored Haipeng Li, MD, Orthopedic Department, Beijing Army General Hospital
- Moderator, plenary session on endogenous triggers of the injury response at the meeting of the Shock Society
- Keynote speaker, 10th Annual Advances in Inflammation Research Symposium, Rhode Island Hospital/Brown University
- Gave an invited plenary lecture on the generation of immunologic “Danger” signals by tissue injury in trauma, shock, and sepsis at the American Heart Association Resuscitation Science (ReSS) Symposium, Los Angeles, CA
- Invited lecturer, Symposium Institut Merieux, Annecy, France
- Invited lecturer, FASEB Meeting (ASIP) Symposium on Biology of Inflammation and Pattern Recognition Receptors
- Distinguished Visiting Professor, 7th Congress of the Chinese Association of Critical Care Medicine, Xiamen, China
- Lectured on the Inflammatory Response to Injury at the Cottage Hospital Trauma Symposium, Santa Barbara, CA
- Visiting Professor, the Karolinska Institute, Stockholm, Sweden
- Plenary Lecturer, Special Session on Surgical Sepsis at the International Surgery Week

Teaching, Training and Education

I am involved in teaching trainees at all levels, including Harvard Medical School students, General Surgery residents, and fellows in our accredited Surgical Critical Care Fellowship Program. In addition, I participate in the Department of Surgery's Clinical Research Program, serving as a mentor to residents conducting clinical research projects. I also helped develop the curriculum for our Surgical Critical Care Fellowship Program.

Selected Research Support

Mitochondrial DAMPs and inflammation after injury; NIH, 2010-2014; PI: Carl J. Hauser, MD

Prospective study of the tissue-resident regulatory T-cell (Treg) function in clinical surgery; Tempero Pharmaceuticals, Inc., 2011-2014; PI: Carl J. Hauser, MD

Activation of innate immunity by surgery and injury; Department of Surgery Affinity Research Collaborative (ARC), 2013-2014; PI: Carl J. Hauser, MD

The study of immunogenic non-formylated mitochondrial peptides in acute surgical illness; Foundation grant by BioMerieux SA, 2013-2014; PI: Carl J. Hauser, MD

Novel small-molecule inhibitors of formyl-peptide receptors; Polyphor Pharmaceuticals, 2013-2014; PI: Carl J. Hauser, MD

Harvard Trauma Inflammation T-32 Training Program; NIH, 2013-2018; Co-Director: Carl J. Hauser, MD (Director: Wolfgang Junger, PhD)

Selected Publications

Davidson BA, Vethanayagam RR, Grimm MJ, Mullan BA, Raghavendran K, Blackwell TS, Freeman ML, Ayyasamy V, Singh KK, Sporn MB, Itagaki K, Hauser CJ, Knight PR, Segal BH. NADPH oxidase and Nrf2 regulate gastric aspiration-induced inflammation and acute lung injury. *J Immunol* 2013;190(4):1714-24.

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Sursal T, Stearns-Kurosawa DJ, Itagaki K, Oh SY, Sun S, Kurosawa S, Hauser CJ. Plasma bacterial and mitochondrial DNA distinguish bacterial sepsis from sterile systemic inflammatory response syndrome and quantify inflammatory tissue injury in nonhuman primates. *Shock* 2013;39(1):55-62.

Liu YJ, Siracuse JJ, Gage T, Hauser CJ. Phlegmonous gastritis presenting as portal venous pneumatosis. *Surg Infect (Larchmt)* 2013;14(2):221-4.

A complete list of publications begins on page 17



Wolfgang G. Junger, PhD

Professor of Surgery

Research Group

Yi Bao, PhD
Eritza Chong
Carola Ledderose, PhD
Linglin Li, MD
Marcus Lidicky
Severin Muehleder
Thomas Seier
Jingping Zhang, MD
Johannes Zipperle

Research Focus

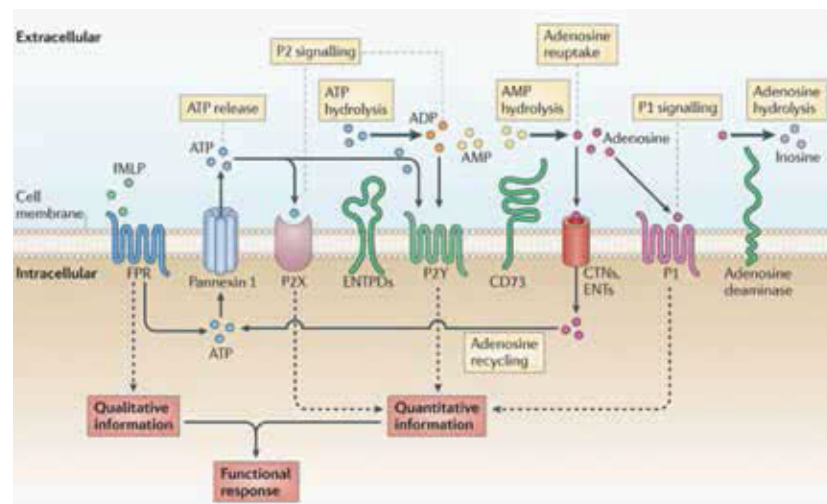
The focus of my laboratory is inflammation and immune regulation in critical care patients. In trauma patients, excessive neutrophil activation damages host organs such as the lungs. On the other hand, impaired T lymphocyte function renders patients prone to infections. The results are multi-organ failure and sepsis, which are leading causes of death in trauma patients. We study the mechanisms by which immune cells are regulated and how trauma impairs these mechanisms. Based on this work, we have developed novel therapeutic strategies to improve clinical outcomes in trauma patients.

One of these strategies, hypertonic resuscitation, has recently been tested in a major multi-center clinical trial in several centers across North America. This study has shown that hypertonic resuscitation of trauma patients can indeed modulate inflammation. However, unfortunately we did not achieve the survival benefits found in our preclinical laboratory studies. During the planning and execution phase of this clinical trial, ongoing work in my laboratory has shown that hypertonic resuscitation alters immune cells by inducing ATP release and activating various types of ATP and adenosine receptors that alter cell function. We believe that these complex autocrine and paracrine feedback mechanisms are altered in some trauma patients, reducing the efficacy of hypertonic resuscitation (Figure 1).

In recent years, we found that ATP release and autocrine feedback via ATP and adenosine receptors are central signaling mechanisms and complex regulators of neutrophil and T lymphocyte functions (Figure 2). We found that these novel inside-out signaling mechanisms via ATP release fine-tune immune cell responses by balancing the better-known outside-in signaling via calcium influx.

In neutrophils, ATP release and autocrine stimulation of ATP receptors initiates cell activation. In T lymphocytes, ATP release amplifies T cell receptor signal transduction events that trigger cascades of events resulting in immune defense. Exogenous ATP that spills from damaged tissues and disrupted cells in trauma patients impairs these subtle endogenous signaling mechanisms. The result is excessive neutrophil activation and impaired inflammatory responses that damage host organs and increase the susceptibility to infections and sepsis. Using this new knowledge, we are developing novel therapeutic strategies to prevent these complications by modulating purinergic signaling.

Figure 2: Purinergic signaling systems regulate immune cell responses. Cell activation signals such as fMLP release ATP via pannexin-1. ATP can stimulate P2X- or P2Y-type receptors or ectonucleotidases (ENTPDs, e.g., CD39 and CD73) can convert ATP to adenosine, which in turn can be taken up by nucleoside transporters (CNT, ENT), hydrolyzed by adenosine deaminase (ADA), or activate suppressive A2a- or stimulatory A3-type P1 receptors. Our current findings suggest that exogenous ATP released from damaged tissues distorts these autocrine signaling systems in trauma patients, overloading the subtle endogenous ATP signaling mechanisms with exogenous ATP that impair normal immune cell functions (from Junger 2011).



Accomplishments 2012-2013

- Reviewer for journals including *Nature*, *Science*, *Nature Reviews*, *Nature Biotechnology*, *Nature Communications*, and *Science Signaling*
- Reviewer of grant proposals submitted to NIH, Swiss, French, Israeli, and Belgium National Research Foundations
- Faculty mentor for underrepresented minority medical students; Harvard Medical School, Boston
- Invited plenary session at Annual Meetings of the European Shock Society in Vienna, Austria
- Chairing session at Annual Shock Society, Vienna, Austria
- Invited seminars at the Hartmannspital, Vienna, Austria
- Interview and short report about our current research by ORF, the Austrian Public Radio and television station
- Nomination to President of Shock Society
- Elected editorial board member, *Acute Medicine & Surgery*

Teaching, Training, and Education

- Advisor and career counseling of Yi Bao, PhD, and Carola Ledderose, PhD, resulting in successful research fellowship from the German Research Fund for Dr. Ledderose
- Thesis advisor of Thomas Seier and Marcus Lidicky, who performed a research project in my laboratory for their MD degrees from the Paracelsus Medical University, Salzburg, Austria
- Thesis advisor of Severin Muehleider, who performed his master's thesis project and received his MA degree from the Fachhochschule Technikum, Vienna, Austria
- Thesis committee member (reader) for Le Qui, PhD, Harvard Medical School
- Faculty mentor of Jamaji Chilaka Nwanaji-Enwerem, who enrolled in the MD/PhD program of Harvard Medical School
- Faculty advisor for Eritza Chong and others
- Faculty advisor for Xiaouo Diana Li, who successfully secured a research fellowship from the Chinese government to perform research in my laboratory
- Faculty advisor for Dr. Tiecheng Yu, who received a full fellowship from the Chinese government to perform research in my laboratory
- Advisor to other faculty and fellows including Drs. Yan Wu, Moritz Schmelzle, Martina Novak, and Nick Haining

Selected Research Support

Purinergic receptors in inflammation; NIH, 2009-2014; PI: Wolfgang Junger, PhD

Neutrophil activation and trauma; NIH, 1999-2017; PI: Wolfgang Junger, PhD

Administrative supplement for neutrophil activation and trauma grant; NIH, 2013-2016; PI: Wolfgang Junger, PhD

Regulation of T cell signaling in trauma; NIH, 2013-2018; PI: Wolfgang Junger, PhD

Harvard Trauma Inflammation Training Program; NIH, 2013-2018; PI: Wolfgang Junger, PhD

Mitochondrial DAMPs and inflammation after injury; NIH, 2010-2015; Co-Investigator: Wolfgang Junger, PhD (PI: Carl Hauser, MD)

Modulation of erythrocyte function by complement; NIH, 2011-2016; Co-Investigator: Wolfgang Junger, PhD (PI: Ionita Ghiran, MD)

Figure 1: Hypertonic resuscitation regulates immune cell function. Hypertonic saline (HS) induces ATP release via pannexin 1 (panx1). CD39 generates adenosine that can promote neutrophil activation via A3 adenosine or block cells via A2a adenosine receptors. In trauma patients, we found that A3 receptor expression is increased and that this diminishes the effectiveness of HS to block neutrophil activation and inflammation.

Selected Publications

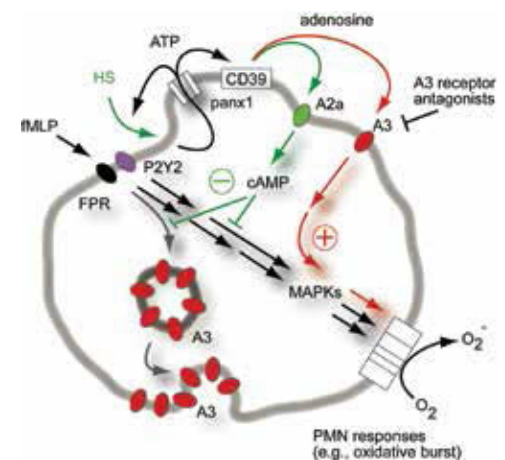
Bao Y, Chen Y, Ledderose C, Li L, Junger WG. Pannexin 1 channels link chemoattractant receptor signaling to local excitation and global inhibition responses at the front and back of polarized neutrophils. *J Biol Chem* 2013;288(31):22650-7.

Bian S, Sun X, Bai A, Zhang C, Li L, Enjyoji K, Junger WG, Robson SC, Wu Y. P2X7 integrates PI3K/AKT and AMPK-PRAS40-mTOR signaling pathways to mediate tumor cell death. *PLoS One* 2013;8(4).

Sun D, Junger WG, Yuan C, Zhang W, Bao Y, Qin D, Wang C, Tan L, Qi B, Zhu D, Zhang X, Yu T. Shockwaves induce osteogenic differentiation of human mesenchymal stem cells through ATP release and activation of P2X7 receptors. *Stem Cells* 2013; 31(6):1170-80.

Junger WG, Rhind SG, Rizoli SB, Cuschieri J, Shiu MY, Baker AJ, Li L, Shek PN, Hoyt DB, Bulger EM. Resuscitation of traumatic hemorrhagic shock patients with hypertonic saline-without dextran-inhibits neutrophil and endothelial cell activation. *Shock* 2012;38(4):341-50.

Manohar M, Hirsh MI, Chen Y, Woehrle T, Karande AA, Junger WG. ATP release and autocrine signaling through P2X4 receptors regulate T cell activation. *J Leukoc Biol* 2012;92(4):787-94.



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Teresa Sanchez, PhD

Assistant Professor of Surgery

Research Group

Gab Seok Kim, PhD
Guoqi Zhang, MD, PhD

Research Focus

My laboratory investigates the role of sphingosine-1-phosphate (S1P) in the regulation of the responses of the vascular endothelium to injury. During injury, the endothelium becomes activated with an increase in permeability and acquisition of a proinflammatory phenotype. Sustained endothelial activation plays a critical role in the pathophysiology of cardiovascular disease. The bioactive lipid, S1P, is a potent modulator of endothelial integrity through its G protein coupled receptors, S1PR. S1PR are attractive targets for drug development; in fact, the recently FDA-approved new treatment for multiple sclerosis, Fingolimod (FTY720), targets S1PR1. We and others have shown that S1PR1 promotes endothelial integrity in a Gi- phosphatidylinositol-3-kinase (PI3K)-Rac dependent way. In sharp contrast, S1PR2 promotes endothelial cell contraction, stress fiber formation, disassembly of adherens junctions and increased permeability in a Rho-ROCK dependent way (Figure 1). In order to study the role of S1PR in endothelial activation we are currently using two different models of vascular injury: sepsis models (inflammatory injury) and stroke models (ischemia-reperfusion injury). Our studies indicate that S1PR2 is a critical modulator of vascular permeability and a potential novel therapeutic target in vascular disorders.

Critical role of stromal S1PR2 in the induction of vascular permeability and sustained vascular and systemic inflammation during endotoxemia

Our recent studies indicate that S1pr2-null mice or wild-type mice treated with the S1PR2 antagonist, JTE013, exhibit a dramatic decrease in vascular permeability and vascular inflammation during endotoxemia, as well as faster resolution of systemic inflammation, compared to wild type, vehicle-treated mice. In addition, experiments with bone marrow chimeras (*S1pr2^{+/+}* to *S1pr2^{+/+}*, *S1pr2^{+/+}* to *S1pr2^{-/-}* and *S1pr2^{-/-}* to *S1pr2^{+/+}*) indicate that S1PR2 in stromal cells, and not in hematopoietic cells, is essential for the induction of vascular permeability and sustained vascular and systemic inflammation. Also, our *in vitro* data indicates the critical role of S1PR2 in the induction of the pro-adhesion and proinflammatory phenotype of endothelial cells via Nuclear Factor κ B (NF κ B) and Stress activated protein kinase activation (Figure 1).

Critical role of S1PR2 in the disruption of cerebrovascular integrity after ischemia-reperfusion (I/R) injury

Using a model of transient focal cerebral ischemia, we have found that genetic deletion of S1PR2 or administration of a S1PR2 antagonist, after reperfusion, potently inhibits cerebrovascular permeability, development of intracerebral hemorrhage, and markedly reduces neuronal injury. Immunohistochemical analysis of human brain samples revealed S1PR2 positivity in the cerebrovascular endothelium from five autopsy specimens. In addition, our *in vitro* studies indicate that S1PR2 plays a critical role in blood-brain barrier disruption after *in vitro* I/R injury via activation of matrix metalloproteases. Altogether our data indicate that S1PR2 receptor could be pharmacologically targeted to promote cerebrovascular integrity at the time of reperfusion in stroke patients.

Accomplishments

- Invitation to be a peer reviewer (Ad-hoc) for *Arteriosclerosis, Thrombosis, and Vascular Biology*
- Invitation to serve on NIH study section, Special Emphasis Panel/Scientific Review Group, HLBP
- Session chair, abstract reviewer, and poster grader in the 8th and the 9th Center for Vascular Biology Research Annual Summer Retreat in North Falmouth, MA (June 2012 and 2013)

Invited Presentations

- Assessment of novel therapeutic targets in stroke, Center for Vascular Biology Research Summer Student Seminar Series, Aug. 2012
- Critical role of sphingosine-1-phosphate receptor-2 in blood brain barrier disruption, intracerebral hemorrhage and neurovascular injury in experimental stroke, Society for Academic Emergency Medicine National Meeting, 2013
- Activation of sphingosine-1-phosphate receptor 1 provides neuroprotection after ischemic brain injury in a brain derived neurotrophic factor (BDNF)-dependent way, Society for Academic Emergency Medicine National Meeting, 2013
- Novel therapeutic approaches for cerebrovascular permeability, Center for Vascular Biology Research Summer Student Seminar Series, 2013

Administrative

- I have continued to be a member of the committee in charge of organizing the Center for Vascular Biology Research Annual Summer Retreats, which were held in North Falmouth, MA, in June 2012 and 2013.
- In addition, I have continued to be part of the Seminar Committee in the Center for Vascular Biology Research. This committee is in charge of organizing all the seminars series that take place in the center: Translational Seminar Series, Visiting Professor Series, Research Seminar Series, and Journal and Data Club.

Teaching, Training, and Education

I have continued to train research fellows and research assistants in the lab. Kieran Ryan, research assistant in my lab, obtained a position in industry after two years of training in the lab. Li Yang, post-doctoral fellow in my lab, obtained a junior faculty position at Texas Tech University.

In addition, I have continued to be the coordinator of the Center for Vascular Biology Research Journal Club and Data Club. 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.

Selected Research Support

Sphingolipid signaling in endothelial responses to injury; NIH, 2009-2014; PI: Teresa Sanchez, PhD

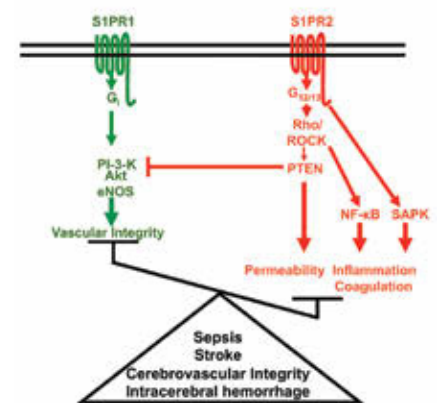
Targeting sphingosine-1-phosphate receptors as vasoprotective therapy for stroke; American Heart Association, 2012-2015; PI: Teresa Sanchez, PhD

Development of novel diagnostic and therapeutic approaches for stroke; Department of Surgery Affinitive Research Collaborative (ARC), 2012-2013; PI: Teresa Sanchez, PhD

Selected Publications

Kluk MJ, Ryan KP, Wang B, Zhang G, Rodig SJ, Sanchez T. Sphingosine-1-phosphate receptor 1 in classical Hodgkin lymphoma: Assessment of expression and role in cell migration. *Lab Invest* 2013;93:462-471.

Zhang G, Yang L, Kim GS, Ryan K, Lu S, O'Donnell RK, Spokes K, Shapiro N, Aird WC, Kluk MJ, Sanchez T. Critical role of sphingosine-1-phosphate receptor 2 (S1PR2) in acute vascular inflammation. *Blood* 2013;122:443-455.



▲ Figure 1: Signaling pathways activated by S1PR in the endothelium. Activation of the Gi- phosphatidylinositol-3-kinase-(PI3K)-Akt pathway by S1PR1 is critical for vascular maturation and the maintenance of vascular integrity. On the contrary, S1PR2 promotes vascular permeability through the G12/13-Rho-ROCK pathway and the activation of the phosphatase PTEN, which antagonizes the actions of PI3K. In addition, our most recent data indicate that S1PR2 induces the expression of proinflammatory and procoagulant molecules in the endothelium through the activation of the NFκB and SAPK pathways. Our studies in mice indicate that S1PR1 and S1PR2 signaling can be pharmacologically modulated to promote vascular integrity in several models of vascular injury. S1PR could become novel targets to promote vascular integrity during acute vascular injury.

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Michael B. Yaffe, MD, PhD

David H. Koch Professor of Biology and Biological Engineering,
Massachusetts Institute of Technology
Joint appointment in Surgical Oncology, BIDMC

Research Group

Ian Cannell, PhD
Yogesh Dayma, PhD
Anh Dinh MS
Scott Floyd MD, PhD
Anna Gattinger, BS
Bob Grant, PhD
Mun-Kyung Hwang, PhD
Brian Joughin, PhD
Jacon Kim, BS
Yi-Wen Kong, PhD
Dan Lim, PhD
Karl Merrick, PhD
Sandra Morandell, PhD
Jesse Patterson, PhD
Laura Peterson, PhD
Johnny Rameseder, MS
Susanne Swartout, PhD

Research Focus

The goal of our research is to understand how cells respond to stress and injury, including genotoxic, traumatic, and septic insults. We are primarily interested in understanding the molecular basis by which cell stress and injury activate specific signaling pathways in the cell, and how these pathways are integrated at the molecular and systems level to control cellular responses. We have a longstanding interest in inventing new technologies including novel proteomic methods, high-throughput signaling assays and peptide library screens, RNAi screens using high-content imaging, and novel computational/bioinformatics methods, together with more traditional techniques from cell biology, physical biochemistry, structural biology, and mouse genetics.

Signaling pathways and networks that control the DNA damage response and cancer

When cells encounter stress or injury such as DNA damage, they activate complex signaling networks that regulate their ability to recover, repair the damage, and return to a homeostatic equilibrium. These networks must integrate a wide variety of signals from inside and outside the cell, transduced through protein kinase and lipid signaling pathways, to ultimately control cell cycle arrest or progression, coordinately regulate specific patterns of gene expression, and/or initiate programmed cell death. Mutations in, or dysfunction of, protein kinase signaling pathways that normally respond to DNA damage, for example, play critical roles in tumor development and progression, while intentional targeting of these pathways can enhance the ability of commonly used DNA-damaging chemotherapy and radiation to cure cancer. We have been attacking this research area along two fronts: 1) characterizing the molecular details of the DNA damage response with a focus on protein kinases, RNA-binding proteins, and epigenetic modulation of chromatin at the site of damage, and 2) examining whether cross-talk between signaling pathways can be pharmacologically manipulated to enhance the response of tumors to DNA damaging agents. We recently discovered that Brd4 modulation of chromatin structure is a primary controller of DNA damage signaling, and are characterizing the signaling response and metabolic alterations that occur following damage. We showed that p53-defective tumor cells become dependent on signaling through the p38-MK2 pathway to resist killing by chemotherapy, and have now created a variety of standard and novel conditional knock-out mice to target this pathway *in vivo* in several cancer models. Finally, we discovered the phenomenon of 'dynamic network re-wiring,' in which tumor cell treatment with a specific schedule of signaling pathway inhibitors and DNA-damaging chemotherapy can be used to dramatically enhance cell killing in a subset of triple-negative breast cancer and non-small cell lung cancer. We are now extending that work into colon, head and neck, and prostate cancer models.

Signaling pathways and networks that control cytokine responses and inflammation

Misregulation of cytokine feedback loops and inappropriate activation of the blood clotting cascade causes dysregulation of cell signaling pathways in neutrophils, macrophages, and lymphocytes, causing tissue damage in auto-inflammatory diseases, and multiple organ failure in states of overwhelming infection and sepsis. Our research is focused on understanding the role of the p38-MK2 pathway in cytokine control, the contribution of endothelial cell signaling to cytokine responses and coagulopathy, cross-talk between cytokines and clotting factors, and the role of neutrophil NADPH oxidase-derived ROS in tissue damage, coagulopathy, and inflammation, using biochemistry, cell biology, and mouse knock-out/knock-in models.

Accomplishments 2012-2013

- Scientific Editor-in-Chief, *Science Signaling*
- Organizer and Chair, 2013 Koch Institute Cell Signaling Technology Symposium on Signaling in Cancer
- Ernst Klenck Distinguished Lecturer 2013, Cologne University, Germany
- Elected to American Society for Biochemistry and Molecular Biology (ASBMB) Publications Committee, 2012
- Invited Speaker, Gordon Research Conference on Cell Proliferation, 2013
- Invited Speaker, Federation of American Societies for Experimental Biology (FASEB) Conference on Protein Kinases, 2013
- Invited Speaker, Keystone Conference on Genomic Instability and DNA Repair, 2013
- Invited Speaker, Shock Society meeting – session on Boston Marathon bombing response, 2013
- Invited Speaker, NIH Geroscience Meeting, 2013
- Invited Speaker, 2013 EMBO Annual Meeting, 2013
- Organizing Committee, Society of Critical Care Medicine Annual Meeting, 2013 and 2014

Teaching, Training, and Education

I am heavily involved in teaching at the undergraduate, graduate, and medical school level. I teach 7.05 (Undergraduate Biochemistry) and 7.10 (Physical Chemistry of Biomolecular Systems) at MIT, as well as 7.61 (Signaling and Cell Biology), a graduate-level overview course. I also teach extensively on critical care topics to ICU residents and fellows. Every two years I teach an EMBL-sponsored Signaling in Cancer course in Spetses, Greece.

Selected Research Support

Protein kinase signaling and cell cycle control; NIH, 2007-2018; PI: Michael Yaffe, MD, PhD

Modeling human phosphorylation networks through kinome-wide profiling; NIH, 2013-2018; Co-PIs: Benjamin Turk, PhD, and Michael Yaffe, MD, PhD

Phospho-binding ligands and targets of BRCA1; NIH, 2012-2014; PI: Michael Yaffe, MD, PhD

Integrated Cancer Biology Program; NIH, 2006-2015; Co-PIs: Doug Lauffenburger, PhD and Michael Yaffe, MD, PhD

Analysis and characterization of trauma-induced coagulopathy; NIH, 2013-2018; Co-PI: Michael Yaffe, MD, PhD (PIs: Charles Esmon, MD, PhD, and Kenneth Mann, PhD)

Selected Publications

Lee MJ, Ye AS, Gardino AK, Heijink AM, Sorger PK, MacBeath G, Yaffe MB. Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks. *Cell* 2012;11(149):780-94.

Floyd SR, Pacold ME, Huang Q, Clarke SM, Lam FC, Cannell IG, Bryson BD, Rameseder J, Lee MJ, Blake EJ, Fydrich A, Ho R, Greenberger BA, Chen GC, Maffa A, Del Rosario AM, Root DE, Carpenter AE, Hahn WC, Sabatini DM, Chen CC, White FM, Bradner JE, Yaffe MB. The bromodomain protein Brd4 insulates chromatin from DNA damage signaling. *Nature* 2013;498(7453):246-50.

Rock JM, Lim D, Stach L, Ogradowicz RW, Keck JM, Jones MH, Wong CC, Yates JR 3rd, Winey M, Smerdon SJ, Yaffe MB, Amon A. Activation of the yeast Hippo pathway by phosphorylation-dependent assembly of signaling complexes. *Science* 2013;340(6134):871-5.

Kang SA, Pacold ME, Cervantes CL, Lim D, Lou HJ, Ottina K, Gray NS, Turk BE, Yaffe MB, Sabatini DM. mTORC1 phosphorylation sites encode their sensitivity to starvation and rapamycin. *Science* 2013;341:1236566.

Reinhardt HC, Yaffe MB. Phospho-Ser/Thr-binding domains: navigating the cell cycle and DNA damage response. *Nat Rev Mol Cell Biol* 2013;14:563-80.

Yaffe MB. The scientific drunk and the lamppost: Massive sequencing efforts in cancer discovery and treatment. *Sci Signal* 2013;6(269):pe13.

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Kamal R. Khabbaz, MD

Associate Professor of Surgery
Chief, Division of Cardiac Surgery

Research Focus

The Valve Research Group primarily investigates the dynamic behavior of heart valves in both normal and pathologic states. Heart valves are complex 3-dimensional (3D) structures that undergo dynamic changes during the cardiac cycle. Investigating this behavior is of critical importance in understanding the pathophysiology of and devising management strategies for valvular disease.

Together with Feroze Mahmood et al we investigate normal and abnormal size, shape, and geometric parameters pertaining to the mitral, tricuspid, and aortic valves. In addition, we also study the impact different surgical interventions (e.g., aortic valve replacement and mitral annuloplasty) have on native valve function and surrounding anatomy. To accomplish this, we analyze 3D echocardiographic data using commercially available software, including Philips Qlab and TomTec Image Arena. These softwares enable us to dynamically track and measure anatomical changes in a clinically feasible fashion.

We are currently in the process of extending similar analyses to normal and pathologic tricuspid valves, leading to a more robust understanding of tricuspid valve behavior. Investigations are also underway to investigate the *in vivo* effects of different annuloplasty devices on dynamic valve motion and geometry. These data and analyses hold significant potential in furthering the evidence base for valve repair strategies and surgical decision-making toward achieving the best outcomes.

We are also engaged in devising new methods of interrogating valvular structures using 3D echocardiography as well as several clinical trials, which include the following:

Multi-Center Experience with the Rapid Deployment EDWARDS INTUITY Valve System For Aortic Valve Replacement (TRANSFORM Trial, Protocol Number 2011-02): The purpose of this clinical investigation is to assess the safety and effectiveness of the investigational EDWARDS INTUITY Valve System in subjects with aortic stenosis or stenosis-insufficiency requiring replacement of the native aortic valve.

Clinical Trial of the On-X Valve Using Low Dose Anticoagulation: The purpose of this study is to define the lowest level of required antithrombotic therapy for mitral or aortic valve replacement using the On-X Valve.

Medtronic Core Valve U.S. Pivotal Trial – Extreme Risk Patients; Medtronic CoreValve® U.S. Pivotal Trial – High Risk Surgical Patients; Medtronic CoreValve® U.S. Continued Access Study; Medtronic CoreValve® U.S. Expanded Use Study; Medtronic CoreValve® SURTAVI Trial: The purpose of this study is to determine the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in high-risk and very high-risk subjects who need aortic valve replacement.

SAPIEN registry: This registry is to expand upon existing data sets to identify patient characteristics and indicators related to complications and clinical benefits for patients with symptomatic severe calcific degenerative aortic stenosis who are undergoing treatment with the commercially available Edwards SAPIEN XT™ Valve and delivery devices.

Value of AP versus PA frontal radiograph for preoperative imaging of patients for cardiac surgery: The purpose of this study is to determine whether a supine AP frontal radiograph (similar to postoperative studies) is superior to the standard upright PA frontal radiograph in the preoperative evaluation of patients scheduled for cardiac surgery.

Accomplishments

Several studies are currently in progress. Studies completed so far have shown promising results. The results of one study demonstrate that left-ventricular outflow tract area is significantly underestimated by two-dimensional (2D) measurements when compared with 3D data. This underestimation of the LVOT area with 2D echocardiography potentially overestimates the degree of aortic stenosis (AS). Such errors in assessing disease severity can have important clinical consequences vis-à-vis the decision to operate vs. not operate.

In another study, we report that the implantation of prosthetic valves in the aortic position is associated with changes in dynamic mitral annular geometry. Earlier, our understanding of the effects of aortic valve replacement was limited to geometric analyses of mitral annular conformation at a single point in the cardiac cycle (end-systole).

We have also successfully demonstrated the use of 3D echocardiography in analyzing mitral valve geometry in patients with functional mitral valve regurgitation (FMR). Previously, the understanding of annular dynamics in FMR was largely limited to information derived from animal models.

Teaching, Training, and Education

As Program Director of the BIDMC Cardiothoracic Surgery Residency Program, I have trained 18 cardiothoracic surgical fellows. Three have gone on to become Chairman or Chief of Cardiothoracic Surgery at their respective institutions; one has become Director of Minimally Invasive Surgery. This training includes weekly seminars, direct operative supervision, teaching cardiac surgery techniques, innovations in percutaneous valve mitral valve repair, and new aortic valve deployment techniques. I also teach BIDMC General Surgery residents (PGY-2, PGY-3) in cardiac surgery techniques, and continue to teach a course on echocardiography at Harvard Medical School. In addition, I teach third- and fourth-year HMS students rotating on cardiothoracic surgery and an elective in thoracic and cardiovascular surgery for fourth-year HMS students.

Abstracts, Posters, and Exhibits

Dynamic analysis of mitral valve geometry in functional mitral regurgitation, American Society of Anesthesiologists Annual Meeting 2012, Washington, DC (oral presentation)

Right ventricle myocardial performance in patients undergoing elective coronary artery bypass graft surgery, the Society of Cardiovascular Anesthesiologists Annual Meeting 2012, Boston MA (poster)

Selected Publications

Mahmood F, Kim H, Chaudary B, Bergman R, Matyal R, Gerstle J, Gorman JH, Gorman RC, Khabbaz KR. Tricuspid annular geometry: A three-dimensional transesophageal echocardiographic study. *J Cardiothorac Vasc Anesth* 2013; 27(4):639-46.

Warraich HJ, Matyal R, Bergman R, Hess PE, Khabbaz K, Manning WJ, Mahmood F. Impact of aortic valve replacement for aortic stenosis on dynamic mitral annular motion and geometry. *Am J Cardiol* 2013; S0002-9149(13)01435-5.

Jainandunsing JS, Mahmood F, Matyal R, Shakil O, Hess PE, Lee J, Panzica PJ, Khabbaz KR. Impact of three-dimensional echocardiography on classification of the severity of aortic stenosis. *Ann Thorac Surg* 2013; 4975(13)01051-5.

Mahmood F, Warraich HJ, Gorman JH, Gorman RC, Chen TH, Panzica P, Maslow A, Khabbaz K. Changes in mitral annular geometry after aortic valve replacement: A three-dimensional transesophageal echocardiographic study. *J Heart Valve Dis* 2012;21(6):696-701.

Khabbaz KR, Mahmood F, Shakil O, Warraich HJ, Gorman JH, Gorman RC, Matyal R, Panzica P, Hess PE. Dynamic 3-dimensional echocardiographic assessment of mitral annular geometry in patients with functional mitral regurgitation. *Ann Thorac Surg* 2013; 95(1):105-10.

Matyal R, Chu L, Mahmood F, Robich MP, Wang A, Hess PE, Shahul S, Pinto DS, Khabbaz K, Sellke FW. Neuropeptide Y improves myocardial perfusion and function in a swine model of hypercholesterolemia and chronic myocardial ischemia. *J Mol Cell Cardiol* 2012; 53(6):891-8.

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Sidney Levitsky, MD

Cheever Professor of Surgery

James D. McCully, PhD

Associate Professor of Surgery

Research Focus

The primary focus of the laboratory is to elucidate the mechanisms and subcellular localization of biochemical and molecular events contributing to myocardial cell death. In particular, we are interested in the discriminant and/or coordinate contribution of necrosis and apoptosis to myocardial cell death in the mature and aged male and female, with particular emphasis on the development of novel and specific cardioprotective protocols. Study designs utilize models of stunning and ischemia/reperfusion injury in the isolated Langendorff perfused and the *in situ* blood perfused heart to determine the relative contribution of these pathways in the aged as compared to the mature male and female cardiac surgical patient. Current research areas are described below.

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, and the mechanisms of cell-based myocardial repair or regeneration remain to be elucidated.

Recently, we have demonstrated 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 and significantly enhances functional recovery.

The transplanted mitochondria initially act extracellularly to enhance energy production in the target organ. Subsequently, these organelles are taken up by the cells and further increase oxygen consumption rates and ATP content. These transplanted mitochondria provide a protective effect in the heart for at least four weeks — the end point of our current studies. This new treatment strategy causes no electrical abnormalities or immunological side effects. Transplanted mitochondria act to increase tissue protective cytokine production and up-regulate the signaling pathways associated with mitochondrial function and energy metabolism.

Autogeneic mitochondrial transplantation provides immunological advantages for practical application without the use of anti-rejection drug therapy. The transplantation of autogeneic mitochondria could be used either as an exclusive intervention to ameliorate myonecrosis and enhance myocardial function, or as a primary intervention prior to subsequent auto-, allo- or xeno-geneic cellular regenerative interventions.

The role of collagen type XI alpha-1 on aortic aneurysm formation

Despite the high incidence of AAAs in the general population and the catastrophic consequences of rupture, relatively little is understood with respect to aortic aneurysm pathology and pathogenesis.

Previously we have shown that ascending thoracic aortic aneurysms (ATAAs) have greater disorganization of extracellular matrix constituents as compared to control, and that ATAAs have an increase in collagen $\alpha 1(XI)$ within regions of cystic medial degenerative lesions. Recently, we have extended these preliminary studies using high throughput proteomic analysis to identify additional biomarkers for use in whole blood real time RT-PCR analysis to allow for the identification of ATAA prior to dissection or rupture. Five biomarkers were identified as being suitable for detection and identification of ATAA using qRT-PCR analysis of whole blood. The over-expression of three of these target genes provides 1.0 specificity, allowing for preliminary and serial identification of ATAA 4.0 cm or greater in males and females.

Research Group

Hiroshi Kondo, MD
Janine Preble, MS

Accomplishments 2012-2013

We have continued our studies to demonstrate the efficacy of autologous mitochondrial transplantation (mitoTX). Our studies demonstrate that mitoTX significantly decreases cell damage following ischemia and reperfusion. Serial echocardiograms showed that mitoTX hearts returned to normal contraction within 10 minutes after starting reperfusion; in contrast to control hearts, which showed persistent hypokinesia up to four weeks recovery. Electrocardiogram and optical mapping studies showed no arrhythmia was associated with mitoTX. The transplanted mitochondria are evident in the interstitial spaces, are internalized by cardiomyocytes two to eight hours after transplantation and enhanced oxygen consumption, high energy phosphate synthesis and the induction of cytokine mediators and proteomic pathways important in preserving myocardial energetics, cell viability, and enhanced post-infarct cardiac function.

Using our in-house non-redundant cDNA library consisting of a compendium of over 3800 rabbit heart cDNAs with an average size of 1.6 kB, we have performed microarray and proteomic analysis to show the differential pathways involved in cardioprotection in the mature and aged male and female heart and in the development of left and right heart pressure overload hypertrophy.

In the mature and aged myocardium, functional enrichment analysis showed that mitochondrial dysfunction, oxidative phosphorylation, and calcium signaling pathways were significantly enriched in all experimental groups. Glycolysis/gluconeogenesis and the pentose phosphate pathway were significantly changed in the aged male only, while glyoxylate/dicarboxylate metabolism was significant in the aged female only. These data indicate that specific pathways associated with the mitochondrion modulate cardioprotection in the aged and, specifically, in the aged female.

In left ventricular hypertrophy (LVH) and right ventricular (RVH) hypertrophy, microarray and proteomic data demonstrate that in LVH there is increased transcript expression levels for oxidative phosphorylation, mitochondria energy pathways, actin, ILK, hypoxia, calcium and protein kinase-A signaling and increased protein expression levels of proteins for cellular macromolecular complex assembly and oxidative phosphorylation. In RV-PAB there is also increased transcript expression levels for cardiac oxidative phosphorylation, but increased protein expression levels for structural constituents of muscle, cardiac muscle tissue development, and calcium handling.

These divergent transcript and protein expression profiles provide new insight into the biological basis of ventricular specific hypertrophy and cardioprotection and should allow for the development of specific therapeutic interventions.

We were a winner in the Federation of American Societies for Experimental Biology (FASEB) BioART contest 2013 (one of the ten winning image entries). See the winning image on the cover of this report and a description on the inside front cover.

Teaching, Training, and Education

I (McCully) have trained 22 cardiothoracic surgical fellows and post-doctoral fellows and nine pre-doctoral fellows. This direct training has allowed the fellows to go on to become leaders in their fields. Four fellows are now chiefs, associate chiefs, or directors of their departments, and seven have academic appointments (six are associate professor). Four students have received their PhDs and five have received or are in the process of receiving their MD degrees.

Selected Research Support

Autogeneic mitochondria: Surgical cardioprotection; NIH, 2010-2014; PI: James D. McCully, PhD

Mitochondrial transplantation for the treatment of cerebral ischemia-reperfusion injury. Boston Children's Hospital, Anesthesia Research Distinguished Trailblazer Award. Co-Investigator: James D. McCully, PhD (PI: Christina Pacak, PhD)

Mitochondrial transplant for therapeutic amelioration, Adelson Medical Research Foundation; pending

Selected Publications

Black KM, Barnett R, Bhasin MK, Daly C, Dillon ST, Libermann TA, Levitsky S, McCully JD. Microarray and proteomic analysis of cardioprotection in the mature and aged male and female. *Physiol Genomics* 2012;44:1027-1041.

Friehe I, Cowan DB, Choi Y-C, Black KM, Barnett R, Bhasin MK, Daly C, Dillon SJ, Libermann TA, McGowan FX, del Nido PJ, Levitsky S, McCully JD. Pressure-overload hypertrophy of the developing heart reveals activation of divergent gene and protein pathways in the left and right ventricular myocardium. *Am J Physiol Heart Circ Physiol* 2013; 304:H697-708.

Masuzawa A, Black KM, Pacak CA, Ericsson M, Barnett RJ, Drumm C, Seth P, Bloch DB, Levitsky S, Cowan DB, McCully JD. Transplantation of autologously-derived mitochondria protects the heart from ischemia-reperfusion injury. *Am J Phys Heart Circ Physiol* 2013;304:H966.

Levitsky S, McCully JD. Myocardial Protection. Chapter 66. In: Sellke FW, Swanson S, del Nido P. Eds. *Sabiston & Spencer Surgery of the Chest*, 8th Edition. Philadelphia, PA. 2013

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Research Group

Finith Jernigan, PhD
Yiqiang Wang, PhD

Lijun Sun, PhD

Director, Center for Drug Discovery and Translational Research

Research Focus

The Center for Drug Discovery and Translational Research has focused its efforts on fostering multidisciplinary collaborations to accelerate the translation of basic research to clinics. Our aspiration is to make available the expertise in drug discovery and development to investigators who are interested in and motivated by extending their cutting-edge science into the development of novel therapies.

Prior to my current position as the Director of the Center, my research in medicinal chemistry and drug discovery led to the clinical development of a number of first-in-class, novel molecular entities with the potential to treat cancers and autoimmune diseases. The Center is positioned to build and expand its capabilities in molecular designs, in silico screening, predictive modeling, drug synthesis, and pharmaceuticals.

Anticancer drug discovery

Metastasis is the leading cause of death in cancer. Yet it is still a poorly understood process. We are developing a research program that is inspired by the natural product migrastatin. It has been shown that migrastatin is capable of inhibiting selectively the migration and invasion of cancer cells *in vitro*, as well as their metastasis and colonization in distant organs *in vivo*. In addition, the actin-bundling protein fascin has been implicated in the invasiveness of breast cancer, glioblastoma, and melanoma. The goal of this project is to generate novel migrastatin analogs and fascin inhibitors that may help improve our understanding of cancer metastasis and identify novel treatment and prevention strategies.

Overcoming drug-induced resistance is a never-ending battle in the war against cancer. Working with an oncology research group at Boston Children's Hospital, we are developing a new series of anticancer agents that possess preferential cytotoxicity in cancer cells that are highly metastatic and resistant to chemotherapies. The original screening hits were identified from a compound library of FDA-approved drugs and found to be nontoxic to normal cells. We have applied structure-based and bioisostere-based drug designs to increase potency against cancer cells and to improve pharmaceutical properties for drug deliveries.

We have also established collaborative drug discovery research targeting aberrant cancer metabolism. To sustain their growth, cancer cells maintain hyperactive lipogenesis machinery to supply building blocks for the construction of cell and subcellular membranes. The overexpression of lipogenic enzymes has been identified in a number of cancers. By targeting one key enzyme critical to lipogenesis, we plan to develop novel small-molecule inhibitors that can potentially alter the stemness of cancer cells that will render them more sensitive toward chemotherapies.

Anti-inflammatory drug discovery

Aryl hydrocarbon receptor (AhR) has recently emerged as a key player in modulating innate and adaptive immunity. AhR agonists have shown significant efficacies in animal models of multiple sclerosis, diabetes, and allograft rejection. The precise mechanism of its anti-inflammatory activity is still actively debated, and the ligands applied in the studies are either environmental pollutants or metabolites that cannot be developed to useful medicine. We aim to develop novel drug-like small-molecule AhR ligands that will help validate AhR as a novel target for treating human diseases.

Accomplishments 2012-2013

Since I joined the Department of Surgery in September 2012, I have initiated a number of discussions with faculty members within our department, at BIDMC, and Harvard Medical School. Many of the discussions have led to collaborations between the principle investigators and the Center. Together we have submitted a number of new grant applications that are under review. In all research proposals, the Center plays a significant role in shaping the study designs and the future directions of the research. As either a Co-Principal Investigator or Co-Investigator, I have contributed to the drafting and submission of the following applications:

- a Center (UH2/HU3) grant application for developing a novel therapy for treating COPD (Co-Investigator)
- multiple R01 grant applications: chronic kidney disease (Co-PI), congestive heart failure (Co-PI), stroke (Co-Investigator), nano-medicine for reperfusion injury (Co-Investigator), and cancer metabolism (Co-Investigator)
- a Department of Defense (DoD) Synergy Award application for prostate cancer research (Co-PI)
- a DoD grant application for developing new cell surface anchored fluorescent probes (Co-Investigator)
- We are actively developing additional ideas into grant submissions in the coming year.

Meanwhile, the Center is establishing its infrastructure by occupying 900 square feet of laboratory space in the Dana research building. We are now functional in conducting research in computational modeling, molecular design, and drug synthesis. In February 2013, we synthesized our first set of compounds for testing. In August, we conducted our first pharmacokinetic and drug metabolism study. In September, we performed our first molecular modeling and structure-based drug design. We are expanding our capacity and capability in drug discovery by installing advanced instruments and developing partnerships with core facilities in the Longwood Medical Area and Harvard University.

In addition, I have participated in two successful ARC (Affinity Research Collaborative) teams funded by the Department of Surgery, one in cancer and metabolism (PI: Barbara Wegiel, PhD) and another in vasculature biology (PI: Teresa Sanchez, PhD). These ARC initiatives brought together investigators with shared interests in biomedical research. I strive to contribute to ARC's success through its lecture series as well as seeding and nurturing new ideas for breakthrough team science.

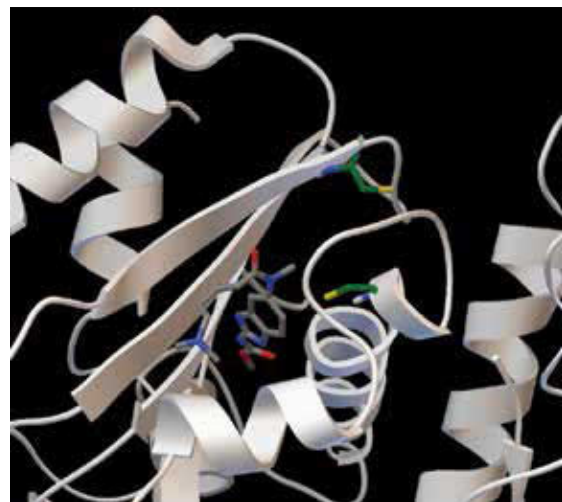
Teaching, Training, and Education

The Center is committed to providing a platform for educating the next-generation research scientists, who will gain broad knowledge and experience in drug discovery and translational research. In the ARC seminar series, I have presented the capabilities in drug discovery we can offer the BIDMC Department of Surgery research community, and will continue the effort to bring awareness of the Center and its model of collaborative research. Via ongoing collaborations, we will expand our efforts in teaching research associates the unique process of conducting drug-discovery research, data interpretation, presentation of scientific results, and problem-solving skills.

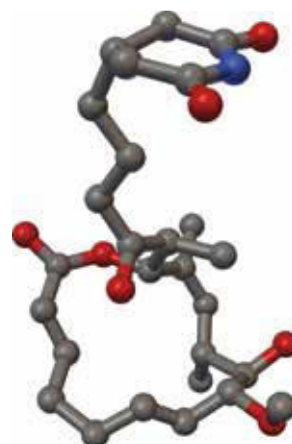
Selected Research Support

BIDMC Department of Surgery start-up package, 2012-2017, PI: Lijun Sun, PhD

Neutrophil activation and trauma (administrative supplement); NIH, 2013-2016; Co-Investigator: Lijun Sun, PhD (PI: Wolfgang Junger, PhD)



▲ Binding pose of a novel inhibitor to its protein target



▲ Natural product migrastatin



Deborah A. Nagle, MD

Assistant Professor of Surgery
Chief, Colon and Rectal Surgery

Research Focus

My research is clinical in nature and has three primary themes:

Perioperative management of patients to optimize outcomes and reduce infections and complications

- Reducing readmissions for dehydration
- Reducing urinary tract infection and other infections in colon and rectal surgery patients
- Optimizing pain control postoperatively

Minimally invasive surgery, including advanced techniques in colon and rectal surgery

- Evaluation of the impact of robotic approach to colon and rectal surgery
- Outcomes with advanced minimally invasive techniques

Colon and rectal cancer with a focus on understanding optimal surgical oncologic management

- Evaluating oncological outcomes in rectal cancer patients on an accelerated surgical pathway
- Evaluating the impact of minimally invasive surgery on oncologic treatment

Accomplishments 2012-2013

This year, our research of the reduction of urinary tract infections led to a very significant decrease in infections in our patient population in a six-month period. This work will soon be published. Last year, we developed a pathway for patient education in the prevention of dehydration after creation of a new ileostomy. This work significantly reduced readmissions to the hospital for our patients. It was presented at both national and international meetings, published in the leading colon and rectal surgery journal, and has been donated to multiple hospitals nationally and internationally. Recently we hosted a graduate student from Switzerland who is designing a similar program for hospitals in her country.

Our administrative achievements include:

- We have successfully recruited a third surgeon, Thomas Cataldo, MD, to the Division of Colon and Rectal Surgery
- A second nurse practitioner has joined our division and has developed an independent practice
- Our service domain has been expanded to include other clinical sites in the Boston area. With the addition of Dr. Cataldo, we are currently developing a presence at a fourth location
- I was elected to the Executive Council of the American Society of Colon and Rectal Surgeons (ASCRS)

Recent invited presentations:

- Advanced laparoscopic anatomy, ASCRS, 2012
- Ileostomy pathway virtually eliminates readmissions in new ostomates, ASCRS, 2012
- Robotic surgery: The learning curve, ASCRS, 2012
- Ileostomy pathway virtually eliminates readmissions in new ostomates, European Society of Coloproctology, Vienna, 2012
- Reducing UTIs in CRS may be easier than you think, ASCRS, 2013
- Emerging surgical therapies for fecal incontinence, NIH/NIDDK, 2013

Teaching, Training, and Education

We developed an integrated hospital service for resident training and education in colon and rectal surgery. We focus on evidence-based care decisions with pathway management to optimize outcomes. We provide a very strong operative experience for the residents with special focus on advanced minimally invasive surgery. Our service initiated the training of residents in robotic colon and rectal surgery at BIDMC.

In the last three years, three graduates from our program have gone on to fellowship training in colon and rectal surgery. Currently, five resident physicians are involved in research efforts in our division in preparation for fellowship application.

Selected Research Support

A phase 3, randomized, double-blind, placebo-controlled, parallel-treatment group, multicenter efficacy and safety study of topical diltiazem hydrochloride 2% cream in subjects with anal fissure; Ventrus, 2012-2013; PI: Deborah Nagle, MD

Selected Publications

Champagne BJ, Papaconstantinou HT, Parmar SS, Nagle DA, Young-Fadok TM, Lee EC, Delaney CP. Single-incision versus standard multiport laparoscopic colectomy: A multicenter, case-controlled comparison. *Ann Surg* 2012;255(1):66-9.

Nagle D, Pare T, Keenan E, Marcet K, Tizio S, Poylin V. Ileostomy pathway virtually eliminates readmissions for dehydration in new ostomates. *Dis Colon Rectum* 2012;55(12):1266-72.

Nagle D. Toward a better understanding of readmissions for physiologic complications of ileostomy. *Dis Colon Rectum* 2013;58(8):933-4.

Gilmore DM, Curran T, Guatam S, Nagle D, Poylin V. Timing is everything—colectomy performed on Monday decreases length of stay. *Am J Surg* 2013;206(3):340-345.

Nagle D, Curran T, Anez-Bustillos L, Poylin V. Reducing urinary tract infections in colon and rectal surgery. *Dis Colon Rectum* 2013; in press.

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Vitaliy Y. Poylin, MD

Instructor in Surgery

Research Focus

A major focus of my research has been on outcomes after colon and rectal surgery, especially minimally invasive colorectal surgery, and ways to improve those outcomes. Some of my recently completed projects include outcomes after laparoscopic rectopexy in the elderly and the effect of laparoscopy on the timing to chemotherapy for advanced colon cancer.

Some of my current projects include research of:

- Prevention and improvement of urinary retention after pelvic surgery
- Improvement of pain after anorectal surgery
- Neuropeptides' effects on inflammatory bowel disease bowel recovery — a collaboration with the laboratory of Frank LoGerfo, MD

Accomplishments 2012-2013

Since the beginning of 2012, I have completed a prospective trial on the effects of gabapentin on recovery after anorectal surgery and am currently starting a randomized double blind control trial on the subject. I have completed a collaborative project with Frank LoGerfo, MD, on the effects of neuropeptides on inflammatory bowel disease and postoperative recovery.

Administratively, I became a Fellow of the American College of Surgeons, and received Board Certification in Colon and Rectal Surgery. I am also a member of the Awards Committee and Young Surgeons Committee for the American Society for Colon and Rectal Surgeons (ASCRS). In addition, I participated in the First Case Start Committee, the Operating Room Code Response Faculty Hour, and the Utilization Review Pathology Advisory Committee at BIDMC.

Recent invited presentations

- Reducing urinary tract infections in colon and rectal surgery may be easier than you think!, Plenary Talk, ASCRS, 2013
- Gabapentin significantly decreases post-hemorrhoidectomy pain: A prospective study, Poster, ASCRS, 2013
- Ileostomy pathway virtually eliminates readmissions in new ostomates – Plenary Talk, ASCRS, 2012
- Laparoscopic colectomy decreases time to start of chemotherapy in advanced colon cancer, Poster, ACS Clinical Congress, 2012
- Changing approaches to rectal prolapse repair in the elderly, Poster, ASCRS, 2012
- Endoscopic resection of rectal neuroendocrine tumors: Establishing guidelines for oncologic endpoints, Poster, Digestive Disease Week, 2012
- Single incision colectomy: The reality of adoption into practice, Poster, SAGES, 2012

Teaching, Training, and Education

This year I participated in Harvard combined courses for primary care physicians and surgeons on colorectal surgery. I have recently given lectures at Harvard Medical School on topics including anal fissures, managing common anal complaints, and technical tips and tricks in colorectal surgery.

Additionally, I participate in resident and medical student training in colorectal surgery as well as mentor residents interested in colon and rectal surgery.

Selected Research Support

The role of neuropeptides in inflammatory bowel disease and postoperative ileus; Eleanor and Miles Shore Fellowship, 2011-2013; PI: Vitaliy Poylin, MD

Selected Publications

Nandivada P, Poylin V, Nagle D. Advances in the surgical management of inflammatory bowel disease. *Curr Opin Gastroenterol* 2012;28(1):47-51.

Nagle D, Poylin V, Pare T, Keenan E, Marcet K, Tizio S. Ileostomy pathway virtually eliminates readmissions for dehydration in new ostomates. *Dis Colon Rectum* 2012;55(12):1266-1272.

Gilmore DM, Curran T, Guatam S, Nagle D, Poylin V. Timing is everything — colectomy performed on Monday decreases length of stay. *Am J Surg* 2013;206(3):340-345.

Nagle D, Curran T, Anez-Bustillos L, Poylin V. Reducing urinary tract infections in colon and rectal surgery. *Dis Colon Rectum* 2013; in press.

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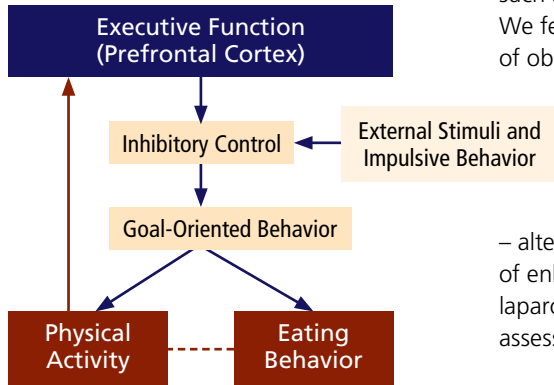
George L. Blackburn, MD, PhD

S. Daniel Abraham Professor in Nutrition Medicine



Research Group

Barbara Ainsley
Miguel Alonso-Alonso, MD
Greta Magerowski
Anne McNamara, BSN, RN
Cleofe Pena-Gomez, PhD



▲ Physical activity affects eating behavior by generating, strengthening, and refining neural circuits in the prefrontal cortex. These enhance executive function and strengthen inhibitory control — prerequisites for setting goals and using self-control to achieve them.

Research Focus

My current research encompasses several different areas. I am one of the original (2004) principle investigators on the NIDDK Look AHEAD clinical trial to study intense lifestyle intervention in T2DM. We are now entering the LookAHEAD Continuation (LookAHEAD-C) phase. This continuation builds on the remarkable success in inducing and sustaining weight loss and retaining participants. The continuation phase of the study addresses important public health priorities for a rapidly growing and under-studied older diabetic segment of the US population in a cost-effective manner (N Engl J Med 2013;369:145-154). In the continuation, we are adding assessments of critical cognitive fitness outcomes that are associated with healthy living.

For several years I have been working in collaboration with the Berenson-Allen Center for Noninvasive Brain Stimulation looking at novel and specific neurocognitive resources to translate nutrition advice into healthy dietary behaviors at the individual level. We are working with neuroscientists on the neurocognitive basis of eating behavior, using an interdisciplinary approach that combines elements of cognitive neuroscience, psychology, nutrition, weight loss surgery, and ingestive behavior. We have a special interest for the neurocognitive basis of interindividual differences in this area, and the development of new brain- and cognition-based therapies to enhance eating control in pathological situations, such as obesity. These efforts are interdisciplinary, innovative, and have clinical relevance. We feel confident that our findings have the potential to directly impact the management of obesity in the future.

Our completed and current projects include the development of an achievable and effective progressive resistance training (PRT) exercise protocol for severely obese patients. Novel studies in this area will target the relations between exercise-induced changes in brain structure, neurochemistry, and executive function — alterations that might affect dietary impulse control. We are also investigating the area of enhancement of the brain circuit of inhibitory control in obese patients undergoing laparoscopic adjusted gastric banding and brain fNIRS-based methodology for the assessment of inhibitory control over food in obesity.

For my most recent project I have assembled a team that includes a nutritionist, diabetologist, and neuroscientist, and brought them together with the Athinoula A. Martinos Center for Biomedical Imaging, a world pioneer in neuroimaging research. The center will provide state-of-the-art facilities and methodologies for data acquisition and analysis in a LookAHEAD ancillary grant entitled Look AHEAD Cognitive Fitness Study.

Complex brain functions (e.g., coordinated movement, memory, attention, executive functions, and speech) are critically dependent on synchronic interactions between brain areas or functional connectivity networks — distributed regions transiently interacting to perform particular cognitive functions. We will use state-of-the-art functional magnetic resonance imaging (fMRI) to explore the relation between the dynamics of complex brain networks, network hubs of functional decline, and predictors of healthy brains in a subcohort of Look AHEAD Study participants with T2DM. We propose a prospective (fMRI) study to address this critical public health issue in a unique, efficient, and cost-effective way. The aims of this research are threefold: to evaluate differences in functional brain organization between the Intensive Lifestyle Intervention Group and control groups approximately 10-12 years after initial randomization; to determine changes in functional brain organization in the two groups over time; and to examine factors contributing to cognitive fitness and changes in it over time in Look AHEAD individuals.

Accomplishments 2012-2013

On July 1, 2012 my appointment as the S. Daniel Abraham Professor in Nutrition Medicine was approved by the President and Provost of Harvard University.

I have been very fortunate during my academic career; I am the first recipient of the Master of the American Board of Obesity Medicine (ABOM) Recognition Award. This award recognizes physicians who have made significant contributions to the science, practice, and/or advancement of obesity medicine and obesity treatment.

I served as the Chair of the Medical Care Subcommittee for the Centers for Disease Control and Prevention Weight of Nation Conference; this was a two-year commitment. I was also part of the steering committee and awards panel. The proceedings from this meeting are being published in the near future.

I continue to be an ad hoc reviewer for several journals (2012 acknowledgement from *Annals of Internal Medicine* as top 10% reviewer) and participate in grant reviews (NIH Loan Repayment Grant review/Harvard Catalyst).

Teaching, Training, and Education

As Associate Director of the Division of Nutrition at Harvard Medical School (HMS), I take an active role in the development of curriculum and the tutoring of our medical students (Fall 13: Human Systems–Nutrition). I am also responsible for the division's Longwood Nutrition Seminar Series (October–June monthly nutrition lecture series). I participate by delivering lectures for the Surgery Core Clerkship and Surgical Grand Rounds. Recently, I participated in the Objective Structured Clinical Exam (OSCE) for second- and fourth-year medical students. I had the pleasure of being a HMS Honors Scholar, thesis evaluator. I also continue to provide our minimally invasive surgery fellows with guidance on their research projects. I presently have a post-doctoral fellow at The Center for the Study of Nutrition Medicine. We also welcome summer research students.

Selected Research Support

Look AHEAD action for health in diabetes-continuation; NIH, 1999-2015; Site PI: George L. Blackburn, MD, PhD

Boston Obesity Nutrition Research Center (BONRC)—Administrative Core; NIH, 2013-2018; Associate Director, 2013-2018

Understanding how patients value bariatric surgery; NIH, 2007-2012; Co-Investigator: George L. Blackburn, MD, PhD (PI: Christina Wee, MD)

Lifestyle intervention study in adjuvant treatment of early breast cancer (LISA); DFCI/Novartis Pharmaceuticals, 2008-2014; Site PI: George L. Blackburn, MD, PhD (DFCI PI: Jennifer Ligibel, MD; PI: Pamela Goodwin, MD)

Selected Publications

Imayama I, Ulrich CM, Alfano CM, Wang C, Xiao L, Wener MH, Campbell KL, Duggan CR, Foster-Schubert KE, Kong A, Mason CE, Wang CY, Blackburn GL, Bain CE, Thompson HJ, McTiernan A. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: A randomized controlled trial. *Cancer Research* 2012;72 (9):2314-26.

Kudsi OY, Huskey K, Grove S, Blackburn GL, Jones DB, Wee CC. Prevalence of postoperative alcohol abuse among patients seeking weight-loss surgery. *Surg Endosc* 2012; October 10. (Epub ahead of print)

Abbenhardt C, McTiernan A, Alfano CM, Wener MH, Campbell KL, Duggan C, Foster-Schubert KE, Kong A, Toriola AT, Potter JD, Mason CE, Xiao L, Blackburn GL, Bain C, Ulrich CM. Effects of individual and combined dietary weight loss and exercise interventions in post menopausal women on adiponectin and leptin levels. *J Intern Med* 2013;274(2):163-75.

Wee CC, Hamel MB, Apovian CM, Blackburn GL, Bolcic-Jankovic D, Colten ME, Hess DT, Huskey KW, Marcantonio ER, Schneider BE, Jones DB. Expectations for weight loss and willingness to accept risk among patients seeking weight loss surgery. *JAMA Surg* 2013;148(3):264-71.

Blackburn GL. Weight of the nation: Moving forward, reversing the trend using medical care. *Am J Clin Nutr* 2012;96:949-50.

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Mark P. Callery, MD

Professor of Surgery
Chief, General Surgery



Research Focus

Clinical outcomes research in pancreaticobiliary surgery

Our group's work focuses on outcomes research in high-acuity pancreaticobiliary surgery. Fueled by a robust clinical practice that focuses on treatment of pancreatic malignancies, cystic lesions, pancreatitis, and complex biliary conditions in a multidisciplinary setting, we perform over 200 major pancreaticobiliary operations per year.

A prospective database of over 4,000 operations and 750 pancreatic resections has been developed and maintained from this practice, providing the substrate for our investigations. Areas of emphasis are 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. We have also explored the impact of surgical complications associated with these operations. We are now also embarking on quality of life analyses for these disease processes. We are currently building a Quality Scorecard for Pancreatic Surgery that reflects the Institute of Medicine health care quality domains.

Additional recent efforts have included investigations into the reasons for readmission after pancreatectomy, with a goal of better understanding causes for readmission in this patient population, as well as decreasing unnecessary readmissions.

Other outcomes studies over the last year have involved the investigation of the relationship between pancreatectomy for cancer, complications, and initiation/completion of adjuvant therapy, and the analysis of outcomes for patients undergoing palliative surgery in the setting of pancreatic cancer. Work is also ongoing to develop, employ, and evaluate a patient-education tool to provide additional and improved information to patients upon discharge after pancreatectomy. The effectiveness of this tool will be evaluated via patient-satisfaction surveys and readmission rate/cause analysis.

Accomplishments 2012-2013

- Elected to the American Surgical Association, 2013
- Editor, HPB
- Invited Guest, British Journal of Surgery Centennial, Oxford, England, 2013
- Executive Council, IHPBA
- Invited Co-Chair, "Minimally Invasive Hepatobiliary and Pancreatic Surgery — The Next Frontier," SAGES/SSAT, 2012
- Invited speaker, "Neoadjuvant therapy is the standard of care for pancreatic cancer," Con-opinion, Debate: AHPBA 2012
- Invited moderator, plenary General Surgery Video Session, American College of Surgeons Annual Meeting, 2012
- Invited Moderator, "Clinical Ward Rounds II — Cysts of the pancreas: Observe, resect, or drain. How to pick the right option for every patient...the first time," SSAT/DDW Meeting, 2013
- Invited Speaker "How to write a high-quality review," Meet-the-Professor Session, SSAT Writers Workshop, SSAT/DDW Meeting, 2013
- The Lister Centennial Invited Professor, The Royal College of Surgeons of Edinburgh, Edinburgh, Scotland, 2012
- Editors Panel, "How to review a manuscript," IHPBA World Congress, Paris, 2012
- Keynote Lecturer, "Molecular diagnosis of pancreatic cancer," IHPBA World Congress Paris, 2012
- Invited Speaker, "Bile duct injuries: Anatomic pitfalls and how to avoid BDI intra-operative recognition—What do I do now?" Symposium, E-AHPBA Annual Meeting, Serbia, 2013
- Treasurer, Executive Committee, Society for Surgery of the Alimentary Tract, 2013

Teaching, Training, and Education

I have taught medical students, residents, and fellow physicians in many settings for over 20 years. I was a founding faculty advisor for Harvard Medical School's John Warren Surgical Society for students interested in surgical careers. For my longstanding efforts as a teacher to Harvard Medical School students, in 2005 I was awarded the George W. Starkey Award for Excellence in Teaching, which is given annually to a faculty member by third-year HMS students. More recently, I was honored to be nominated by HMS students to receive the S. Robert Stone Award for Excellence in Teaching, which is presented annually to a member of the BIDMC faculty for outstanding achievement in the teaching of medical students. In 2013, I was elected to the Harvard Medical School Committee on Admissions.

Abstracts, Posters, and Exhibits

Kalish BT, Vollmer CM, Kent TS, Nealon W, Tseng JF, and Callery MP. Quality assessment in pancreatic surgery: What might tomorrow require? Plenary Oral Presentation/Top Prize – Residents Research Day. SSAT 52nd Annual meeting and Pancreas Club meeting for Digestive Disease Week, San Diego, CA, 2012

Chau Z, West JK, Zhou Z, McDade TP, Smith JK, Ng SC, Kent TS, Callery MP, Moser AJ, Tseng JF. Rankings vs reality for pancreatic cancer surgery: A real world comparison. Oral presentation, American Hepato-Pancreato-Biliary Association Annual Meeting, Miami, FL, 2013

Mazer LM, Vollmer CM, Callery MP, Kent TS. Predictors of initiation and completion of adjuvant therapy after surgical resection for pancreatic adenocarcinoma. Oral presentation, American Hepato-Pancreato-Biliary Association Annual Meeting, Miami, FL, 2013

Selected Publications

Vollmer CM, Sanchez NJ, Gondek S, McAuliffe J, Kent TS, Christein JD, Callery MP; The Pancreatic Surgery Mortality Study Group. A root-cause analysis of mortality following major pancreatectomy. *J Gastrointest Surg* 2012;16:89-102.

Kent TS, Sachs TE, Callery MP, Vollmer, Jr. CM. The burden of infections for elective pancreatic resections. *Surgery* 2013;153:86-94.

Lewis R, Drebin JA, Callery MP, Fraker D, Kent TS, Gates J, Vollmer, Jr. CM. A contemporary analysis of survival for pancreatic ductal adenocarcinoma. *HPB* 2013;15:49-60.

Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer, Jr. CM. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 2013;216:1-14.

Kalish BT, Vollmer CM, Kent TS, Nealon WH, Tseng JF, Callery MP. Quality assessment in pancreatic surgery: What might tomorrow require? *J Gastrointest Surg* 2013;17:86-93.

Sachs TE, Pratt WB, Kent TS, Callery MP, Vollmer CM Jr. The pancreaticojejunal anastomotic stent: Friend or foe? *Surgery* 2013;153:651-662.

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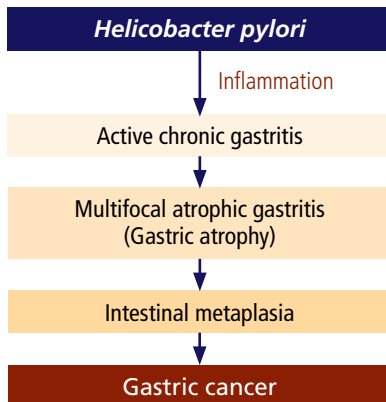
Susan J. Hagen, PhD

Associate Professor of Surgery
Associate Vice Chair for Research



Research Group

Lay-Hong Ang, PhD
Andrea Calhoun
Mia Leibermann, DVM
Lena Liu
Ji Hye Seo, PhD
Suzanne White
Yi Zheng, PhD



▲ Figure 1: Schematic diagram of the gastric cancer cascade.

Research Focus

The focus of my laboratory is to understand how gastric atrophy occurs during *Helicobacter pylori* infection, which is a pivotal step in the gastric cancer cascade that occurs after long-term, chronic active gastritis (Figure 1). Gastric cancer is the third most common cancer and the second most common cause of cancer deaths worldwide. Despite the global prominence of *H. pylori* infection and gastric cancer, little is known about how gastric cancer develops.

Gastric atrophy occurs when mature epithelial cells, namely parietal and chief cells, die during infection and the stomach is re-populated with metaplastic epithelial cells. We thus approach our work by studying cell survival and death mechanisms. In particular, we are interested in the protective, cell survival mechanisms utilized by parietal and chief cells, which normally confer homeostasis to the gastric mucosa. When these processes are dysregulated in *H. pylori* infection, particularly during inflammation, the acceleration of cell death and gastric atrophy occurs. We approach this problem from two different perspectives.

In the first approach, we study protective mechanisms at the tissue level to gain an understanding of how tissue-specific protective functions are dysregulated to facilitate cancer development. We have a longstanding interest in gastric mucosal barrier function. While there are numerous components of the barrier that are protective and may be affected by *H. pylori* infection, we study the role of tight junctions in protecting parietal and chief cells from injury and cell death.

Tight junction dysfunction during *H. pylori* infection, which is one risk factor for gastric cancer development, allows the permeation of luminal contents across the mucosa. This dysfunction in the stomach is particularly toxic to epithelial cells because it allows the permeation of gastric acid. We study the role of claudin-18 in mucosal homeostasis and gastric cancer development. Claudin-18 is a cation-specific tight junction barrier protein that is specific to the stomach and is transcriptionally down-regulated in *H. pylori* infection. In claudin-18 knockout mice, atrophy occurs at three days after birth from the permeation of luminal acid, which kills parietal and chief cells. Because little is known about the transcriptional regulation of claudin-18 or how it protects cells against injury, we approach this problem using *in vivo* infected mice and claudin-18 knockout mice, as well as cultured primary cells and immortalized gastric cancer cell lines.

In a second approach, we study how survival and death mechanisms are regulated at the cellular level to gain an understanding of how these pathways are blocked in cancer development. This approach has been challenging in parietal cells, for instance, because they do not express any of the classical BCL-2-family cell survival/death proteins like BCL-2, BAX, BAK, etc. Rather, we determined that parietal cells transcriptionally regulate cell survival effectors via N-methyl-D-aspartate (NMDA) channel-mediated calcium influx (Figure 2). This cell survival regulation occurs in concert with gastric acid secretion. We have a major effort in the lab to determine how NMDA channels regulate atrophy and cancer development using mouse models and primary cultured parietal cells.

Accomplishments 2012-2013

Individual Accomplishments

Keynote speaker at the 7th International Symposium on Cell/Tissue Injury and Cytoprotection (see below). Also acted as a moderator in a number of scientific sessions at this meeting

In addition to the regular reviewer requests I receive, I was asked to review this year by *PLoS One*, *Journal of Nutrition*, *BMC Microbiology*, *International Journal of Biochemistry and Cell Biology*, *Nutrients*, and the *Journal of Physiology and Pharmacology*

Served as Co-Chair of the Affinity Research Collaborative (ARC), Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School

Served as an interviewer for surgical resident applicants in Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Served as a judge for the 29th Annual Research Science Institute's Final Research Presentations, MIT campus, August 2012

Invited Presentations (selected)

IL-1 β and tight junction dysfunction in *Helicobacter pylori*-induced gastric cancer pathogenesis. Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, MA, January 2012

N-methyl-D-aspartate (NMDA) channels: Potent regulators of calcium signaling during gastric acid secretion. 7th International Symposium on Cell/Tissue Injury and Cytoprotection/ Organoprotection: Focus on the GI tract. Honolulu, Hawaii, September 2012

An overview of gastric cancer: Mucosal pathogenesis that is an infection-mediated process. Beth Israel Deaconess Medical Center, Affinity Research Collaborative (ARC) series, Cancer and Metabolism, April 2013

Teaching, Training, and Education

In addition to teaching post-doctoral fellows in the research laboratory, I taught investigators to use the electron microscope and to do electron microscopy (EM) tomography in the EM facility at BIDMC.

Undergraduate and Medical School Courses

Human Body course at Harvard Medical School in 2012 and 2013 as Director of the Cannon Society histology laboratory

Resident Courses

Module Leader in 2012 and 2013 for the Physiology Course at Mount Desert Island Biological Laboratory (MDIBL). The MDIBL course module was "Acid Secretion," with approximately 12 medical/surgical residents rotating through the module during the one-week course.

Selected Research Support

Biology of alimentary epithelia in health and disease; NIH, Harvard Digestive Diseases Center Grant, 2010-2015; Subcontract PI/ Imaging Core B Director: Susan J. Hagen, PhD (PI: Wayne Lencer, MD, Boston Children's Hospital)

Biomedical research training for veterinary scientists; NIH, 2013-2018; Mentor: Susan J. Hagen, PhD (PI: James G. Fox, DVM, MIT)

Regulation of parietal cell survival in gastric atrophy by NMDA channels; NIH, 2014-2019; PI: Susan J. Hagen, PhD

Regulation of parietal cell survival by N-methyl-D-aspartate channel-mediated gene transcription; Funderberg Research Award in Gastric Cancer, 2014-2015; PI: Susan J. Hagen, PhD

Departmental bridge funding

Selected Publications

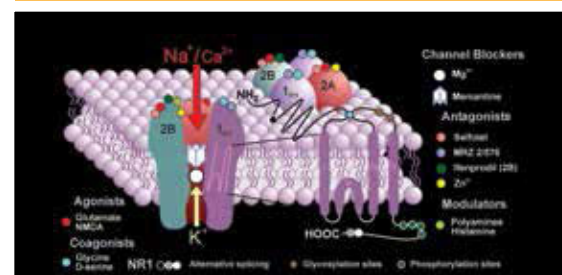
Adolph TE, Tomczak MF, Jeong-Ko H, Bock J, Niederreiter L, Tscurtschenthaler M, Martinez-Nerves E, Hartwig J, Hosomi S, Flak M, Billmann-Born S, Kweon M-N, Lee A-H, Hagen SJ, Glickman J, Choi A, Schreiber S, Rosenstiel P, Kaser A, Blumberg RS. Endoplasmic reticulum stress converts epithelial autophagy defects into intestinal inflammation. *Nature* 2013; in press.

Kang HW, Ozdemir C, Kawano Y, Leclair KB, Vernochet C, Kahn RC, Hagen SJ, and Cohen DE. Thioesterase superfamily member 2/acyl-coA thioesterase 13 (Them2/Acot13) regulates adaptive thermogenesis in mice. *J Biol Chem* 2013; in press.

Zhang S, Seo JH, Tashima K, Fox JG, Hagen SJ. Attenuation of claudin-18 during *H. pylori* infection occurs via TNF- and IFN-induced IL-1R1/IL-1RAcP signaling in stomach. *Gastroenterology*; submitted September 2013.

Seo JH, Itagaki K, Hagen SJ. Novel role of N-methyl-D-aspartate channels in regulating histamine-mediated calcium signalling in gastric parietal cells. *J Biol Chem*; submitted September 2013.

Hagen SJ. Glutamine supplementation in *H. pylori* infection. In: Rajendram R, Preedy VR, and Patel VB, editors. *Glutamine in Health and Disease*. Chapter 3, Protective role of glutamine in cellular and organ damage. London: Springer; 2013; in press.



▲ Figure 2: Schematic diagram of a polarized epithelial cell with the a junctional complexes highlighted. Note the apical location of the tight junction, with claudins (green) as a major membrane-spanning component.

A complete list of publications begins on page 17

Daniel B. Jones, MD, MS

Professor of Surgery

Vice Chairman, Surgery (Technology and Innovation)

Chief, Section of Minimally Invasive Surgery; Director, Bariatric Surgery Program



Research Group

Souheil Adra, MD
 Robert Andrews, MD*
 Chris Awtrey, MD
 George Blackburn, MD, PhD
 Caroline Cao, PhD
 Charity Celeste, MD
 Amine Chellali, PhD
 Suvranu De, PhD
 David Fobert
 Abe Frech, MD
 Yusef Kudsi, MD
 Michael McBride, RN
 Jaisa Olasky, MD
 Caroline Park, MD
 Ganesh Sankaranarayanan, PhD
 Benjamin Schneider, MD
 Steven Schwaitzberg, MD
 Robert Sung, MD
 Darren Tavernelli, RN
 Linda Trainor, RN
 Hussna Wakily, MD
 Christina Wee, MD, MPH

*Through August 2013

Research Focus

My education-based research has established a technical skills laboratory validating new teaching tools and instituting curriculums for medical students, residents and surgeons in practice. Using group video trainers, we demonstrated for the first time in Surgery that intense skills training improved operative performance. Computer trainers which provided immediate feedback further improved trainees' ability to perform a laparoscopic cholecystectomy. Other simulators included novel models for laparoscopic hernia repair, common bile duct exploration, and ultrasound-guided breast biopsy. Studies demonstrated error with sleep deprivation among post-call surgical residents. Furthermore, programs for medical students suggest the benefit from early exposure to simulation.

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

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

Virtual Basic Laparoscopic Skills Trainer (VBLaST) is a virtual reality trainer that replicates the FLS tasks for skills training. In this project, a specialized interface with haptic feedback was to replicate the FLS box for the VBLaST. Validation studies are conducted at the Carl J. Shapiro Simulation and Skills Center.

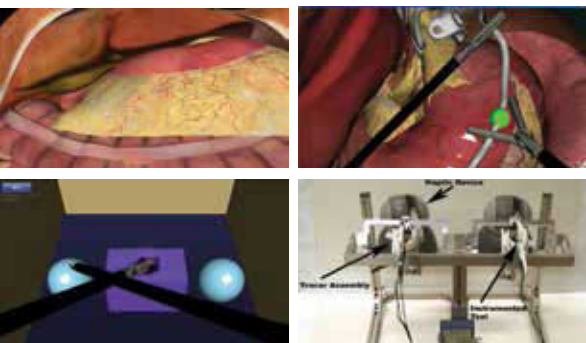
Virtual Natural Orifice Transluminal Endoscopic Surgery (VR-NOTES) simulator provides a training and testing platform for both transgastric and transvaginal NOTES cholecystectomy. Currently the VR-NOTES simulator has virtual organ models through which a fly-through simulation can be done along the predetermined path for a transgastric approach. A haptic interface with a realistic flexible endoscope is being developed to interact with the VR-NOTES simulator.

Generation (Gen) 2 cognitive simulator seeks to create a Star Trek hallodeck experience by creating an environment as close to real surgery as possible, including the operating room environment, devices, avatars, and room noises, making the training very realistic.

Virtual Electrosurgery Trainer (VEST) is an ongoing project that includes basic modules to teach ways to avoid patient injury during an electrosurgery procedure. The VEST can simulate insulation failure, capacitive and direct coupling. An interface with two ports for trocar and tool placement whose motion are captured by optical and gyroscope sensors was built to interface the VEST for testing.

Bariatric surgery

My research also focuses on the clinical outcomes. In collaboration with Christina Wee, MD, MPH (Department of Medicine, BIDMC) we have a large database from which we have published this year on the following topics: expectations for weight loss and willingness to accept risk, quality of life among obese patients, obesity-related stigmata and functional status, patient factors associated with undergoing laparoscopic adjustable gastric banding vs Roux-en-Y gastric bypass, and high-risk alcohol use after weight loss surgery. This research is funded by the NIH.



▲ Clockwise, from top left: VR-NOTES, Gen 2 cognitive simulator, VBLaST, and VEST

Accomplishments

- President-Elect; Association for Surgical Education (ASE)
- Chair; Public Policy and Advocacy Committee, Society for Surgery of the Alimentary Tract (SSAT)
- Society of American Gastrointestinal and Endoscopic Surgeons (SAGES): Board of Governors; Chair; Quality, Outcomes and Safety Committee; Chair; FUSE Task Force
- Chair; Patient Safety Committee, American Society of Metabolic and Bariatric Surgery (ASMBS)
- Program Chair; 2012 Annual Meeting for the SAGES Surgical Spring Week, San Diego, CA
- Co-Chair; ACS-ASMBS Committee on Metabolic and Bariatric Surgery. Established national accreditation guidelines for bariatric surgery centers
- Attended; HSPH, Leadership Development for Physicians in Academic Health Centers

Invited Presentations

Safe use of surgical energy, BIDMC Combined Safety Grand Rounds

Simulation: Perfect practice makes perfect, BIDMC Surgery Grand Rounds

Obesity surgery: Everything the internist and general surgeon needs to know, Grand Rounds, Cambridge Health Alliance, Cambridge, MA

Surgery for obesity: Facts, risks and results, Harvard Medical School BIDMC Mini-Medical School Lecture Series

Teaching, Training, and Education

- Co-Director, Carl J. Shapiro Simulation and Skills Center, BIDMC
- Co-Director; ASE/ACS Skills-based Simulation Curriculum for Medical School Years 1-3; Released national curriculum for medical students using educational theory and assessment metrics
- HMS Longitudinal Bariatric Experience
- Chair; SAGES (FUSE) — National program to teach the proper, safe use of devices in the OR
- Site Director; OR CRICO Team Training with Simulation

Simulation: Challenges of training surgical residents in the new millennium, CRICO - Harvard Medical School, Boston

Bariatric surgery, roundtable on biomedical engineering materials and applications (BEMA): Addressing obesity-medical device therapies, gender issues, The National Academies, Washington, DC

Surgical treatment of obesity, Update in Internal Medicine, 2013, Boston, MA

Early detection, management and prevention of bariatric surgery complications, 15th WFSA World Congress of Anesthesiology, Buenos Aires, Argentina

First report of the ACS Bariatric Surgery Center Network: Laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and gastric bypass, 4th Annual International Consensus Summit for Sleeve Gastrectomy, New York, NY

Recognition and Awards

- Best Doctors in America; Top Doctors, *Boston Magazine*, *US News & World Report*; America's Top Surgeons, Consumers Research Council of America
- SAGES Excellence in Medical Leadership Award

Editorial Roles

- Editorial Board: *Surgical Endoscopy*, *Bariatric Times*, and *UpToDate*; and ad hoc reviewer: *New England Journal of Medicine*, *Journal of the American College of Surgeons*, *Obesity Surgery*, *Annals of Surgery*, *Simulation in Healthcare*, *Surgical Innovation*, *JAMA*

Selected Research Support

Understanding how patients value bariatric surgery; NIH, 2007-2012; PI: Christina Wee, MD, MPH

Development and validation of a virtual basic laparoscopic skill trainer (VBLAST); NIH, 2009-2013; PI: Daniel Jones, MD, MS

Developing physics-based virtual simulation technology for natural orifice transluminal endoscopic surgery; NIH, 2009-2013; PI: Daniel Jones, MD, MS

Development and validation of a virtual electrosurgical skill trainer (VEST); NIH, 2011-2015; PI: Daniel Jones, MD, MS

Physically realistic virtual surgery; NIH, 2011-2015; PI: Daniel Jones, MD, MS

Selected Publications

Jones DB. Master Techniques in Surgery—Hernia. Philadelphia; Lippincott Williams & Wilkins, 2013.

Wee CC, Hamel MB, Apovian CM, Blackburn G, Bolcic-Janovic D, Colten M, Hess DT, Huskey KW, Marcantonio ER, Schneider BE, Jones DB. Expectations for weight loss and willingness to accept risk among patients seeking weight loss surgery. *JAMA Surg*;148(3):264-271, 2013.

Mechanick JL, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, Heinberg LR, Adams T, Shikora S, Dixon D, Brethauer B. AACE/TOS/ASMBS Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient – 2013 update; co-sponsored by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery. *SOARD* 9:159-191, 2013. (Concurrently published in *Obesity* 2013;21:S1-27, and *Endocrine Practice* 2013)

Tichansky DS, Morton J, Jones DB. The SAGES Manual of Quality, Outcomes and Patient Safety, Springer, New York, 2012.

Feldman L, Fuchshuber P, Jones DB. The SAGES Manual on Fundamental Use of Surgical Energy (FUSE), Springer, New York, 2012.

A complete list of publications begins on page 17

Tara S. Kent, MD, MS

Assistant Professor of Surgery



Research Focus

Clinical outcomes research in pancreaticobiliary surgery

Our group's work focuses on outcomes research in high-acuity pancreaticobiliary surgery. Fueled by a robust clinical practice that focuses on treatment of pancreatic malignancies, cystic lesions, pancreatitis, and complex biliary conditions in a multidisciplinary setting, we perform over 200 major pancreaticobiliary operations per year.

A prospective database of over 4,000 operations and 750 pancreatic resections has been developed and maintained from this practice, providing the substrate for our investigations. Areas of emphasis are 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. We have also explored the impact of surgical complications associated with these operations. We are now also embarking on quality of life analyses for these disease processes. We are currently building a Quality Scorecard for Pancreatic Surgery that reflects the Institute of Medicine health care quality domains.

Additional recent efforts have included investigations into the reasons for readmission after pancreatectomy, with a goal of better understanding causes for readmission in this patient population, as well as of decreasing unnecessary readmissions.

Other outcomes studies over the last year have involved the investigation of the relationship between pancreatectomy for cancer, complications, and initiation/completion of adjuvant therapy, and the analysis of outcomes for patients undergoing palliative surgery in the setting of pancreatic cancer. Work is also ongoing to develop, employ, and evaluate a patient-education tool to provide additional and improved information to patients upon discharge after pancreatectomy. The effectiveness of this tool will be evaluated via patient-satisfaction surveys and readmission rate/cause analysis.

Patient education improvement/research

With the support of the Eleanor and Miles Shore Fellowship, and working with Charity Glass, MD, MPP, one of our surgical residents, we completed a pilot study of patients' perceptions of discharge planning adequacy. Based on those results, work is ongoing with Dr. Glass and Ammara Abbasi, MD, our current research fellow, to develop, employ, and now evaluate a patient-education tool to provide additional and improved information to patients upon discharge after pancreatectomy. The effectiveness of this tool will be evaluated via patient-satisfaction surveys and readmission rate/cause analysis.

Surgical education research

Our growing surgical education research effort includes the study of factors influencing in-training exam scores; the impact of duty hour restrictions on case volume and experience. We have also initiated a prospective study of the impact of an e-mail teaching tips/reference program on the residents' perception of their role as teachers. In collaboration with colleagues in the international HPB community, I have undertaken a curriculum needs assessment for HPB fellows.

Accomplishments 2012-2013

- Invited moderator, AHPBA symposium on “Building your HPB Practice,” 2012
- Invited moderator, SSAT Public Policy and Advocacy Panel, “Will there be a general surgeon when you need one?,” 2012
- Program Director, BIDMC General Surgery Residency, 2012
- Invited speaker, “Teaching residents to teach in the operating room,” Harvard Medical School Resident-as-Teacher Symposium, 2013
- Recipient of Harold Bengloff Award for Humanism in Teaching, 2013

Teaching, Training, and Education

- I became the Program Director of the General Surgery Residency in September 2012, administering the training of our 45 categorical and 15 preliminary trainees
- I currently have one resident research fellow, Ammara Abbasi, MD, who is supported by the Eleanor and Miles Shore Fellowship
- Other team members include: Charity Glass, MD, MPP, Laura Mazer, MD, MPH, Bharath Nath, MD, PhD, and Lorenzo Anez-Bustillos, MD
- Through my involvement with the AHPBA Education and Training Committee, I have developed an online curriculum for HPB fellows

Abstracts, Posters, and Exhibits

Gondek SP, Glass CC, Vollmer Jr. CM, Callery MP, Kent TS. Readmission following pancreatectomy: What can we do better? Best Oral Session, International Hepato-Pancreato-Biliary Association 10th World Congress, Paris, France, July 2012

Miller, BC, Christein JC, Callery MP, Drebin JA, Kent TS, Pratt WB, Vollmer CM. Assessing the impact of fistulas after pancreaticoduodenectomy using the postoperative morbidity index. Oral presentation at the American Hepato-Pancreato-Biliary Association Annual Meeting, Miami, FL, February 2013

Chau Z, West JK, Zhou Z, McDade TP, Smith JK, Ng SC, Kent TS, Callery MP, Moser AJ, Tseng JF. Rankings vs reality for pancreatic cancer surgery: A real world comparison. Oral presentation, American Hepato-Pancreato-Biliary Association Annual Meeting, Miami, FL, February 2013

Nath B, Tizio S, Mazer L, Kent TS, Moser AJ, Johnson SR, Hanto DW. Elevated risk of bile leak following hepatic resection among patients exposed to bevacizumab. Oral presentation, American Hepato-Pancreato-Biliary Association Annual Meeting, Miami, FL, February 2013

Mazer LM, Vollmer CM, Callery MP, Kent TS. Predictors of initiation and completion of adjuvant therapy after surgical resection for pancreatic adenocarcinoma. Oral presentation, American Hepato-Pancreato-Biliary Association Annual Meeting, Miami, FL, February 2013

Kamine T, Lagisetty K, Gondek S, Kent TS. Trends in national surgery resident case load: 1999-2013. Poster Presentation, Harvard Surgery Resident Research Day, May 2013

Selected Publications

Vollmer CM, Sanchez NJ, Gondek S, McAuliffe J, Kent TS, Christein JD, Callery MP; The Pancreatic Surgery Mortality Study Group. A root-cause analysis of mortality following major pancreatectomy. *J Gastrointest Surg* 2012;16:89-102.

Kent TS, Sachs TE, Callery MP, Vollmer, Jr. CM. The burden of infections for elective pancreatic resections. *Surgery* 2013;153:86-94.

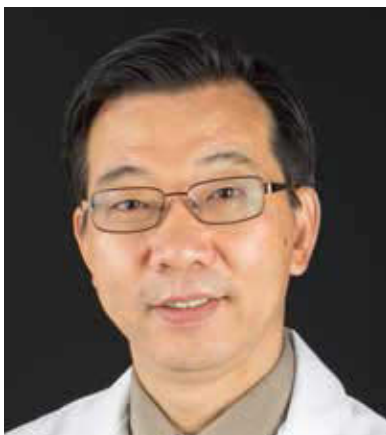
Lewis R, Drebin JA, Callery MP, Fraker D, Kent TS, Gates J, Vollmer, Jr CM. A contemporary analysis of survival for pancreatic ductal adenocarcinoma. *HPB* 2013;15:49-60.

Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer, Jr. CM. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 2013;216:1-14.

Kalish BT, Vollmer CM, Kent TS, Nealon WH, Tseng JF, Callery MP. Quality assessment in pancreatic surgery: What might tomorrow require? *J Gastrointest Surg* 2013;17:86-93.

Sachs TE, Pratt WB, Kent TS, Callery MP, Vollmer CM Jr. The pancreaticojejunal anastomotic stent: Friend or foe? *Surgery* 2013;153:651-662.

A complete list of publications begins on page 17



Jin-Rong Zhou, PhD

Associate Professor of Surgery

Director, Nutrition/Metabolism Laboratory

Research Group

Hamid Abdolmaleky, MD

Mohamad-Reza Eskandari, MD

Yi Gong, PhD

Research Focus

The long-term goal of my research is to define efficacious and safe nutritional and bioactive regimens for the prevention and therapy of cancer. My laboratory has focused on evaluating the efficacy and safety of several bioactive natural compounds on the growth, progression, and metastasis of certain types of cancer in both *in vitro* and *in vivo* model systems, and investigating the mechanisms of action of these bioactive components. Since cancer stem cells are recognized to be responsible for drug resistance and metastasis of cancer, our special effort has been in identifying bioactive components for targeting cancer stem cells. In the past two years, my laboratory has focused on the following projects.

Ampelopsin (AMP) as potent anti-metastasis agent against prostate cancer by targeting CXCR4

CXCR4 is suggested to be a critical factor in the growth, invasion, and metastasis of cancer, and a potential molecular target for cancer therapy. Bioactive compounds that downregulate CXCR4 expression and function may serve as candidate anti-cancer agents. Our preliminary studies found that AMP inhibited the growth of prostate cancer and downregulated the gene expression and protein level of CXCR4. AMP is a natural flavonoid in the Chinese herb *Ampelopsis grossedentata*. We further evaluated the efficacy and safety of AMP supplementation on the growth and metastasis of PC-3 human prostate tumors in an orthotopic prostate tumor animal model. AMP significantly inhibited the growth and, to a more extent, the metastasis of PC-3 tumors associated with downregulation of CXCR4 protein levels in tumors. On the other hand, AMP at efficacious doses minimally affected food intake or body weight, suggesting its limited adverse effect.

Tanshinones as potent anti-cancer agents by targeting Aurora A kinase

Our preliminary screening bioassays have identified tanshinones, which include cryptotanshinone (CT), tanshinone I (T1) and tanshinone IIA (T2A), with potent anti-proliferating activities against several types of cancer cell lines. Tanshinones are a group of compounds present in the Chinese herb Danshen (*Salvia miltiorrhiza Bunge*), one of the most commonly used herbs in traditional Chinese medical practice. Further investigations showed that T1 had the most potent anti-cancer activity and inhibited the growth of prostate tumors and lung tumors in animal models, with minimal side effects. Further mechanism studies demonstrated that downregulation of Aurora A kinase was an important mechanism shared by all three tanshinones, but each of these compounds had other distinguished molecular target(s). For example, CT, but not T1 or T2A, upregulates Sirt1 gene expression and function.

Tanshinones as potent anti-cancer stem cell agents

In addition to the anti-cancer growth activities, tanshinones are also found to have potent activities in inhibiting the self-renewal of cancer stem cells from a variety of cancer types, such as breast, prostate, lung, and pancreatic cancers. Among the panel of anti-cancer natural compounds, tanshinones, especially T1 and T2A, are the most potent ones in inhibiting cancer stem cells. These promising findings, together with the efficacious and safe nature of tanshinones, warrant further investigation for developing tanshinones as promising anti-cancer agents.

Accomplishments 2012-2013

Administrative Leadership

Co-Chair, Diet and Cancer: Translational, Clinical and Survivorship; Experimental Biology Annual Meeting, April 2012, San Diego, CA

Grant Review Activities

- Review panel, National Science Foundation of China, 2012
- Research grant review panel, Singapore National Medical Research Council, 2012
- Ad hoc member, Chemo/Dietary Prevention (CDP) Study Section, Center for Scientific Review/NIH, 2012
- Ad hoc member, Cancer Therapeutics AREA Grant Review Panel, Center for Scientific Review/NIH, 2012
- Ad hoc member, Provocative Questions SEP, Center for Scientific Review/NIH, 2012
- Review panel, The James and Esther King Biomedical Research Program and the Bankhead-Coley Cancer Research Program, Florida Department of Public Health, 2012
- Ad hoc member, Cancer Screening and Biomarker Omnibus SEP, NCI/NIH, 2013
- Ad hoc member, Oncological Sciences AREA Grant Application Study Section, Center for Scientific Review/NIH, 2013

Editorial Services

- Ad hoc manuscript reviewer: 23 scientific journals, including *Lancet Oncology Review*
- Editor-in-Chief: *Nutrition and Metabolic Insights* (2012-present), *Journal of Health Sciences* (2013-present)

Invited Presentations

- Pharmacological activities and mechanisms of tanshinones as anti-cancer agents, Association of Chinese Medicinal Pharmacology Conference, Nanjing, China, 2012
- Targeting metabolic syndrome by nutritional manipulation for cancer prevention, 11th China Nutrition Science Conference and International DRIs Summit, Hangzhou, China, 2013
- Zhou J-R, Gong Y, Abdolmaleky HM, Blackburn GL. Tanshinones inhibit androgen-dependent prostate cancer via downregulation of Aurora A and suppression of androgen-receptor signaling. Experimental Biology Annual Meeting, San Diego, CA, April 2012 (oral presentation)
- Gong Y, Zhou J-R. Tea compounds inhibit prostate cancer stem cells (PCSC) via downregulation of Bmi1. Experimental Biology Annual Meeting, Boston, MA, 2013 (poster)

Teaching, Training, and Education

I have been training post-doctoral fellows on a daily basis for the past two years. In addition, I gave two educational lectures — one on nutrition and cancer and the other on nutrition and diabetes — in the Non-Communicable Diseases in Developing Countries Course held in the International Centre for Genetics Engineering and Biotechnology, University of Cape Town, South Africa, in October 2012. I also gave an educational presentation entitled “Maternal nutritional status and disease of offspring: Scientific evidence and underlying mechanisms” in the West Lake Frontiers in Nutrition Research Training Program in Hangzhou, China, in May 2013.

Selected Research Support

Tanshinones for prevention of bladder cancer progression; NIH, 2011-2013; PI: Jin-Rong Zhou, PhD

Targeting prostate cancer stem cells to delay prostate cancer progression; NIH, 2011-2013, PI: Jin-Rong Zhou, PhD

Selected Publications

Zhang YW, Yan DL, Wang W, Zhao HW, Lu X, Wu JZ, Zhou JR. Knockdown of insulin-like growth factor I receptor inhibits the growth and enhances chemo-sensitivity of liver cancer cells. *Curr Cancer Drug Targets* 2013;12(1):74-84.

Gong Y, Li Y, Abdolmaleky HM, Li L, Zhou J-R. Tanshinones inhibit the growth of breast cancer cells through epigenetic modification of Aurora A expression and function. *PLoS ONE* 2012;7(4):e33656.

Feng N, Gong Y, Li L, Abdolmaleky HM, Zhou J-R. Flavonoid ampelopsin inhibits the growth and metastasis of prostate cancer *in vitro* and in mice. *PLoS ONE* 2012;7(6):e38802.

Li Y, Gong Y, Li L, Abdolmaleky HM, Zhou J-R. Bioactive tanshinone I inhibits the growth of lung cancer via downregulation of Aurora A function. *Mol Carcinogenesis* 2013;52:535-43.

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Jeffrey Arle, MD, PhD

Associate Professor of Surgery
Associate Chief, Neurosurgery



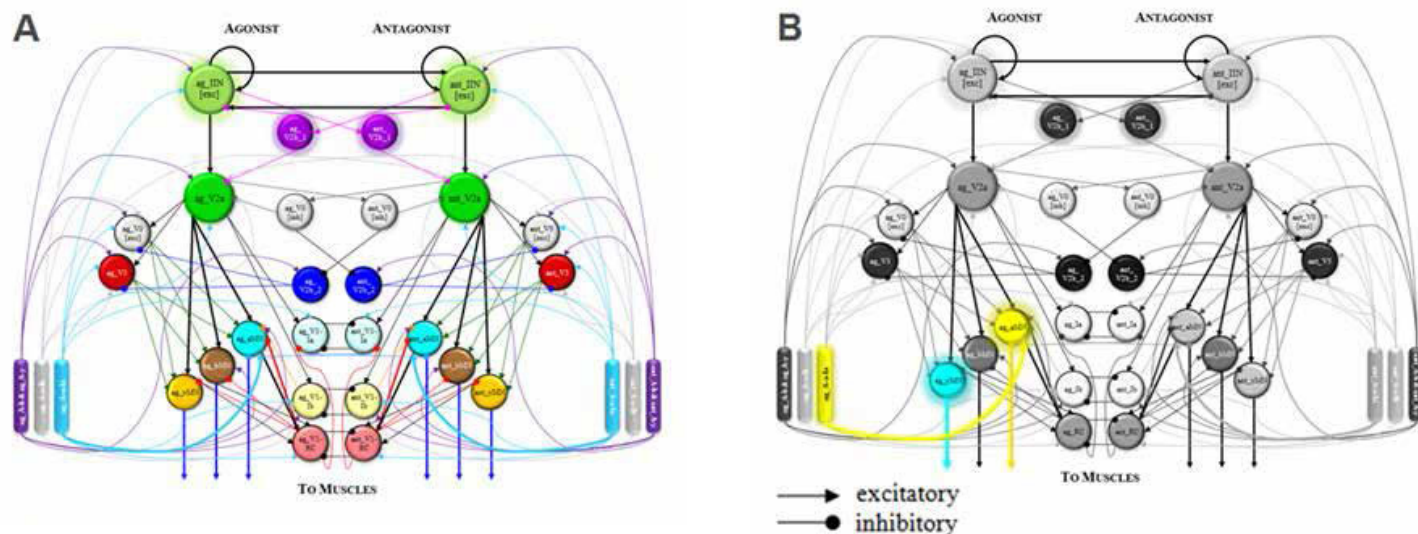
Research Group

Kristen Carlson
LZ Mei, MS
Jay Shils, PhD

Research Focus

Our research efforts have focused on computational modeling of neural stimulation and circuitry related to devices and therapies used in neuromodulation. These therapies include deep brain stimulation (DBS), spinal cord stimulation (SCS), vagus nerve stimulation (VNS), motor cortex stimulation (MCS), and other related aspects of neural processing. Modeling has included circuitry models of the basal ganglia in Parkinson's disease and the DBS electrode in a discrete solution, M1 and S1 regions of cortex with cortico-thalamic processing, three-dimensional modeling of the activating function and fibers of passage, and patterns of stimulation and power in tremor control.

Over the past year, we have developed and refined our detailed model of the human spinal cord circuitry, involving over 360,000 individual neurons and over 60 million individual synapses in exploring the effects of scar on the electrical environment in spinal cord stimulation. Our paper has been accepted recently for publication in *Neuromodulation*. We continue to examine the fundamental mechanisms of neuromodulation therapies, an area of rapidly developing technology and innovation. This work has been generously funded by the Sydney Family Foundation, and recently with grants from Cyberonics and Boston Scientific.



▲ Figure from the recently submitted manuscript "Mechanism of Therapeutic Benefit with Dorsal Column Stimulation Using a Computational Model of the Spinal Cord" (see "Selected Publications") shows a close-up view of the motor division of the main circuitry in one half of the spinal cord.

Accomplishments 2012-2013

Organizational and Academic Work

- Appointed to the North American Neuromodulation Society (NANS) Policy and Advocacy Committee
- Appointed to the NANS Scientific Program Committee
- Nominated for the NANS Board of Directors (vote upcoming)
- Abstract Review Committee for the International Neuromodulation Society (INS) meeting in Berlin, 2013
- Appointed member of Stroke Steering Committee at Mount Auburn Hospital, Cambridge, MA
- Continued work as Associate Editor at *Neurosurgery*
- Continued as a frequent reviewer at *Neuromodulation*

Invited Presentations and Meetings

- World Society for Stereotactic and Functional Neurosurgery (WSSFN), moderating session, Tokyo, 2013
- American Society for Neurophysiological Monitoring (ASNM), moderating two sessions, Boston, 2013
- Spinal cord stimulation therapy and the circuitry of the spinal cord, Invited Talk, ASNM, Boston, 2013
- The IOM interface in functional neurosurgery: Surgeon, neurophysiologist, and making the most of the relationship, Invited Talk, ASNM, Boston, 2013
- Invited Talk, The decision interface: Surgeon, neurophysiologist, and making the best decisions during surgery, ACNS, Miami, FL, 2013
- Panel member, daylong special program on Innovation and the Neurosurgeon, AANS, New Orleans, LA, 2013
- Invited Talk, Cortical and deep brain stimulation for pain, American Association of Neurological Surgeons (AANS), New Orleans, LA, 2013
- Neurostimulation for facial pain, AANS-Pain Biennial Joint Section meeting, Invited Talk, New Orleans, LA 2013

Research

- Letter of Intent submitted for three-year project to develop novel treatment device for spinal cord injury, The Nielsen Foundation
- Letter of Intent submitted for three-year project to develop novel treatment device for spinal cord injury, Wings For Life

Patents

- Method and Apparatus for Electrical Stimulation of the Nervous System

Selected Research Support

- Modeling of the vagus nerve stimulating electrode and related seizure control circuitry; Cyberonics, 2013-present; PI: Jeffrey Arle, MD, PhD
- Modeling of related circuitry and high frequency stimulation with dorsal column stimulators; Boston Scientific, 2013-present; PI: Jeffrey Arle, MD, PhD
- Post-marketing study on the use of the Varilift® device in the cervical spine; Wenzel Spine, 2012-present; PI: Jeffrey Arle, MD, PhD
- Novel expandable percutaneous dorsal column stimulator paddle design and development; Wyss Institute, 2012-present; Co-Investigator: Jeffrey Arle, MD, PhD (PIs: Samuel Kessner, PhD, and Conor Walsh, PhD)
- INNOVATE-Heart Failure (HF) project to study the use of a novel vagus nerve-stimulating device to treat HF; BioControl Medical, 2013-present; Co-Investigator: Jeffrey Arle, MD, PhD (PI: Robb Kociol, MD)

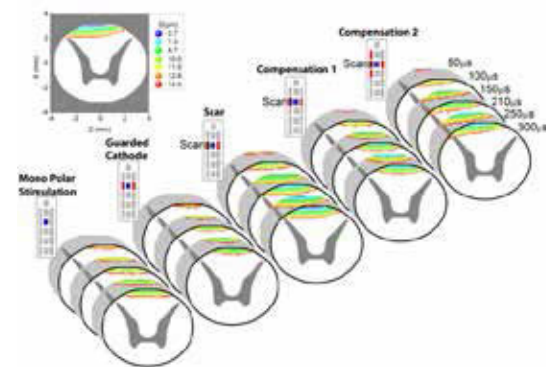
Selected Publications

Arle JE, Carlson KW, Mei L, Shils JL. Modeling effects of scar on patterns of dorsal column stimulation. *Neuromodulation*, in press.

Arle JE, Carlson KW, Mei L, Iftimia N, Shils JL. Mechanism of therapeutic benefit with dorsal column stimulation using a computational model of the spinal cord. *Neuromodulation*, in review.

Arle J, Shils JL, Malik WQ. Localized intraspinal microstimulation and recording for targeted peripheral muscle excitation. Invited paper, Institute of Electrical and Electronics Engineers.

Jang S, Gill J, Arle J, Simopoulos T. Case series on variable presentation of ligamentum flavum stimulation following percutaneous cylindrical spinal cord stimulator lead implants. *Neuromodulation*, in review.



▲ Figure from the paper "Modeling Effects of Scar on Patterns of Dorsal Column Stimulation" (see "Selected Publications") showing differential effects of scar and compensatory stimulation paradigms on the spinal cord in spinal cord stimulation.

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Jorge G. Arroyo, MD, MPH

Associate Professor of Ophthalmology



Research Group

Kyle Kovacs
Mark Kuperwaser, MD
Kyle V. Marra
Carole Uminski

Research Focus

Our lab's recent research has investigated the efficacy and outcome of novel surgical techniques, the intraocular cytokine levels of eyes with various ocular conditions, and novel risk factors for age-related macular degeneration (AMD).

Surgical techniques

Modern ophthalmic surgical technology now allows for the combination of cataract surgery with other vitreoretinal surgeries, such as epiretinal membrane (ERM) peeling. As one of the first ophthalmology groups to routinely perform combination surgery in the area, we conducted a retrospective case series of 81 eyes comparing the visual and anatomical outcomes between combined ERM peeling and cataract surgery versus ERM peeling alone. Our data suggested that the outcomes after combination cataract and vitreoretinal surgery were similar to those after vitreoretinal surgery alone.

As one of the leaders in the use of endoscopy in vitreoretinal surgery, we have submitted three manuscripts/book chapters providing systematic reviews of the indications and limitations for the use of an endoscope in surgical procedures for various ocular conditions. These manuscripts describe the role of endoscopy in endocyclophotocoagulation for glaucoma, cyclitic membrane peeling in hypotony, retinal detachments, intraocular foreign bodies, severe endophthalmitis, and pediatric traumatic vitreoretinal surgery.

We are currently comparing the efficacy of a novel procedure known as endocyclophotocoagulation (ECP) against the current "standard of care" for the treatment of acute cases of neovascular glaucoma (NVG). This retrospective case series of 54 eyes found that ECP significantly lowered intraocular pressure while exhibiting similar visual outcomes when compared to treatments that current literature defines as the "standard care" for NVG.

Intraocular cytokine levels

We ran a multiplex assay of 35 cytokines on vitreous fluid excised during vitreoretinal surgery. With this large dataset of patients' clinical information and pro-inflammatory and pro-angiogenic factors, we have conducted numerous statistical analyses to test various hypotheses addressing the trends in these cytokine levels.

We have found elevated cytokines in the vitreous of patients who are one-year post cataract surgery. This finding might help explain the development of cystoid macular edema after cataract surgery (Irvine-Gass syndrome).

Risk factors for age-related macular degeneration (AMD)

Using the large nationally representative datasets from the National Health and Nutrition Examination Survey, we ran multivariate models to confirm and discover risk factors for AMD.

AMD is the leading cause of irreversible vision loss in developed nations. With limited treatments, prevention remains the best option for reducing the impact of this debilitating disease. Using a population-based, cross-sectional study, we are the first to identify a significant relationship between periodontal disease (PD) and the risk for AMD. This risk was especially elevated in subjects under 60 years of age, increasing their risk of having any AMD by a factor of two.

Factors such as chronic infection and inflammation have been proposed to play a key role behind the progression of AMD. Since C-reactive protein (CRP) is a well-studied inflammatory marker that is commonly used to measure levels of systemic inflammation, we ran multivariate regression models on data from the NHANES to find a significant independent association between CRP and AMD.

Accomplishments 2012-2013

Presentations

Our research team attended the annual meeting for the Association for Research in Vision and Ophthalmology, where we presented our discovery of PD as a novel risk factor for AMD and our assessment of the use of ECP for treating NVG. I have continued routinely presenting at the Retina and Macula societies and in May was the moderator for the New England Ophthalmology Society's retina symposium. Later this year, I will once again be moderator for an American Academy of Ophthalmology symposium discussing the events and learning points derived from our experience with the Boston Marathon bombings.

Ongoing Projects

We are collaborating with MRI researchers on a study that, if successful, will be the first work to quantify blood flow changes in the choroid (the retina's underlying tissue for blood and nutrient delivery) at various stages of AMD. We expect to compare a total of 21 eyes among three groups: controls, intermediate (dry) AMD, and neovascular (wet) AMD. Findings from this study may aid in understanding links between choroidal blood flow and thickness, and the stages of AMD.

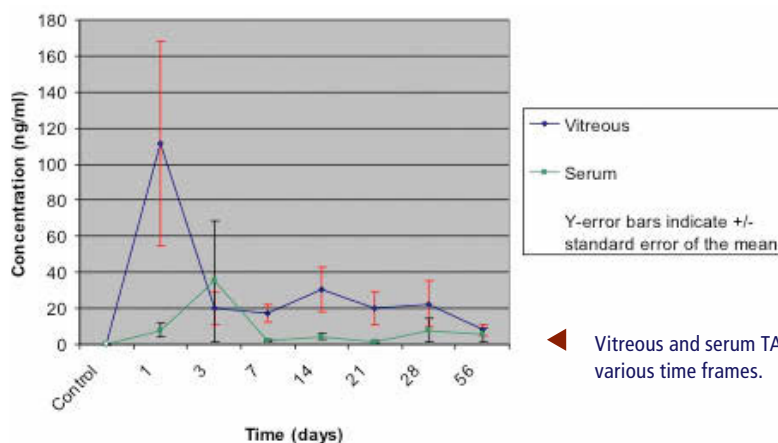
Another study seeks to test the hypothesis that patients with the Apolipoprotein A1-Milano mutation are protected from developing drusen and dry macular degeneration. The data collected from these subjects included: 1) a complete eye examination; 2) digital fundus photographs; 3) fluorescein angiogram in patients with evidence of macular degeneration; and 4) a blood sample for a cholesterol panel. This study seeks to answer the question as to whether or not the Apolipoprotein A1-Milano mutation is protective for the development of macular degeneration. The results of this study may help support future studies using synthesized Apolipoprotein A1-Milano in patients with severe dry macular degeneration.

Teaching, Training, and Education

I have trained rotating residents, fellows, and summer medical school students in clinical, surgical, and research settings for 16 years. After clinic, we discuss interesting and/or classic cases of the day, and students leverage the understanding gained from these small-group discussions to publish in peer-reviewed journals. For instance, we submitted an editorial on our experience with various subconjunctival anesthesia prior to intravitreal injections and submitted a case report discussing an adverse event following an intravitreal injection of the enzyme ocriplasmin.

In addition, I offer a two-year opportunity to serve as a Clinical Assistant and Research Coordinator. Kyle Marra, a Presidential Scholar who graduated from Boston College in 2012, is currently fulfilling this role.

Triamcinolone Acetonide Concentrations



◀ Vitreous and serum TA concentrations at various time frames.

Selected Publications

Kovacs KD, Wagley S, Quirk MT, Ceron OM, Silva PS, Singh RJ, Gukasyan HJ, Arroyo JG. Pharmacokinetic study of vitreous and serum concentrations of triamcinolone acetonide after posterior sub-tenon's injection. *Am J Ophthalmol* 2012;153:939-948.

Yiu G, Marra KV, Wagley S, Krishnan S, Sandhu H, Kovacs K, Kuperwaser M, Arroyo JG. Surgical outcomes after epiretinal membrane peeling combined with phacoemulsification and intraocular lens implantation versus membrane peeling alone. *Br J Ophthalmol* 2013;97(9):1197-201.

Marra KV, Yanekawa Y, Papakostas T, Arroyo JG. Indications and techniques of endoscope-assisted vitrectomy. *JOVR* 2013;8(3):1-9.

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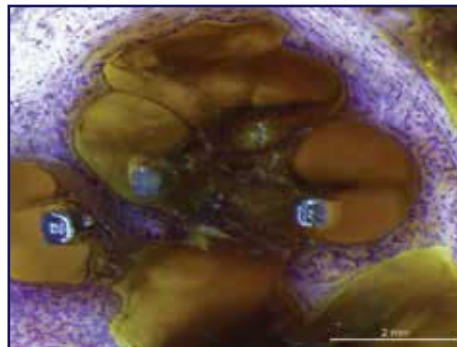
Research Focus

My major research interests are centered on the treatment and prevention of hearing loss. I am in the process of completing a PhD with a research focus on oxidative stress as related to age-related hearing loss (presbycusis) and antioxidant therapies as a potential preventive therapy for prevention or treatment of hearing loss in a mouse model. I will be continuing with this research, optimizing combination therapy and evaluating novel drug-delivery techniques for the prevention of age-related hearing loss and other forms of acquired hearing loss.

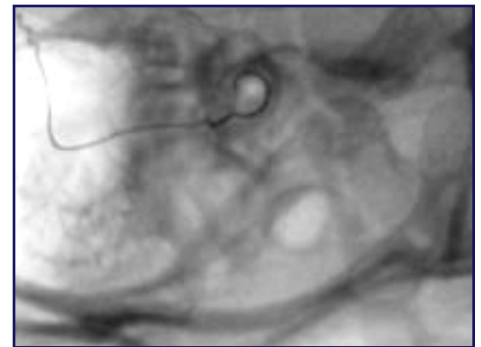
In addition to basic science research, I have significant interests in clinical studies. In particular, I have an interest in outcomes research in skull base surgery and modified surgical techniques to improve operative outcomes in skull base surgery. I am passionate about cochlear implantation and have performed clinical outcomes research in cochlear implantation related to complicated cases (e.g. malformed cochlea, revision techniques).



▲ Figure 1: Histological section of the cochlea demonstrating cochlear implant electrode within the scala tympani of the cochlea. Image from Roland JT Jr, Heman-Ackah SE. Human temporal bone studies with a modiolar research array (MRA)



▲ Figure 2A: Cochlear implantation in a patient with cochlear malformation with appropriate contouring of the cochlear implant electrode without internal auditory canal insertion. With keen understanding of the surgical anatomy and utilizing appropriate techniques, internal auditory canal insertion can be prevented or safely corrected if encountered. From Heman-Ackah SE, Friedmann DR, Cosetti MK, Waltzman SB, Roland JT Jr. Techniques for revision cochlear implantation following internal auditory canal insertion.



▲ Figure 2B: Internal auditory canal insertion following attempted cochlear implantation in a patient with cochlear malformation. From Heman-Ackah SE, Friedmann DR, Cosetti MK, Waltzman SB, Roland JT Jr. Techniques for revision cochlear implantation following internal auditory canal insertion.

Accomplishments 2012-2013

Since joining Beth Israel Deaconess Medical Center in 2012, I was appointed as the Medical Director of Otology, Neurotology, and Audiology and have worked to revolutionize these services within the hospital system. This has included hiring two new audiologists — Lydia Colón, AuD, and Lydia Gregoret, PhD, AuD — who have an interest and expertise in cochlear implant programming, auditory rehabilitation, and related research. In September 2013, I launched the BIDMC Cochlear Implant Program, which focuses on auditory rehabilitation in the adult population. Together with the other members of the team, I aspire to build a clinical research center related to cochlear implantation and related technologies.

Teaching, Training, and Education

Teaching and mentoring are among my passions. I have the opportunity to work with residents within the operating theatre to provide training and instruction in otologic operative technique. Additionally I interact with residents on the wards and in the emergency care of patients with otologic and otolaryngologic disorders. I am passionate about my role as mentor and always welcome the opportunity to foster students' interests in otology and otolaryngology. I mentor students and residents from high school through fellowship level at institutions throughout the United States and abroad.

In addition to individualized training and mentorship, I participate in didactic education. I have participated in teaching the physical examination of the head and neck to pre-clinical Harvard Medical School students. I have also presented Grand Rounds for the Department of Surgery and for various care groups.

Abstract, Posters, and Exhibits

Heman-Ackah SE, Gupta S, Heman-Ackah SM, Cosetti MK, Golfinos JG, Roland JT Jr. Atypical schwannoma: A 10-year experience. 22nd Annual North American Skull Base Society meeting. Las Vegas, NV, 2012

Heman-Ackah SE, Gupta S, Golfinos JG, Roland JT Jr. Dural sinus thrombosis following translabyrinthine approach acoustic neuroma microsurgery. 115th Annual Triological Society meeting. San Diego, CA, 2012

Heman-Ackah SE, Gupta S, Cosetti MK, Waltzman SB, Roland JT Jr. Revision cochlear implantation from the Nucleus CI-512 to the Nucleus Freedom device: Techniques and cochlear implant performance. 12th International Conference on Cochlear Implants and Other Implantable Auditory Technologies. Baltimore, MD, 2012

Roland JT Jr, Heman-Ackah SE. Human temporal bone studies with a modiolar research array (MRA). 12th International Conference on Cochlear Implants and Other Implantable Auditory Technologies. Baltimore, MD, 2012

Heman-Ackah SE, Cosetti MK, Friedmann DR, Perez R, Waltzman SB, Roland JT Jr. Cochlear implantation in patients with X-linked deafness: Radiographic findings, surgical techniques, and outcomes. 12th International Conference on Cochlear Implants and Other Implantable Auditory Technologies. Baltimore, MD, 2012

Selected Publications

Heman-Ackah SE, Golfinos JG, Roland JT Jr. Management of surgical complications and failures in acoustic neuroma surgery. *Otolaryngol Clin North Am* 2012;45:455-70.

Heman-Ackah SE, Roland JT Jr, Waltzman SB. Cochlear implantation in late childhood and adolescence: Is there such a thing as "too late"? *Expert Rev Med Devices* 2012;9:201-4.

Heman-Ackah SE, Cosetti MK, Gupta S, Golfinos JG, Roland JT Jr. Retrosigmoid approach to cerebellopontine angle tumor resection: Surgical modifications. *Laryngoscope* 2012;122(11):2519-23.

Heman-Ackah SE, Roland JT Jr, Haynes D, Waltzman S. Pediatric cochlear implantation: Candidacy evaluation, medical and surgical considerations and expanding criteria. *Otolaryngol Clin North Am* 2012;45:41-67.

Cosetti MK, Friedmann DR, Zhu BZ, Heman-Ackah SE, Fang Y, Keller RG, Shapiro WH, Roland JT Jr., Waltzman SB. The effects of residual hearing in traditional cochlear implant candidates after implantation with a conventional electrode. *Otol Neurotol* 2013;34(3):516-21.

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Research Group

Alexandra Anastasopoulos, MD
Azra Ashraf, MD
Ian Buchanan, MD
Danielle Chuang
Salih Colakoglu, MD
Daniel Gittings
John Nguyen, MD
Priti Patel, MD
Jason Silvestre, BS
Christina Vargas, MD
Jacob Zhang

Research Focus

Over the last several years, my basic science research has focused on near infrared imaging (NIR) technologies to identify perfusion characteristics of flaps in reconstructive surgery. In collaboration with John V. Frangioni, MD, PhD, we are using two imaging modalities: Fluorescence-Assisted Resection and Exploration (FLARE) system and Spatial Frequency Domain Imaging (SFDI). We have successfully translated this technology from large animal models to first-in-human clinical trials.

In addition, we have an active clinical research group examining outcomes and patient satisfaction after breast cancer and reconstructive surgery. Using a large institutional database at BIDMC, as well as national databases from the ACS-NSQIP, we have been able to explore risk factors that lead to complications. In addition, we have been able to understand the relationships between type of reconstruction and patient satisfaction.

Near infrared imaging systems

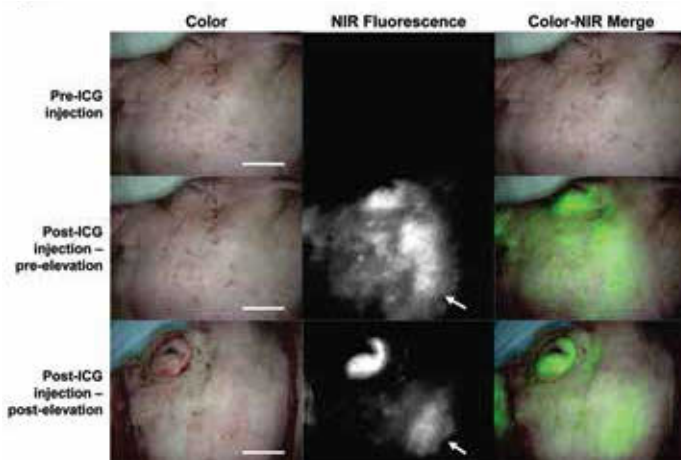
We have examined multiple animal models for flap perfusion. The most recent studies have focused on perfusion of various types of tissue including bone, muscle, fat, and skin. Using the FLARE system, a fluorophore (such as indocyanine green or methylene blue) is used to provide illumination of the underlying vessels through the surface of the skin. We have used this technology to assess composite tissue allografts, such as in face transplantation, in order to provide real-time perfusion characteristics and image guidance during surgery.

The latest technology, SFDI, enables the surgeon to identify perfusion characteristics by targeting tissue constituents (such as hemoglobin). Through the use of this NIR system, we can examine oxygenation of tissue over a large field of view. This can provide a gradient map of the reconstructive flaps for guidance in the operating room and during surgery. We have studied the use of SFDI in multiple animal models, including composite tissue flaps and face transplantation models. Finally, we have successfully translated this technology for use in a clinical trial in patients undergoing microsurgical breast reconstruction.

Clinical outcomes and patient satisfaction in breast reconstruction

At BIDMC, we have a large clinical program that focuses on microsurgical breast reconstruction. The deep inferior epigastric perforator (DIEP) flap is a new technique that isolates the abdominal tissue for reconstruction of the breast while sparing the underlying rectus abdominis muscle. We have performed over 1000 cases at BIDMC and we have an active clinical research team that examines our outcomes, as well as process improvement.

Using an institutional database, we have also been working on comparing the different types of breast reconstruction (implants vs autologous tissue). We have been able to compare the complications and risk factors associated with breast reconstruction. In addition, we have administered patient-satisfaction surveys to examine the relationships between satisfaction and complications. This research extends into larger national databases where we have used the ACS-NSQIP database to assess risk factors in patients undergoing breast cancer surgery and reconstruction.



▲ Imaging of a hemifacial transplant flap model prior to injection (top row), prior to elevation (middle row), and after elevation (bottom row). The imaging system provides surgical anatomy (left column), NIR fluorescence imaging (middle column), and a merged image of the two (right column). The arrow depicts the perforator location within the flap. Scale bar=3 cm.

Accomplishments 2012-2013

I am currently the Acting Chief of the Division of Plastic and Reconstructive Surgery at BIDMC. I serve on multiple national committees at the American Society of Plastic Surgeons (In-Service Examination, Scientific Program and Instructional Course, Health Policy, and Quality and Performance Measurement Committees) and American Association of Plastic Surgeons (Awards and Research and Education Committees).

This year I was appointed the new Editor-in-Chief of the *Journal of Reconstructive Microsurgery*. I serve on the editorial boards of *Annals of Plastic Surgery* and *ePlasty*. I am also an editor of a three-volume textbook on reconstructive surgery, *Encyclopedia of Flaps*.

Presentations

- Near infrared imaging for intra-operative assessment of perfusion in vascularized bone flaps; Massachusetts Chapter, American College of Surgeons and Academic Surgical Congress
- Assessment of perfusion in a partial face transplantation model with a near infrared imaging system; Massachusetts Chapter, American College of Surgeons, Academic Surgical Congress, and Academic Surgical Congress
- Utilization of spatial frequency domain imaging to monitor composite facial transplantation with microsurgical vascular anastomosis; New England Society of Plastic and Reconstructive Surgeons, American Society for Reconstructive Microsurgery, and World Society of Reconstructive Microsurgery
- A novel pilot study using spatial frequency domain imaging and gradient mapping to assess oxygenation of perforator flaps during breast reconstructive surgery; Northeastern Society of Plastic Surgeons
- Fat necrosis in autologous abdominal based breast reconstruction: A systematic review; Northeastern Society of Plastic Surgeons
- Spatial frequency domain imaging to effectively monitor viability of composite tissue facial flaps; Plastic Surgery Research Council and American College of Surgeons
- Optimal sequencing of radiotherapy and types of reconstruction post-mastectomy; American Society for Radiation Oncology
- Patient involvement in the decision-making process improves satisfaction and quality of life in postmastectomy breast reconstruction; Academic Surgical Congress
- Intraoperative near-infrared fluorescence imaging systems for evaluation of thrombosis in microsurgery; Academic Surgical Congress
- Testosterone is essential for skeletal muscle rejuvenation of aged mice in heterochronic parabiosis; American Association of Plastic Surgeons

Teaching, Training, and Education

I have been training medical students, general surgery and plastic surgery residents, clinical fellows, and research fellows for the past 10 years. We have had multiple students supported by Doris Duke Clinical Research Fellowships as well as through Harvard Medical School (HMS). I serve as the course director for the plastic surgery medical student clerkship at BIDMC, as a mentor in the Holmes Society, and as a mentor for medical students applying in plastic surgery. I was awarded the Young Mentor Award by HMS in 2012 and the Harvard Plastic Surgery Residency Teaching Award in 2013.

Selected Research Support

Real-time flap viability monitoring during facial transplantation using SFDI; NIH, 2013-2018; PIs: John V. Frangioni, MD, PhD, and Bernard T. Lee, MD, MBA

Intraoperative near-infrared fluorescence imaging; NIH, 2010-2015; Co-Investigator: Bernard T. Lee, MD, MBA (PI: John V. Frangioni, MD, PhD)

Outcomes research in reconstructive breast surgery, Peter Jay Sharp Foundation, 2004-2014; PIs: Adam Tobias, MD, and Bernard T. Lee, MD, MBA

Selected Publications

Momoh AO, Colakoglu S, Westvik TS, Curtis MS, Yueh JH, de Blacam C, Tobias AM, Lee BT. Analysis of complications and patient satisfaction in pedicled TRAM and DIEP flap breast reconstruction. *Ann Plast Surg* 2012;69(1):19-23.

de Blacam C, Ogunleye AA, Momoh AO, Colakoglu S, Tobias AM, Sharma R, Houlihan MJ, Lee BT. High body mass index and smoking predict morbidity in breast cancer surgery: A multivariate analysis of 26,988 patients from the NSQIP database. *Ann Surg* 2012;255(3):551-5.

Nguyen JT, Ashitate Y, Buchanan IA, Ibrahim AMS, Gioux S, Patel PP, Frangioni JV, Lee BT. Face transplant perfusion assessment using near-infrared fluorescence imaging. *J Surg Res* 2012;177(2):e83-8.

Caterson SA, Fox SE, Tobias AM, Lee BT. Functional MRI to evaluate "sense of self" following perforator flap breast reconstruction. *PLoS One* 2012;7(11):e49883.

Nguyen JT, Lin SJ, Tobias AM, Gioux S, Mazhar A, Cuccia DJ, Ashitate Y, Stockdale A, Oketokoun R, Durr NJ, Moffitt LA, Durkin AJ, Tromberg BJ, Frangioni JV, Lee BT. A novel pilot study using spatial frequency domain imaging to assess oxygenation of perforator flaps during reconstructive breast surgery. *Ann Plast Surg* 2013;71(3):308-15.

Khansa I, Momoh AO, Patel PP, Nguyen JT, Miller MJ, Lee BT. Fat necrosis in autologous abdominal-based breast reconstruction: A systematic review. *Plast Reconstr Surg* 2013;131:443-52.

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Research Group

Jordan Blanche
Ahmed Ibrahim, MD
Kuylhee Kim, MD
Pieter Koolen, MD
Marina Shuster
Hani Sinno, MD
Yong-ak Song, PhD

Research Focus

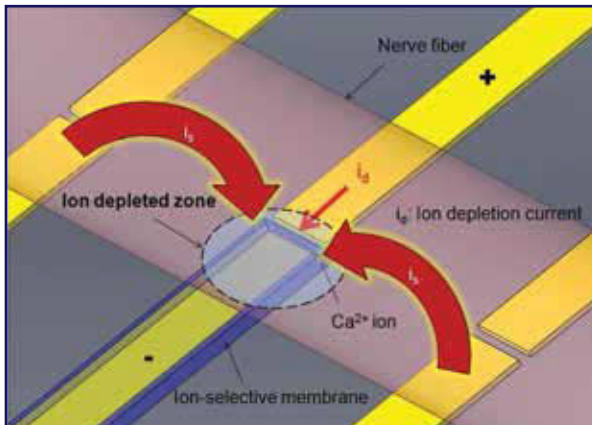
Over the last several years, my basic science research has focused in two primary areas. These are both collaborative projects utilizing the expertise and experiences of scientists, engineers, and clinicians.

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

This is a collaborative effort with the Massachusetts Institute of Technology (MIT). The primary focus of our work is the development of an electrochemical nerve stimulation and blocking method via local modulation of ion concentrations at the peripheral nerve surface using a microelectromechanical systems (MEMS) device. Our goal is to fabricate innovative neuroprosthetic devices that can reduce the threshold for nerve stimulation to aid in paralysis/paresis and/or block nerve firing to reduce pain. It is hoped that such future devices will lead to therapeutic advancement in treating conditions such as facial nerve paralysis, chronic pain, and nerve dysfunction syndromes.

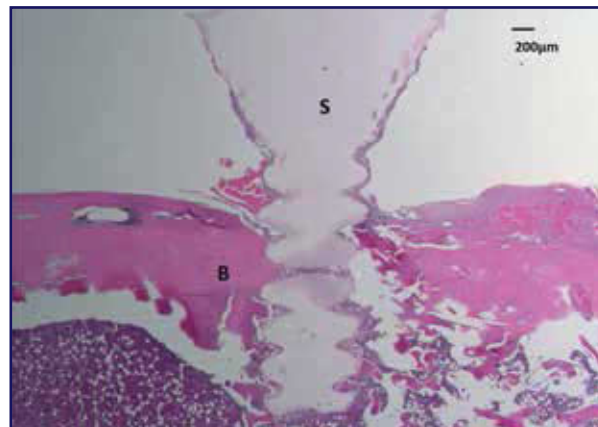
A use of silk-based orthopedic devices to modulate healing

This project is a collaborative effort with scientists and engineers at Tufts University in which we are developing degradable silk protein-based orthopedic devices (screws and plates). These will be able to provide immediate surgical stabilization for orthopedic repairs, promote active repair, and reduce infections by releasing therapeutics, and also be fully degrading, avoiding the need for future surgeries for removal.



▲ Schematic of neuromuscular system with modulation of ion concentrations using ion-selective membrane

In addition to our basic science projects, we also have an active clinical research group examining outcomes, techniques, and patient satisfaction following various types of reconstructive and aesthetic plastic surgery procedures, including the head and neck, breast, and abdominal areas. Using a large institutional database at BIDMC, as well as a national database from the ACS-NSQIP, we have been able to explore risk factors that lead to complications. In addition, we have been able to understand the relationships between type of reconstruction and positive outcomes.



▲ Histological characterization of bioresorbable screw after 4 weeks *in vivo* in a rat femur model. Full perspective image of screw [S] fixed in bone [B] after 4 weeks *in vivo*.

Accomplishments 2012-2013

- Over the last two years, I have been focused upon the development of medical devices that derive from our research in electrical stimulation and neural blocking, as well as our research in bioresorbable devices. Currently, we have five inventions that are pending patents.
- I serve as a member of the Research Grant Review Committee for the Plastic Surgery Foundation.
- My editorial activities include serving as Academic Editor of Public Library of Science (*PLoS One*) and Associate Editor of *Plastic and Reconstructive Surgery-Global Open*.
- I am also ad hoc reviewer for: *Plastic and Reconstructive Surgery*, *Annals of Plastic Surgery*, *The Laryngoscope*, *Microsurgery*, *Journal of Neurology*, *Neurosurgery*, and *Psychiatry*, *Head and Neck*, *International Journal of Surgery Case Reports*, and the *International Journal of Surgery*.

Awards

- 2013; The National Endowment for Plastic Surgery, The Plastic Surgery Foundation
- 2013; Finalist, Technology in Plastic Surgery (TIPS) Innovation Challenge, American Society of Plastic Surgeons (ASPS)/The Plastic Surgery Foundation
- 2013; Excellence in Mentoring Award, Harvard Medical School
- 2012-2014; Academic Scholar Award, American Association of Plastic Surgeons (AAPS)
- 2012; 2nd Place Best Research Award, Association des Spécialistes en Chirurgie Plastique et Esthétique du Québec (ASCPEQ) Tremblant, Quebec Plastic Surgery Meeting
- 2012; 2nd Place Prize, Basic Science, Harvard Medical School Surgery Research Day
- National Courses and Forums
- 2012; National Academy of Sciences, BEMA forum. Roundtable on Biomedical Engineering Materials and Applications: Effects of Obesity and Gender on Medical Device Therapies, Washington, D.C.
- 2012; Lin SJ, Bartlett R. Basics of Keeping Patients Breathing after Rhinoplasty. ASPS Instructional Course Plastic Surgery, American Society of Plastic Surgeons, the Plastic Surgery Foundation, and American Society of Maxillofacial Surgeons, New Orleans, LA.

Teaching, Training, and Education

I have been training medical students, general surgery, and plastic surgery residents, clinical and research fellows for the past seven years. Currently, I serve as the BIDMC Residency Site Director for the Combined Harvard Plastic Surgery Residency Program. In this role, I oversee the medical education and experience of residents who rotate on plastic surgery. I am also the co-director of the Aesthetic and Reconstructive Plastic Surgery Fellowship. In addition to my work with fellows and residents, I also help mentor medical students from Harvard Medical School (HMS) and other U.S. and international medical schools. I was awarded a Young Mentor Award by HMS in 2013.

Selected Research Support

Electrochemical activation and inhibition of neuromuscular systems with modulation of ion concentrations using ion-selective membranes; Department of Surgery Affinity Research Collaborative (ARC); PI: Samuel J. Lin, MD

Developing a facial nerve paralysis neuroprosthetic device using ion selective membranes; AAPS/PSF Research Scholarship Grant; PI: Samuel J. Lin, MD

Use of silk-based orthopedic devices to modulate healing; PSF National Endowment Research Grant; PI: Samuel J. Lin, MD

Selected Publications

Ibrahim AM, Gerstle T, Rabie AN, Song YA, Melik R, Han J, Lin SJ. Nanotechnology in plastic surgery. *Plast Reconstr Surg* 2012;130(6):879e-887e.

Rabie AN, Ibrahim AM, Kim PS, Medina MA, Upton J, Lee BT, Lin SJ. Dynamic rehabilitation of facial nerve injury: A review of the literature. *J Reconstr Microsurg* 2013;29(5):283-96.

Song YA, Ibrahim AM, Rabie AN, Han J, Lin SJ. Electrical interfaces in biomedical systems: Fundamentals and applications in neural prosthetics and neural engineering. Accepted, *Biotechnol Genet Eng Rev* 2013.

Gerstle TL, Ibrahim A, Kim PS, Lee BT, Lin SJ. A plastic surgery application in evolution: 3-dimensional printing. Accepted, *Plast Reconstr Surg*; August 2013.

Kim PS, Malin E, Kirkham J, Helliwell L, Ibrahim, A, Upton J, Tobias AM, Lee BT, Lin SJ. The Boston Marathon bombings: The plastic surgery experience of one Boston hospital. Accepted, *Plast Reconstr Surg*; July 2013.

Kim K, Ibrahim AM, Koolen PG, Lee BT, Lin SJ. Trends in facial fractures treatment using the ACS-NSQIP database. Accepted, *Plast Reconstr Surg*, September 2013.

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Research Focus

With broad training in general surgery, orthopedics, and hand surgery, I was initially recruited to start reconstructive microsurgery in Boston 37 years ago. Since that time my research has been dedicated to clinical surgery. Most of my research efforts at BIDMC are concerned with the planning and treatment of complicated secondary hand reconstruction, free tissue transfers, and the initial diagnosis and care of common hand problems.

At the Shriners Burn Institute, where I have worked for several decades, the primary focus is on the resurfacing of severe contractures of both upper and lower extremities and the treatment of congenital hand problems. At Boston Children's Hospital, I am a member of the Vascular Anomalies Center, where I treat all of the upper limb vascular malformations. There the focus is on both surgical and nonsurgical treatments, the diagnosis and separation of various different types of anomalies, as well as the clinical outcomes of both fast flow and slow flow vascular malformations.

My practice draws patients from well beyond the New England region and is known nationally and internationally for the treatment of congenital hand anomalies and complex hand reconstruction. I have also had the good fortune to act as a consultant to surgeons around the world.

Most recent publications listed in this report are concerned with both the clinical outcomes of various types of malformations as well as their molecular diagnosis in collaboration with the clinical diagnosis.

Currently, I am conducting research in the following clinical areas:

- static treatment modalities in facial paralysis
- two-stage distraction lengthening of the forearm and hand
- dynamic rehabilitation of facial nerve injury
- the presentation and management of mandibular tumors in the pediatric population
- the presentation and treatment of macrodactyly



▲ These unique hand molds of congenital malformations are part of a permanent exhibit at the Boston Museum of Science that has been on display for more than 30 years.

Accomplishments 2012-2013

- Director, Hand/Microsurgery Fellowship Program since its initiation in the 1980s
- Director, Integrated Plastic/Orthopaedic Hand Clinic at BIDMC since 1990
- Served on multiple national and international editorial review boards for plastic surgery and hand surgery, including the *Journal of Hand Surgery*
- Contributing Editor, American Society for Surgery of the Hand (ASSH), *Updates in Hand Surgery*
- Provided unique hand molds of congenital malformations, which are part of a permanent exhibit at the Boston Museum of Science that has been on display for more than 30 years
- Longtime member, Board of Directors of the Helping Hands Foundation, whose goal is to connect families of children with upper limb loss

Invited Presentations

- Medical College of Wisconsin: A Series of Presentations—What Is Your Surgical IQ?, Pediatric Microsurgery, Congenital Hand Surgery, Common Pediatric Problems, Vascular Malformations of the Upper Extremity, Congenital Case Presentations, 2012
- The Buncke Lecture, American Association for Reconstructive Microsurgery, 2013

Teaching, Training, and Education

I have been training medical students; general surgery residents; and plastic surgery residents, clinical fellows, and research fellows for the past 35 years. The fellowship program is in its 32nd year and attracts trainees from across the world. I also teach a yearly flap dissection course at Duke University.

Selected Publications

Upton J. Vascular Malformations of the Extremities: Vascular Anomalies Hemangiomas and Malformations, Second Edition, 2013:905.

Ibrahim AM, Rabie AN, Kim PS, Medina M, Upton J, Lee BT, Lin SJ. Static treatment modalities in facial paralysis: Review. *J Reconstr Microsurg* 2013;29(4):223-32.

Taghinia AH, Al-Sheikh AA, Panossian AE, Upton J. Two-state distraction lengthening of the forearm. *J Craniofac Surg* 2013;24(1):78-84.

Rabie AN, Ibrahim AM, Kim PS, Medina M, Upton J, Lee BT, Lin SJ. Dynamic rehabilitation of facial nerve injury: A review of the literature. *J Reconstr Microsurg* 2013;29(5):283-96.

Benoit MM, Vargas SO, Bhattacharyya N, McGill TA, Robson CD, Ferraro N, Didas AE, Labow BI, Upton J, Taghinia A, Meara JG, Marcus KJ, Mack J, Rodriguez-Galindo C, Rahbar R. The presentation and management of mandibular tumors in the pediatric population. *Laryngoscope* 2013.

Kim PS, Malin E, Kirkham J, Helliwell L, Ibrahim, A, Upton J, Tobias AM, Lee BT, Lin SJ. The Boston Marathon bombings: The plastic surgery experience of one Boston hospital. Accepted, *Plast Reconstr Surg*; July 2013.

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Research Group

Michael Auster
Dimitrios Baltzis
Camille Borland
Thanh Dinh, DPM
Rhianna Hibbler
Ermelindo Leal, PhD
Yana Ostrovsky
Francesco Tecilazich, MD
Ana Tellechea

Research Focus

I am mainly involved in “bench to bedside” research. My main research field is diabetes and its complications, with the main emphasis on wound healing and cardiovascular disease.

Translational research

This is a major part of my research activities. My work mainly focuses on the interaction between neuropathy and microvascular disease in the development of diabetic foot ulceration and the subsequent wound healing impairment. I also work on the effect of sleep apnea on cardiovascular function in diabetic and non-diabetic subjects. This work has been supported by NIH funding and nonprofit organizations. I collaborate with investigators from various departments of my hospital, the Beth Israel Deaconess Medical Center, and investigators from other institutions, such as the Brigham and Women’s Hospital, to conduct additional translational research.

Clinical research

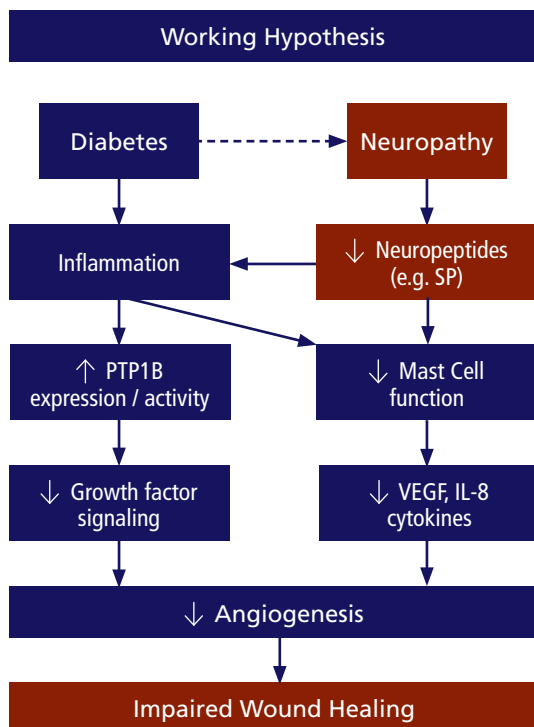
I conduct investigator-initiated research studies that examine the effects of various FDA-approved medications on cardiovascular function. These studies, although funded by industry, have been conceived, designed and executed by my unit and focus on possible new mechanisms through which these medications exert their beneficial effects. In the past I have served as the leading investigator and the leading author in industry sponsored multicenter trials that investigated the efficacy of new therapeutic interventions for the management of diabetic foot ulceration. Presently, I participate in multicenter phase III clinical trials that study the efficacy of new treatments.

Basic research

I also run my own basic research laboratory that mainly explores the findings of the translational research and tries to identify mechanisms that are related to the observed results. My laboratory works closely with Dr. Frank LoGerfo’s laboratory and other laboratories in the Beth Israel Deaconess Medical Center and is funded by NIH grants. I also collaborate with Drs. David Mooney and William Smith at the Wyss Institute and Harvard School of Engineering and Applied Sciences, and Dr. Jonathan Garlick at Tufts Medical Center; the main aim of our collaboration is the development of new wound-healing products. This collaboration has resulted in NIH funding. We employ various animal models, such as transgenic mice, rats, and rabbits and perform mechanistic and interventional studies with new biomaterials and/or factors that can improve diabetic wound healing.

I also work with small industries in the development of new therapeutic approaches in studies that are mainly funded by NIH funding allocated for small business. We have already completed numerous phase I studies and we are in the process of applying for Phase II funding.

In summary, I am mainly involved in bench to bedside research regarding diabetes complications which includes collaborations from various departments of this institution and other institutions. My research is mainly funded by NIH and other nonprofit organizations while I also conduct investigator initiated research funded by industry. I also participate in teaching activities that mainly focus on the training of fellows and junior faculty.



Accomplishments 2012-2013

In a prospective cohort study we showed that while neuropathy and vascular factors are associated with the development of diabetic foot ulceration, the main factors that are associated with failure to heal these ulcers are preexisting increased serum levels of inflammatory cytokines, MMP-9 and various growth factors. At the skin level, diabetes was associated with inflammation and increased expression of MMP-9 and PTP1B, factors that are associated with inflammation, can lead to resistance of the growth factor action and may be responsible for the observed raised levels in the patients who failed to heal their ulcer. These results have led to the working hypothesis shown in Figure 1.

In another study we also showed that the post-exercise time of recovery of the Pi/PCr ratio and PCr levels, a measurement of mitochondrial oxidative phosphorylation, was equally present in T2DM patients with peripheral neuropathy and patients with both peripheral neuropathy and mild PAD. In contrast, no differences were observed between the healthy controls and type 2 diabetic subjects without long-term complications. In addition, the two diabetic groups with complications had increased inflammatory cytokines and the observed increases were strongly associated with the observed mitochondrial dysfunction.

In a prospective study of subjects with diabetes, we found that the majority of neurophysiologic tests did not appreciably change over a 36-month period in patients with diabetes. Those tests that detected progression of neuropathy over 36 months included 1) laser-Doppler flowmetry, 2) Semmes-Weinstein monofilaments, and 3) the sural nerve amplitude. We found that other tests of neurophysiologic function and quantified examination scores did not detect a meaningful change during the course of this study. Those risk factors associated with neuropathy progression in individual neurophysiologic tests included smoking, age, blood pressure, duration of diabetes, body mass index, glucose control, cholesterol and triglyceride levels.

Finally, a study based on the rabbit animal model reported that the presence of neuroischemia results in the worst healing rates. Wound healing impairment due to neuroischemia was so severe that additional presence of diabetes does not further impair wound healing.

Teaching, Training, and Education

My teaching responsibilities include participation in the training of the podiatry residents, supervision of the fellows and junior faculty in my lab and participation in mentorship committees of junior faculty members from other units. I am also involved in educational activities of the Center for Education of the Beth Israel Deaconess Medical Center, which provides guidance to candidates for NIH K series awards. In addition, I was involved in the Engineering Sciences 96: Engineering Design Projects Course of the School of Engineering and Applied Sciences, Harvard University.

Finally, I participated as series editor, book editor, or co-editor and author in numerous textbooks. One of these textbooks ("Diabetes and Cardiovascular Disease") has been already translated to the Italian language and another one ("Diabetic Foot") to the Greek language.

Selected Research Support

Role of neuropeptides in diabetic foot problems; NIH, 2010-2015; Co-PI/
Contact PI: Aristidis Veves, MD, DSc

Mechanisms of neuropeptides action in diabetes; NIH, 2011-2015; Co-PI/
Contact PI: Aristidis Veves, MD, DSc

Obstructive sleep apnea increases cardiovascular risk in type 2 diabetes; NIH, 2011-2016; Co-PI/Contact PI:
Aristidis Veves, MD, DSc

Novel therapeutic approaches for the management of diabetic foot ulceration; NIH, 2012-2014; Co-PI/Contact PI:
Aristidis Veves, MD, DSc

Selected Publications

Dinh T, Tecilazich F, Kafanas A, Doupis J, Gnardellis C, Leal EC, Tellechea A, Pradhan L, Lyons TE, Giurini JM, Veves A. Mechanisms involved in the development and healing of diabetic foot ulceration. *Diabetes* 2012; 61(11):2937-47.

Tecilazich F, Dinh T, Lyons TE, Guest J, Villafuerte R, Sampanis C, Gnardellis C, Zuo C, Veves A. Post-exercise phosphocreatine recovery, an index of mitochondrial oxidative phosphorylation, is reduced in diabetic patients with lower extremity complications. *J Vasc Surg* 2013; 57(4):997-1005.

Pradhan Nabzdyk L, Kuchibhotla S, Guthrie P, Chun M, Auster ME, Nabzdyk C, LoGerfo FW, Veves A. Expression of neuropeptides and cytokines in a rabbit model of diabetic neuroischemic wound-healing. *J Vasc Surg* 2013;58(3):766-775.

Tellechea A, Kafanas A, Leal EC, Tecilazich F, Kuchibhotla S, Auster ME, Kontoes I, Paolino J, Carvalho E, Pradhan Nabzdyk L, Veves A. Increased skin inflammation and blood vessel density in human and experimental diabetes. *Int J Low Extrem Wounds* 2013;12(1):4-11.

Gibbons C, Freeman R, Tecilazich F, Dinh T, Lyons T, Gnardellis C, Veves A. The evolving natural history of neurophysiologic function in patients with well controlled diabetes. *J Peripher Nerv Syst* 2013;18(2):153-61.

Dushay JR, Tecilazich F, Kafanas A, Magargee ML, Auster MA, Gnardellis C, Dinh T, Veves A. Aliskiren improves vascular smooth muscle function in the skin microcirculation of Type 2 diabetic patients with normal renal function. 2013 May 13. (Epub ahead of print)

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Per-Olof Hasselgren, MD, PhD

George H.A. Clowes Professor of Surgery
Vice Chairman for Research
Director of Endocrine Surgery



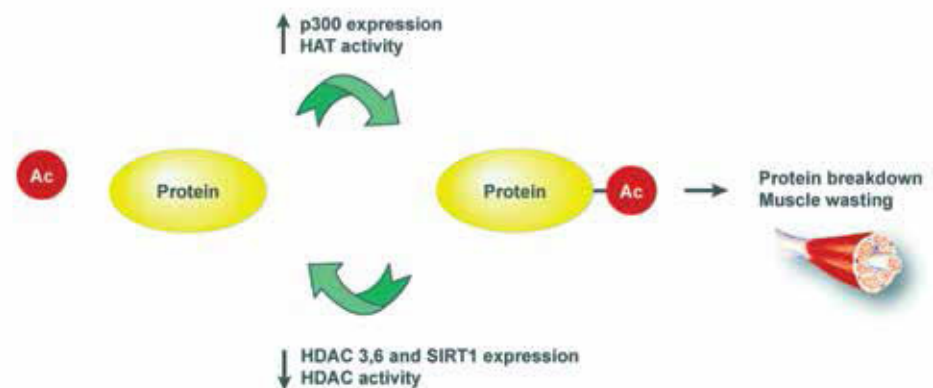
Research Group

Nima Alamdari, PhD
Zaira Aversa, MD
Estibaliz Castillero, PhD

Research Focus

During the last several years, the research in our group has been 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. The loss of muscle mass in these conditions mainly reflects activation of ubiquitin-proteasome-dependent and autophagy/lysosomal degradation of muscle proteins, although reduced protein synthesis contributes as well. The catabolic response in skeletal muscle has several significant clinical consequences, including muscle weakness and fatigue, delayed ambulation with risk of thromboembolic and pulmonary complications, and prolonged stay in the intensive care unit.

Recent research in our laboratory has focused on the role of different transcription factors regulating the expression of factors involved in the regulation of muscle proteolysis. Those transcription factors include NF- κ B, C/EBP β and δ , FOXO1 and 3a, and PPAR β / δ . In addition, our research has been focused on nuclear cofactors involved in the activation of transcription factors. In particular, our most recent efforts have examined the role of the histone acetyl transferase p300 and various histone deacetylases, such as SIRT1. Those studies have been important because they have highlighted the role of acetylation of transcription factors as well as other muscle proteins in the regulation of muscle mass. The role of acetylation and deacetylation in the regulation of muscle protein breakdown was summarized in a recent review from our laboratory (Metabolism 62:1-11, 2013). In this model, increased expression of p300 results in acetylation of transcription factors as well as other muscle proteins, making them susceptible to degradation. The state of hyperacetylation is further aggravated by reduced expression and activity of various histone-deacetylases, including SIRT1 (Figure 1). An important implication of these findings is that muscle wasting may be prevented and treated by agents that decrease p300 activity or by agents that activate SIRT1 and other histone deacetylases.



▲ Figure 1: Muscle wasting, mainly reflecting ubiquitin-proteasome and autophagy-lysosomal myofibrillar protein breakdown, may at least in part reflect hyperacetylation of cellular proteins regulated by increased p300/HAT expression and activity and decreased expression and activity of HDAC3 and 6 and SIRT1.

Accomplishments 2012-2013

- Research in our group has highlighted the importance of acetylation and deacetylation for expression and activity of transcription factors as well as structural muscle proteins. Our laboratory was first to report increased expression and activity of p300 and reduced expression and activity of histone deacetylases HDAC3 and 6, changes working in concert to increase protein acetylation (J Cell Biochem 2005;94:1058-1067; Am J Physiol 2007; 292:R337-R344). These observations were the foundation for continued work during 2012-2013 demonstrating hyperacetylation of C/EBP β and δ , FOXO1 and 3a, and NF- κ B/p65 in muscle cells exposed to glucocorticoids (Biochem Cell Biol 2012;90:200-208; Metabolism 2013;62:1-11). Those observations are important because patients treated with high doses of glucocorticoids suffer from loss of muscle mass and glucocorticoids also mediate catabolic effects of sepsis and severe injury.
- The role of hyperacetylation was further supported by recent experiments in which resveratrol prevented muscle wasting through a SIRT1-dependent mechanism, an observation with obvious clinical implications (Biochem Biophys Res Commun 2012;17:528-533).
- In other recent studies we examined the influence of catabolic conditions on muscle strength making the novel observation that loss of muscle strength during sepsis reflects reduced cross-bridge formation and function between the contractile proteins actin and myosin resulting in reduced muscle fiber stiffness (Am J Physiol 2012;303:R1090-R1099). These functional consequences of the catabolic response in skeletal muscle were regulated by glucocorticoids and may explain why patients with sepsis, severe injury, and cancer experience muscle weakness.
- In recent experiments, we examined the role of PPAR β / δ in expression and activity of FOXO1 and regulation of muscle mass (PLoS One 2013; 8:e59726). Those experiments were important because they increase our understanding of the role of transcriptional regulation in muscle wasting.
- With members of the Division of Endocrinology at BIDMC, I have participated in a project localizing and characterizing brown fat in the neck of adult human patients, studies that are important for understanding the imbalance between energy intake and expenditure in patients with diabetes and obesity (Nat Med 2013;19:635-639).

Teaching, Training, and Education

In the research laboratory, I have been actively involved in the teaching and training of research fellows, with regards to experimental design, interpretation of data, and writing of manuscripts.

Clinically, I am involved in the mentoring of surgical residents conducting clinical research, in particular in the field of endocrine surgery. We are presently pursuing three such projects: 1) Studies aimed at examining the frequency of the follicular variant of papillary thyroid carcinoma and its role in the management of patients with thyroid cancer; 2) Studies aimed at determining the occurrence of hypothyroidism after hemithyroidectomy; and 3) Studies aimed at testing the hypothesis that high TSH levels are associated with increased risk of thyroid cancer.

Selected Publications

Alamdari N, Aversa Z, Castellero E, Gurav A, Petkova V, Tizio S, Hasselgren PO. Resveratrol prevents dexamethasone-induced expression of the muscle atrophy-related ubiquitin ligases atrogin-1 and MuRF1 in cultured myotubes through a SIRT1-dependent mechanism. *Biochem Biophys Res Commun* 2012;417:528-533.

Chamberlain W, Gonnella P, Alamdari N, Aversa Z, Hasselgren PO. Multiple muscle wasting-related transcription factors are acetylated in dexamethasone-treated muscle cells. *Biochem Cell Biol* 2012;90:200-208.

Alamdari N, Toraldo G, Aversa Z, Smith I, Castellero E, Renaud G, Qaisar R, Larsson L, Jasuja R, Hasselgren PO. Loss of muscle strength during sepsis is in part regulated by glucocorticoids and is associated with reduced muscle fiber stiffness. *Am J Physiol Regul Integr Comp Physiol* 2012;303:R1090-R1099.

Alamdari N, Aversa Z, Castellero E, Hasselgren PO. Acetylation and deacetylation – novel factors in muscle wasting. *Metabolism* 2013;62:1-11.

Castillero E, Alamdari N, Aversa Z, Gurav A, Hasselgren PO. PPAR β / δ regulates glucocorticoid- and sepsis-induced FOXO1 activation and muscle wasting. *PLoS One* 2013;8(3):e59726.

Castillero E, Alamdari N, Lecker SH, Hasselgren PO. Suppression of atrogin-1 and MuRF1 prevents dexamethasone-induced atrophy of cultured myotubes. *Metabolism* Jul 15, 2013 (Epub ahead of print).

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Ranjna Sharma, MD

Instructor in Surgery



Research Focus

My clinical research interests include:

Outcomes of breast reconstruction following partial mastectomy

Our group has developed a protocol to retrospectively study prospectively collected patient data examining the oncoplastic reconstruction of partial mastectomy defects. We are reviewing clinical outcomes, patient satisfaction, and financial costs associated with the procedures.

Outcomes of breast cancer treatment in the octogenarian patient population

Our group has received IRB approval for a protocol to retrospectively study the treatment decisions and clinical outcomes in the octogenarian patient population, as compared to younger patients, diagnosed with early breast cancer. We will examine a cohort of patients who are 80-89 years old versus a cohort who are 50-59 years old and compare their clinical outcomes.

Upgrade rate of common breast atypias

Our group has developed a protocol and database to retrospectively review radiologic and pathologic features that may contribute to the upgrade rate from atypia to carcinoma in patients with atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and lobular carcinoma *in situ* (LCIS) found on image-guided core needle biopsy to determine optimal management of these high-risk lesions.

Wide local excision alone for the treatment of breast cancer

We are developing a protocol to study clinical outcomes of recurrence and survival in patients who have breast-conserving surgery, without adjuvant radiation therapy, for treatment of in situ and invasive breast cancer. By reviewing this data, we will determine factors influencing patient care decisions, as well as an appropriate imaging schedule for this group of patients.

My translational research interests include:

Intraoperative real time breast cancer margin assessment with nonlinear microscopy

We are developing a protocol using Acridine Orange dye with nonlinear microscopy for intra-operative evaluation of surgical margins in oncologic resection specimens.

PRESENT Study: Prevention of Recurrence in Early-Stage, Node-Positive Breast Cancer with Low to Intermediate HER2 Expression with NeuVax™ Treatment Phase 3 Trial

BIDMC is participating as a site in this multicenter, multinational, prospective, randomized, double-blind study, which is being conducted to assess the efficacy and safety of a new immunogenic peptide combined with an adjuvant in patients with early stage node-positive breast cancer whose tumors express low or intermediate levels of the Her2/neu oncoprotein (HER2 1+ and 2+) and are not eligible for Herceptin, following completion of standard of care therapy.

Accomplishments 2012-2013

- Breast cancer Section Editor, Dynamed web-based education resource
- Speaker, annual Celebration of Life Event sponsored by BIDMC: New Considerations for Treatment of Early Breast Cancer
- BIDMC General Surgery Residency applicant interviewer
- Member, BIDMC Cancer Committee
- Member: Society of Surgical Oncology, American Society of Clinical Oncology, American College of Surgeons, Boston Surgical Society

Teaching, Training, and Education

- Patient-Doctor II Course: Lifestyles of a Surgeon
- HMS/BIDMC Pre-Internship Surgical Boot Camp: taught fourth-year Harvard Medical School students fine-needle aspiration, core biopsy, and incision and drainage techniques
- Development of the breast-rotation surgical skills simulation curriculum and model: wire-localized partial mastectomy
- Clinical Scholarship Program projects:
 - The upgrade rate of common breast atypias; Ali Linsk, MD, general surgery resident
 - Outcomes of breast cancer treatment in the octogenarian patient population; Anita Mamtani, MD, general surgery resident
- Society of Surgical Oncology (SSO) Annual Meeting Highlights presentation at multidisciplinary Tumor Board Conference
- Best-in-Practice BIDMC MRI Lecture Series Fall Symposium: The use of MRI in a surgical practice

Selected Publications

de Blacam C, Ogunleye AA, Momoh AO, Colakoglu S, Tobias AM, Sharma R, Houlihan MJ, Lee BT. High BMI and smoking predict morbidity in breast cancer surgery: A multivariate analysis of 26,988 patients from the NSQIP database. *Ann Surg* 2012; 255 (3): 551-555.

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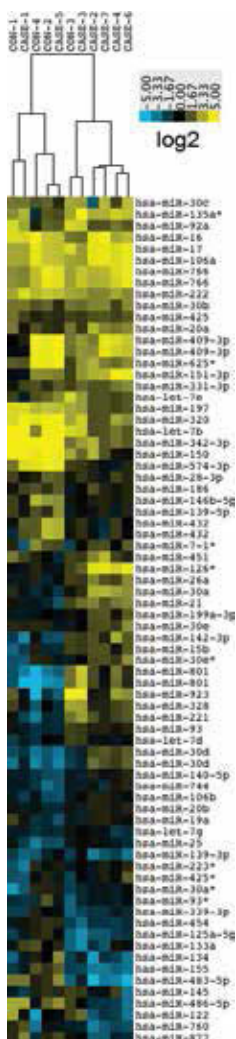
Jennifer F. Tseng, MD, MPH

Associate Professor of Surgery
Chief, Surgical Oncology

Research Group

Lindsay Bliss, MD
Nikki Burrish
Zeling Chau, MD*
Sing-Chau Ng, MS
Catherine Yang, MD

*completed June 2013

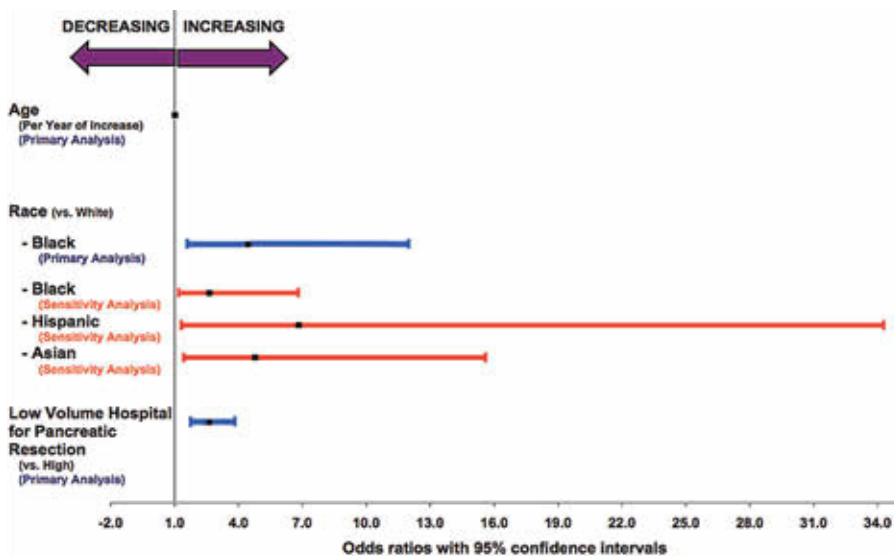


Research Focus

The overall focus of my research is predicting risk for hepatopancreaticobiliary (HPB) and upper GI malignancy and related diseases, as well as assessing the risks and benefits of various modalities employed in their treatment. To achieve that end, I have pursued several complementary avenues of investigation including: 1) health services research, including large administrative databases, registries, and institutional databases; 2) biobanking and biomarker discovery for pancreatic malignancy; and 3) decision analysis and decision modeling.

My investigative achievements have centered on building predictive models for pancreatic cancer and related diseases. Using large national databases, I have led widely cited research on perioperative morbidity and mortality for pancreatic cancer and for pancreatectomy. Disparities in diagnosis, receipt of care, and outcome are under active investigation. We have used national data to build simple risk scores for HPB surgery that can be easily calculated by hand, computer, or handheld. We have used institutional data to explore predictors of receiving care; learning curves in surgery; neoadjuvant therapy prior to surgical resection; and vascular resection in order to allow for more potentially curative surgery. With the goal of integrating molecular information in risk prediction and determining best strategies for individual patients, I have established a novel pancreatic biobank, with whole blood, serum, plasma, and patient tissues, together with potentially biomarker-rich fluids such as pancreatic juice and cystic fluid. In collaboration with basic scientists, I have embarked on microRNA and proteomic profiling of these fluids to identify markers of malignancy as well as response to therapy.

Odds of traveling ≤ 10 miles to resection hospital



▲ Data from the Massachusetts Department of Public Health, demonstrating disparities in which patients receive access to high-volume hospitals for pancreatectomy

◀ mirTaqman microRNA assay courtesy of Victor Ambros

Accomplishments 2012-2013

In previous and ongoing work we have used large databases to observe that patients who are in higher insured areas have better outcomes for most solid cancers, with larger effects seen in cancers that have more effective screening and treatment, e.g. breast and colon cancers, and smaller but distinct effects on patients with less effective screened or treated tumors, e.g. pancreatic cancer (Smith JK et al, *Journal of Surgical Research*, epub 2013).

In 2013, we have concentrated considerable efforts on our collaboration with the Massachusetts Department of Public Health (DPH), using its Discharge Database, and more recently, applying to link these data with the statewide cancer registry. Using Massachusetts Division of Health Care Finance and Policy (DHCFP) data, we are investigating regionalization of surgery for pancreatic cancer, its potential effect on perioperative outcomes, and possible disparities in access to high-volume pancreatic cancer surgery centers. Dr. Lindsay Bliss, a research resident from the University of Connecticut, has become the third full-time research fellow under my supervision to work at the Massachusetts DPH.

In parallel, we are analyzing BIDMC data. Mariam Eskandar, MD, PGY-2 clinical surgical resident at BIDMC, established a database using the BIDMC tumor registry and electronic medical records of all patients seen at BIDMC for pancreatic cancer 2001-2012. She determined in preliminary analyses that insurance status was strongly associated with outcomes, including stage of diagnosis and overall survival. Dr. Eskandar was awarded third place at the 94th Annual Meeting of the New England Surgical Society in the Resident Paper competition in September 2013.

Teaching, Training, and Education

- Co-director, Surgical Outcomes Analysis & Research (SOAR), a productive and collaborative research group focused on health services research; weekly resident teaching conference
- Co-director, Multidisciplinary Pancreaticobiliary Conference, weekly conference with HMS CME offered for pancreaticobiliary education
- Mentored/mentoring the following research fellows on a full-time basis:

2011-2013

Zeling Chau, MD; Research resident; 2nd UMMS Scholar in Residence at Mass DPH. Currently completing MPH thesis (previous coursework at Columbia; completed academic studies at HSPH); surgery resident at UMMS.

2012

Nikki Burish, BS; Medical student (University of Wisconsin), MPH Student at HSPH

2013

Lindsay Bliss, MD; Research resident (University of Connecticut surgery resident); ongoing; MPH student at HSPH

Catherine Yang, MD; Research resident (Fullbright Fellow, New Zealand); ongoing; MPH student at HSPH

- Ongoing mentoring of three (two primary, one secondary) categorical PGY-1 and PGY-2 surgical residents in the BIDMC Department of Surgery Clinical Scholarship Program

Selected Publications

Witkowski EM, Smith JK, Ragulin-Coyne E, Ng SC, Shah SA, Tseng JF. Is it worth looking? Abdominal imaging after pancreatic cancer resection: A national study. *J Gastrointest Surg* 2012;16(1):121-8.

Ragulin-Coyne E, Carroll JE, Smith JK, Witkowski ER, Ng SC, Shah SA, Zhou Z, Tseng JF. Perioperative mortality after pancreatectomy: A risk score to aid decision-making. *Surgery* 2012;152(3 Suppl 1):S120-7.

Ragulin-Coyne E, Witkowski ER, Chau Z, Ng SC, Santry HP, Callery MP, Shah SA, Tseng JF. Is routine intraoperative cholangiogram necessary in the twenty-first century? A national view. *J Gastrointest Surg* 2013;17(3):434-42.

Smith JK, Ng SC, Zhou Z, Carroll JE, McDade TP, Shah SA, Tseng JF. Does increasing insurance improve outcomes in cancer patients? *J Surg Res* 2013 (Epub June 5 ahead of print).

Chau Z, West JK, Zhou Z, McDade TP, Smith JK, Ng SC, Kent TS, Callery MP, Moser AJ, Tseng JF. Rankings versus reality for pancreatic cancer surgery: A real world comparison. *HPB*, in press.

Eskandar M, Chau Z, Ng SC, Kent TS, Callery MP, Tseng JF. Impact of insurance type on pancreatic cancer outcomes: A decade in review. Submitted to *J Am Coll Surg*, September 2013.

Selected Research Support

Howard Hughes Medical Institute Early Career Grant, 2010-2014; PI: Jennifer Tseng, MD, MPH

American Cancer Society Mentored Research Scholar Grant, 2010-2014; PI: Jennifer Tseng, MD, MPH

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Research Group

Aishatu Aloma, MBBS, MPH
Omar Ibrahim, MD
Amit Mahajan, MD
Adnan Majid, MD
Eugene Shostak, MD

Erik Folch, MD, MSc

Instructor in Medicine

Associate Director, Interventional Pulmonology

Research Focus

My research is clinical in nature with a focus on interventional pulmonology.

Staging of lung cancer

Until recently, the staging of lung cancer was incomplete and guided by imaging studies. However, the IP community around the world rallied behind a minimally invasive technique to biopsy the lymph nodes in the chest with ultrasound guidance. Five years later, the 2013 ACCP guidelines now recommend it as the first-line invasive mediastinal staging strategy.

- Linear Endobronchial Ultrasound (EBUS). This is a minimally invasive approach to lung cancer staging that has revolutionized current clinical practice. It uses a bronchoscope with a linear ultrasound probe attached to the distal end for real time sampling of mediastinal and hilar lymph nodes/masses.
- Radial Endobronchial Ultrasound (EBUS). This technology has significant prognostic and therapeutic implications; it uses a high-frequency radial ultrasound, allowing us to characterize the different layers of the airway wall and helps determine the stage of the tumor.

Pleurodesis techniques

The palliative treatment of malignant pleural effusions is very important in the management of advanced lung cancer. At BIDMC, we have pioneered pleurodesis techniques that are successful in over 90% of cases. These techniques combine the benefits of pleurodesis agents and tunneled pleural catheters to minimize time spent in the hospital and maximize quality of life.

Advanced thoracic endoscopy

Electromagnetic Navigation Bronchoscopy (EMNB) is the use of an electromagnetic field, a steerable sensor at the tip of the bronchoscope, and CT images to guide bronchoscopic tools toward the periphery of the lung. This has revolutionized biopsy techniques for peripheral lung lesions in a minimally invasive way.

Accomplishments 2012-2013

At this time, I am involved in the development of new bronchoscopic technologies including a clinician-initiated prospective study to evaluate the use of advanced techniques to enhance the yield of bronchoscopy in the diagnosis of small lung nodules. This protocol was considered interesting and meaningful to a device company that decided to support it through an unrestricted equipment grant.

I am currently a reviewer for the *American Journal of Transplantation*, *CHEST*, *The American Journal of Bronchology and Interventional Pulmonology*, and *Respiratory Care*.

In 2013, I became the Associate Director of Interventional Pulmonology at BIDMC.

Clinical Innovations

- Linear Endobronchial Ultrasound (EBUS)
- Radial Endobronchial Ultrasound (EBUS)
- Electromagnetic Navigation Bronchoscopy (EMNB)
- Bronchial Thermoplasty—FDA approved, catheter-based therapy, which uses radiofrequency energy to ablate the smooth muscle within the airway wall of patients with severe persistent asthma.
- Endobronchial valves—These devices act as one-way valves to prevent entry of air into specific bronchi, thus causing functional obstruction for treatment of persistent air leaks into the pleural space. The procedure is FDA approved for humanitarian use.

Invited Presentations

- Empyema, thoracostomy tubes, and thoracentesis, First Interventional Pulmonary Board Review, American Association of Bronchology and Interventional Pulmonology, CHEST Conference, Chicago, IL, 2013
- Management of malignant pleural effusions, LXXVII National Conference of Pulmonary and Thoracic Surgery, Mérida, Mexico, 2013
- Diagnosis and management of malignant pleural effusions, Pulmonary and Critical Care Medicine Grand Rounds, Jefferson University Hospital, Philadelphia, PA, 2013
- Treatment options for severe asthma: Bronchial thermoplasty, Medical Grand Rounds, Beth Israel Deaconess-Milton Hospital, Milton, MA, 2013
- Percutaneous tracheostomy workshop, American Association of Bronchology and Interventional Pulmonology, CHEST 2012, Atlanta, GA, 2012

Teaching, Training, and Education

Recognizing the importance of training new pulmonary fellows in basic pulmonary procedures and bronchoscopy as well as senior fellows in advanced techniques, I act as the Co-Director of two yearly courses that bring together 40 to 60 physicians from New England and around the country. I have been asked to participate at the Boston International Live Endoscopy Course (BILEC) in the area of lymph node sampling. For a pulmonologist, this is a great privilege, as BILEC is a course designed and attended by expert gastroenterologists. The Interventional Pulmonary Fellowship of BIDMC has recently merged with Massachusetts General Hospital for a combined training program including three IP fellows per year. This is one of the largest IP training programs in the nation.

Abstracts, Posters, and Exhibits

Folch E, Yamaguchi N, VanderLaan PA, Kocherr ON, Boucher DH, Goldstein MA, Huberman MS, Kent MS, Gangadharan SP, Costa DB, Majid AM. Use of lymph node aspirates from CP-EBUS-guided TBNA for multiple tumor genotyping techniques in non-small cell lung cancer. CHEST Conference Chicago 2013 (oral presentation)

Vanderlaan PA, Yamaguchi N, Folch E, Kocher ON, Boucher DH, Goldstein MA, Huberman MS, Kent MS, Gangadharan SP, Majid A, Costa DB. Success and failure rates of tumor genotyping techniques in routine pathological samples with non-small-cell lung cancer. ASCO Conference, Chicago, 2013 (poster)

Selected Publications

Folch E, Yamaguchi N, VanderLaan PA, Kocherr ON, Boucher DH, Goldstein MA, Huberman MS, Kent MS, Gangadharan SP, Costa DB, Majid AM. Use of lymph node aspirates from CP-EBUS-guided TBNA for multiple tumor genotyping techniques in non-small cell lung cancer. *J Thorac Oncol* 2013; 8(11):1438-44.

Folch E, Majid A. Are >50 supervised procedures required to develop competency in performing endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal staging? Yes. *Chest* 2013;143(4):888-891.

Inaty H, Folch E, Stephen C, Majid A. Tracheobronchial amyloidosis in a patient with Sjogren syndrome. *J Bronchology Interv Pulmonol* 2013;20(3):261-5.

Kinsey MC, Folch E, Majid A, Channick C. Evaluation and management of pill aspiration: Case discussion and review of the literature. *Chest* 2013;143(6).

Majid A, Palkar A, Myers R, Berger RL, Folch E. Cryotechnology for staged removal of self-expandable metallic airway stents. *Ann Thorac Surg* 2013; 96(1):336-8.

Lee HJ, Feller-Kopman D, Shepherd RW, Almeida FA, Bechara R, Berkowitz D, Chawla M, Folch E, Haas A, Gillespie C, Lee R, Majid A, Malhotra R, Musani A, Puchalski D, Serman D, Yarmus L. Validation of an interventional pulmonary examination. *Chest* 2013;143(6):1667-70.

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Sidharta P. Gangadharan, MD

Assistant Professor of Surgery

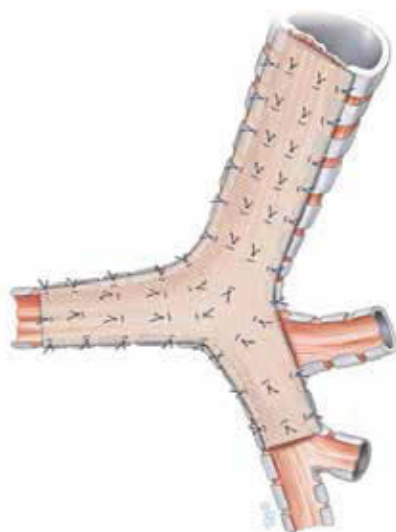
Chief, Thoracic Surgery and Interventional Pulmonology

Research Focus

I perform clinical outcomes research that spans the range of thoracic diseases, but with a particular interest in tracheobronchomalacia. Through our research, our group has helped define best practices in the evaluation and treatment of this disease. Further areas of investigation include the development of novel therapies for and the understanding of the pathophysiology of this disease. In addition, I have also been investigating novel methods of staging lung cancer utilizing near-infrared imaging technology.

I am Co-Investigator on a Harvard Catalyst Advanced Imaging Pilot Research Grant (“Real-Time Endoscopic Guidance using Near-Infrared Fluorescent Light for Thoracic Surgery”). This project’s scope is to design, validate, and translate an NIR-compatible endoscopic fluorescence imaging system in combination with a fluorescent tracer for intraoperative guidance. This system will be tested preclinically in an animal model and translated to a pilot human study in lung cancer. This study aims to improve identification of metastatic foci within mediastinal lymph nodes in lung cancer.

I am also the principle investigator of “AirTight: A Prospective Controlled Post-Approval Study of NeoMend ProGEL Pleural Air Leak Sealant in the Treatment of Visible Pleural Air Leaks after Standard Pleural Closure.” This is a post-approval study of the safety profile for sealant utilized for air leaks following lung resection.



◀ Schematic of tracheobronchomalacia treatment

Accomplishments 2012-2013

- Early lung cancer treatment in 2012, Grand Rounds and Clinical Crossroads Conference, Department of Surgery, BIDMC, and *Journal of the American Medical Association*, 2012
- Early lung cancer, Grand Rounds, Beverly Hospital, Beverly, MA, 2012
- Novel techniques in esophageal and tracheal surgery-tracheal surgery techniques; invited faculty for the Society of Thoracic Surgeons University Course, Society of Thoracic Surgeons annual meeting, Ft. Lauderdale, FL, 2012
- Tracheobronchomalacia: What is the optimal treatment?, Invited speaker, 17th World Congress for Bronchology and Interventional Pulmonology, Cleveland, OH, 2012
- Tracheobronchoplasty for tracheobronchomalacia; Invited speaker for the General Thoracic Symposium, American Association for Thoracic Surgery annual meeting, Minneapolis, MN, 2013

Teaching, Training, and Education

I have been involved in education administration for the Department of Surgery as the Associate Program Director for Cardiothoracic Surgery and as an Assistant Program Director for the General Surgery Residency Program. I also served as Interim Program Director for General Surgery for a six-month period in 2012. From a teaching perspective, I deliver regular didactic sessions and simulation sessions for residents. On a national level, I present didactic lectures and hands-on training courses on complex tracheal diseases and surgical treatments.

Selected Research Support

Real-time endoscopic guidance using near-infrared fluorescent light for thoracic surgery; Harvard Catalyst Advanced Imaging Pilot Research Grant, 2012-2014; Co-Investigator: Sidharta P. Gangadharan, MD

AirTight: A prospective controlled post-approval study of NeoMend ProGEL pleural air leak sealant in the treatment of visible pleural air leaks after standard pleural closure; NeoMend, 2012-2014; PI: Sidharta P. Gangadharan, MD

Selected Publications

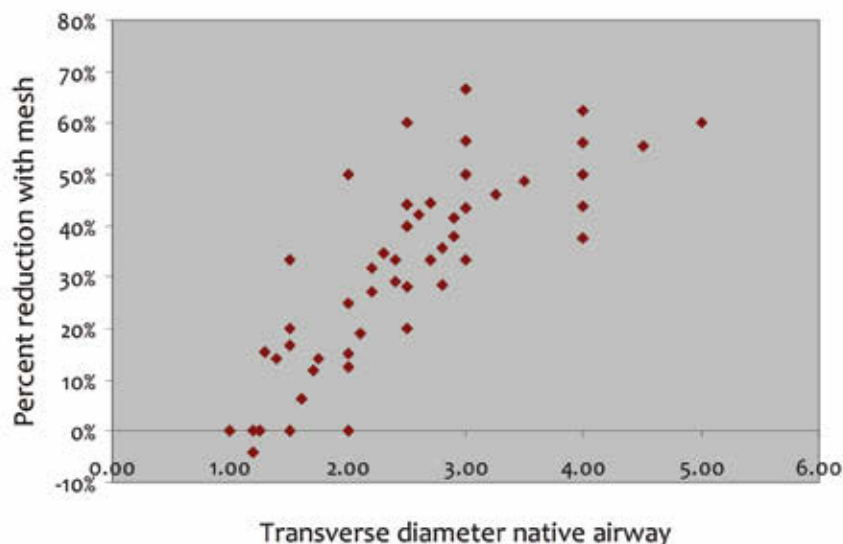
Tsukada H, Majid A, Kent MS, Ernst A, DeCamp MM, Gangadharan SP. Two-stage end-to-end reconstruction of long segment tracheal defects using a bioabsorbable scaffold grafting technique in a canine model. *Ann Thorac Surg* 2012;93(4):1088-92.

Boffa DJ, Gangadharan S, Kent M, Kerendi F, Onaitis M, Verrier E, Roselli E. Self-perceived video-assisted thoracic surgery lobectomy proficiency by recent graduates of North American thoracic residencies. *Interact Cardiovasc Thorac Surg* 2012;14(6):797-800.

Lagisetty KH, Gangadharan SP. Tracheobronchoplasty for the treatment of tracheobronchomalacia. *J Thorac Cardiovasc Surg* 2012;144(3):S58-9.

Majid A, Sosa AF, Ernst A, Feller-Kopman D, Folch E, Singh A, Gangadharan S. Pulmonary function and flow volume loop patterns in patients with tracheobronchomalacia. *Respir Care* 2013. Epub ahead of print.

Proximal tracheal remodeling



▲ Results of tracheobronchomalacia remodeling

A complete list of publications begins on page 17



Adnan Majid, MD

Assistant Professor of Medicine
Director, Chest Disease Center

Research Group

Aishatu Aloma, MBBS, MPH
George Cheng, MD, PhD
Erik Folch, MD, MSc
Omar Ibrahim, MD
Hanine Inaty, MD
Ahmed Jawad, MD
Amit Mahajan, MD
Faisal Malik, MD
Atul Palkar, MD

Research Focus

Our research is clinical in nature and aims at improving care for patients with a variety of lung and airway disorders. Our research areas include:

Emphysema

Our area of interest in emphysema is endoscopic lung volume reduction and we are actively enrolling patients in two FDA-approved multicenter phase 3 clinical trials:

We are the only center in New England participating in the Lung Volume Reduction Coil (LVRC) Treatment in Patients with Emphysema (RENEW) Study. We are assessing the safety and effectiveness of the LVRC. The primary effectiveness outcome is the absolute change in the six-minute walk test (6MWT) comparing the treatment and the control group. There are several secondary endpoints, including change in forced expiratory volume in one second (FEV1) and St. George's Respiratory Questionnaire (SGRQ). Benefits to patients include:

- Reduction in lung volume
- Improvement in lung function
- Reduction in number and severity of symptoms related to emphysema
- Improved quality of life and exercise tolerance

We are also the only center in New England participating in the Prospective, Randomized, Controlled Multicenter Clinical Study to Evaluate the Safety and Effectiveness of the IBV® Valve System for the Single Lobe Treatment of Severe Emphysema (EMPROVE). We are evaluating the improvement of lung function after treatment with the IBV® Valve System compared to medical management. We are also assessing the safety and effectiveness of the IBV Valve System for the treatment of severe emphysema. The primary effectiveness outcome is the difference between the treatment and control groups in the mean change in forced expiratory volume in one second (FEV1) from baseline at six months. Benefits to patients include:

- Reduction in lung volume
- Improvement in pulmonary function and quality of life

Asthma

Post-approval Study for Bronchial Thermoplasty: This is a phase 4 multicenter, open-label, single-arm study designed to demonstrate durability of the treatment effect and to evaluate the short-term and longer-term safety profile of the Alair System. Benefits to patients include:

- Significant improvement in asthma-related quality of life
- Reduction in the number of days lost from work or school due to asthma symptoms
- Reduction in number of asthma-related emergency room visits

Tracheobronchomalacia

Our division maintains the largest tracheobronchomalacia (TBM) registry in the United States, which has enabled us to develop current guidelines for medical, endoscopic, and surgical therapy.

Other research interests include:

- Electromagnetic navigation bronchoscopy
- Therapeutic use of endobronchial ultrasound

Accomplishments 2012-2013

We are the only center in New England involved in the RENEW and EMPROVE studies for patients with severe emphysema. We have been collaborating with pulmonary physicians, interventional pulmonologists, and physicians from other pulmonary specialties to increase patient referrals and enrollment into these studies.

Invited Presentations

- Management of complicated parapneumonic effusions and empyema: The interventional pulmonologist perspective, American College of Chest Physicians meeting (CHEST), Atlanta, GA, 2012
- Percutaneous tracheostomy workshop, CHEST 2012, American Association of Bronchology and Interventional Pulmonology, Atlanta, GA, 2012
- Advances in interventional bronchoscopy, Clinical Alemana-Universidad Del Desarrollo, Santiago de Chile, 2013
- Bronchial thermoplasty for severe asthma, Clinical Alemana-Universidad Del Desarrollo, Santiago de Chile, 2013
- Endoscopic lung volume reduction for emphysema, Clinical Alemana-Universidad Del Desarrollo, Santiago de Chile, 2013
- Advances in bronchoscopy. Brigham and Women's Hospital, Boston, 2013
- Endoscopic treatment for COPD: Where do we stand?, Longwood Pulmonary Grand Rounds, BIDMC, Boston, 2013
- A pulmonologist's view on the central airway, MEEI, Boston, 2013
- Complicated parapneumonic effusions and empyema: The interventional pulmonologist perspective, Tufts University School of Medicine, Boston, 2013

Teaching, Training, and Education

The Interventional Pulmonary (IP) Fellowship Program at BIDMC started in 2000 and merged with the Massachusetts General Hospital (MGH) IP fellowship in 2012 to create the Combined BIDMC-MGH IP Fellowship Program, of which I am the director. Our fellowship is one of the largest in the nation. Each year we accept three physicians into the competitive one-year program. Over the last 12 years, 17 fellows have graduated from the program and moved on to develop successful programs around the United States.

We also offer a variety of educational activities for trainees and faculty at BIDMC and around the world, including our annual "Introduction to Interventional Pulmonology" course.

Abstracts, Posters, and Exhibits

Paul MP, Mallur PS, Gangadharan SP, Bauman LA, Folch E, Majid A. Paradoxical vocal fold motion coexistent with tracheobronchomalacia: A potential confounder in managing symptomatic dyspnea. ATS Conference, Philadelphia, PA, 2013 (poster)

Folch E, Jawad A, Fashjian M, Maskey A, Paul M, Majid A. Pleural manometry: A simultaneous comparison of pleural pressure measurement with water-column and electronic portable manometer for routine patient care. ATS Conference, Philadelphia, PA, 2013 (poster)

Vanderlaan PA, Yamaguchi N, Folch E, Kocher ON, Boucher DH, Goldstein MA, Huberman MS, Kent MS, Gangadharan SP, Majid A, Costa DB. Success and failure rates of tumor genotyping techniques in routine pathological samples with non-small-cell lung cancer. ASCO Conference, Chicago, IL, 2013 (poster)

Maskey A, Folch E, Fashjian M, Paul M, Majid A. Response-based intrapleural installation of alteplase and DNAase for complicated pleural effusions. ACCP Conference, Chicago, IL, 2013 (poster)

Inaty, H, Folch E, Berger, R, Fernandez-Bussy S, Majid A. Cryodebridement for airway obstruction: A retrospective outcome and safety analysis: Single institution experience. ACCP Conference, Chicago, IL, 2013 (poster)

Selected Publications

Majid, A, Palkar A, Myers R, Berger R, Folch E. Cryotechnology for staged removal of self-expandable metallic airway stents. *Ann Thoracic Surg* 2013;96(1):336-8.

Majid A, Sosa A, Ernst A, Feller-Kopman D, Folch E, Singh A, Gangadharan S. Pulmonary function and flow volume loop patterns in patients with tracheobronchomalacia. *Respir Care* 2013; Mar 12 (Epub ahead of print).

Kinsey, M, Folch E, Majid A, Channick C. Evaluation and management of pill aspiration: Case discussion and review of the literature. *CHEST* 2013;143(6):1791.

Inaty, H, Folch E, Stephen C, Majid A. A rare case of tracheobronchial amyloidosis in a patient with Sjogren's syndrome presenting with hemoptysis and post-obstructive pneumonia. *J Bronchology Interv Pulmonol* 2013;20(3):261-265.

Shakil O, Majid A, Gangadharan S, Ferroze M. Tracheobronchomalacia and a full-thickness tracheal tear repair using cardiopulmonary bypass. *J Bronchology Interv Pulmonol* 2013;20 (3):290-292.

Guerrero J, Mallur P, Folch E, Keyes C, Stillman I, Gangadharan S, Majid A. Necrotizing tracheitis secondary to corynebacterium species presenting with central airway obstruction. *Respir Care* 2013 Jun 13 (Epub ahead of print).

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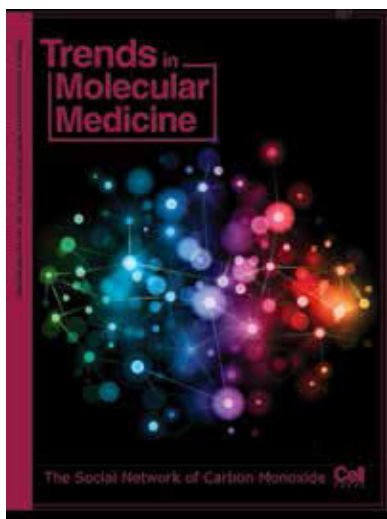
Leo E. Otterbein, PhD

Associate Professor of Surgery



Research Group

Matheus Correa Costa, PhD
Eva Csizmadia, MS
Amanda Galenkamp
David Gallo
Mariana Miyagi
Nils Schallner, MD



▲ The Otterbein research group was selected to provide a cover image for a review entitled "The Social Network of Carbon Monoxide."

Research Focus

Inhaled carbon monoxide is in numerous FDA phase trials in large part from the research that has arisen from my laboratory over the past decade. We continue to maintain a focus on the innate immune response and defense mechanisms in models of trauma, infection, ischemia reperfusion injury, and regenerative responses to tissue damage. The foundation of our work lies in the study of protective genes and in particular those that degrade heme and include heme oxygenase-1 (HO-1) and biliverdin reductase (BVR), both of which are intimately involved in the stress response. We have designed and developed innovative molecular tools including the first BVR floxed mouse that allows us to delete BVR in a tissue- and cell-specific manner and regulate knockdown of HO-1. We are well integrated with the laboratory of Barbara Wegiel, PhD, who studies the role of HO-1 and BVR in models of cancer and the role of BVR as a DNA surface receptor.

Role of HO-1, CO, and BVR in trauma and infection

This year we reinforced collaborative efforts in models of trauma and the impact on susceptibility to pneumonia. Supported in part by an ARC grant from the Department of Surgery, the research involves interactive studies with Carl Hauser, MD (BIDMC), Jim Lederer, PhD (Brigham and Women's), and Mike Yaffe, MD, PhD (BIDMC and MIT). Our data in sepsis models, generated with Barbara Wegiel, PhD, shows that HO-1 derived CO acts on bacteria, coercing them to generate ATP, which activates local immune cells and initiates a full immune response to clear bacteria through an inflammasome-mediated mechanism of action. Interestingly we find that BVR serves not only to convert biliverdin to bilirubin, but also acts as a DNA recognition receptor on the surface of macrophages following cell death. Finally, we have an ongoing collaboration with Brian Zuckerbraun, MD, at the University of Pittsburgh studying the role of HO-1 and BVR in wound infection and hemorrhagic shock. This has been submitted to the Department of Defense for funding in conjunction with Sangart, Inc., which has designed a human CO-saturated hemoglobin that is in phase trials.

HO-1 and neuroinflammation

We are collaborating with Khalid Hanafy, MD, PhD, in the Department of Neurology in the study of hemorrhagic stroke, where we find that HO-1 is critical in resolution of injury and impacts neurotransmission as it relates to memory. We have also initiated a collaboration with Rami Burstein, PhD, on HO-1 in migraine, where we find that individuals with migraine have very low HO-1 expression.

Role of the microbiome and liver regeneration

It has been known that the intestinal microbiome is important in numerous immune regulatory functions. We find that lack of HO-1 leads to poor regeneration of the liver and, moreover, that HO-1 via CO interacts directly with bacteria to generate ATP. This finding initiated a collaborative project with Simon Robson, MD, PhD, to integrate purinergic signaling and metabolism with heme biology. Preliminary data generated with this collaboration was submitted as a collaborative NIH R01.

Accomplishments 2012-2013

We continue to be one of the leaders the field in the area of heme metabolism and the stress response, providing mechanistic insight into the bioactive products carbon monoxide and the bile pigments. Together our publications continue to provide important contributions toward therapeutic use of these molecules in the clinic. We consider ourselves a team with excellent technical skills combined with creative and innovative approaches to research design. The individuals involved in the research include David Gallo, Barbara Wegiel, PhD, Matheus Costa, PhD, Zsuzsanna Nemeth, Eva Csizmadia, Kavita Bisht, Mailin Li, Mariana Miyagi, and Nils Schallner, MD.

Invited Presentations

- 8th Banff Inflammation Workshop, Calgary, Canada
- Hemoglobin Based Oxygen Carriers in Medicine, San Diego, CA
- 11th World Congress of Inflammation, Natal, Brazil
- Macrophage symposium, Paris, France
- 17th Biennial Meeting of Society for Free Radical Research International, Kyoto, Japan

Other Accomplishments

- Elected to three editorial boards, including *Medical Gas Research*, *Journal of Transplantation*, and *Journal of Pulmonary Medicine*
- Center for Integration of Medicine and Innovative Technology (CIMIT) Site Miner for BIDMC
- Continued in my tenth year as a regular NIH study section member for K01, K08, K02, and K99 grant applications
- Served as reviewer for Wellcome Trust, United Kingdom Medical Research Council, Israel Science Foundation, Yale University Pepper awards, New Zealand Research Foundation, and Pasteur Institute

Teaching, Training, and Education

I continue to participate in the training of graduate students, post-doctoral fellows, surgical residents, and junior faculty in basic research. As the BIDMC CIMIT site miner, I also advise potential applicants for CIMIT grants, which are primarily clinical-based point-of-care projects and proposals. In addition to the science, I also provide input on potential commercialization of ideas, interactions with the Technology Ventures Office, and various accelerator and venture opportunities.

Selected Research Support

Gas molecules as transcriptional regulators; NIH (EUREKA), 2009-2013; PI: Leo E. Otterbein, PhD

Heme Oxygenase-1 and transplant tolerance; NIH, 2011-2013; PI: Leo E. Otterbein, PhD

Effects of MP4CO in bacterial pneumonia in mice; Sangart, Inc., 2012-2014; PI: Leo E. Otterbein, PhD

Cancer and metabolism; Department of Surgery Affinity Research Collaborative (ARC), 2012-2014; PI: Leo E. Otterbein, PhD

Sepsis and trauma; Department of Surgery Affinity Research Collaborative (ARC), 2011-2014; Co-PI, Leo E. Otterbein, PhD (PI: Carl Hauser, MD)

Training in trauma and sepsis research; NIH T32 Training Grant, 2013-2018; Preceptor: Leo E. Otterbein, PhD (Director: Wolfgang Junger, PhD)

Selected Publications

Haschemi A, Kosma P, Gille L, Evans CR, Burant CF, Starkl P, Knapp B, Haas R, Schmid JA, Jandl C, Amir S, Lubec G, Park J, Esterbauer H, Bilban M, Brizuela L, Pospisilik JA, Wagner O*, Otterbein LE*. The sedoheptulose kinase CARKL directs macrophage polarization through control of glucose metabolism. *Cell Metab* 2012;15:813-26. *denotes equal contribution

Mahan VL, Zurakowski D, Pigula FA*, Otterbein LE*. Inhaled carbon monoxide provides cerebral cytoprotection in pigs. *PLoS One* 2012;7:e41982. *denotes equal contribution

Onyiah JC, Sheikh SZ, Maharshak N, Steinbach EC, Russo SM, Kobayashi T, Mackey LC, Hansen JJ, Moeser AJ, Rawls JF, Borst LB, Otterbein LE, Plevy SE. Carbon monoxide and heme oxygenase-1 prevent intestinal inflammation in mice by promoting bacterial clearance. *Gastroenterology* 2013;114:789-98.

Sun S, Sursla T, Adibnia Y, Zhao C, Zheng Y, Li H, Otterbein LE, Hauser CJ, Itagaki K. Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways. *PLoS One* 2013;8:e59989.

Kuramitsu K, Sverdlov DY, Liu SB, Csizmadia E, Burkly L, Schuppan D, Hanto DW, Otterbein LE, Popov Y. Failure of fibrotic liver regeneration in mice is linked to a severe fibrogenic response driven by hepatic progenitor cell activation. *Am J Pathol* 2013;183:182-194.

Andria B, Bracco A, Attanasio C, Castaldo S, Cerrito MG, Cozzolino S, Di Napoli D, Giovannoni R, Mancini A, Musumeci A, Mezza E, Nasti M, Scuderi V, Staibano S, Lavitrano M, Otterbein, LE,* Calise F. Biliverdin protects against liver ischemia reperfusion injury in swine. *PLoS One* 2013; in press. *Communicating author

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James R. Rodrigue, PhD

Associate Professor of Psychology

Director, Center for Transplant Outcomes and Quality Improvement

Director, Behavioral Health Services and Research, The Transplant Institute

Research Group

Jodi-Ann Dattadeen

Lauren Finnigan

Aaron Fleishman

Alexa Hiley

Maeve Moore

Matthew Paek, MA

Sucheta Ravindran

Denny Tsai

Tanya Vishnevsky, PhD

Research Focus

My research program focuses on one central question: “How can we reduce the gap between the number of people who need transplants and the availability of organs for transplantation?” The success of transplantation is limited by the shortage of donated organs. In the United States in recent years, the number of deceased donors has remained flat and the number of living donors has declined. Meanwhile, the number of individuals needing transplantation continues to rise, with over 118,000 people currently on the national transplant waiting list.

Together with colleagues in the Transplant Institute (Michael Curry, MD, Amy Evenson, MD, Didier Mandelbrot, MD, and Martha Pavlakis, MD) and the New England Organ Bank (Waltham, MA), we are developing novel strategies to increase rates of deceased and living donation. These strategies address individual and systems barriers that have been shown in my earlier research to be associated with lower organ donation rates. The success of our research program is due largely to the collaborative partnerships we have with federal and state governments, organ procurement organizations, and researchers from diverse professional backgrounds (behavioral sciences, medicine, surgery, public health, bioethics, nursing, and health services).

From willingness to action: Increasing the number of registered organ donors in New England

The majority of the American public has very favorable views toward organ donation, yet fewer than half are registered organ donors. We are examining how to most effectively and efficiently move individuals from favorable attitudes to behavioral action (i.e., documenting donation intention). Since the Department of Motor Vehicles (DMV) in every state is required by law to ask the organ donation question and to document donation intention, we use DMV offices as the venue for intervention delivery. Based on our successful preliminary work in Florida, we are currently conducting randomized trials to evaluate the effectiveness of a DMV staff training, organ donation messaging, and community-based campaigns to increase rates of donor registration at the state population level in Massachusetts and Rhode Island.

Old-fashioned house calls: Closing the disparity gap in living kidney donation

For most adults with end-stage renal disease, live donor kidney transplantation yields better patient and graft survival outcomes compared to long-term dialysis or deceased donor transplantation. However, blacks are nearly five times less likely to receive a kidney from a living donor. We have developed a novel intervention designed to remove barriers to living donation in the black community and thereby reduce the racial disparity in live donor kidney transplantation. In two prior studies, we found that making “house calls” and directly engaging the patient’s family and social network in the transplant process can increase rates of living donation in the black community. Trained health educators visit patients and their support system in the family home, addressing common concerns and barriers to living donation, reducing misperceptions and distrust, and enabling more shared decision-making. In a new clinical trial, we are evaluating whether supplementing the House Calls intervention with an online patient-centered decision support component further reduces racial disparity in rates of live donor kidney transplantation.



Accomplishments 2012-2013

We received NIH funding to evaluate strategies to reduce racial and income disparities in live donor kidney transplantation. Also, we continue our NIH-funded multi-site Kidney Donor Outcomes Cohort (KDOC) study, which evaluates surgical, medical, psychological, and cost outcomes following living donation.

I co-authored several manuscripts describing the decline in living kidney donation in the U.S. and factors contributing to it (Transplantation, 2013), challenges to research and innovation to optimize deceased donor organ quality and quantity (Am J Transplant, 2013), and challenges inhibiting optimal adoption of kidney paired donation (Am J Transplant, 2013). I accepted invitations to present our work at the International Congress of The Transplantation Society in Berlin; the Ethical, Legal, and Psychosocial Aspects of Transplantation meeting in Rotterdam; the American Transplant Congress in Seattle; and the European Society of Transplantation in Vienna.

Other recent accomplishments include:

- Invitations to serve on the editorial boards of *Transplantation*, *Open J Transplant Surg*, and *J Surg Transplant Science*
- Invitation to serve on NIH Study Section (Behavioral Medicine)
- Invitation to serve on Steering Committee for the Invitational Meeting on Pediatric Organ Donation and Transplantation in Geneva
- Selected to Executive Committees of both the Living Donation Community of Practice and the Psychosocial Community of Practice in the American Society of Transplantation
- Selected to represent the American Society of Transplantation on the Joint Societies Working Group on Living Liver Donation

Teaching, Training, and Education

I continue to provide training and mentorship to post-doctoral fellows and research assistants. Other activities include:

- Co-Director (with Marc Schermerhorn, MD, and Tara Kent, MD, MS) of the department's Clinical Scholarship Program, providing first-year residents with mentored clinical research experience
- Co-Director (with Marc Schermerhorn, MD, and Jennifer Tseng, MD, MPH) of Surgical Outcomes Analysis & Research (SOAR) program, the epicenter of clinical research in the department
- IRB Facilitator for Research and Academic Affairs, helping faculty and trainees successfully navigate and adhere to regulations pertaining to human research protections
- Implemented the department's Pre-Submission Grant Review Program, providing faculty with feedback on research grant proposals prior to submission

Selected Research Support

A randomized trial to reduce the disparity in live donor kidney transplantation; NIH, 2007-2013; PI: James Rodrigue, PhD

Kidney Donor Outcomes Cohort (KDOC) Study; NIH, 2011-2015; PI: James Rodrigue, PhD

Increasing donor registry enrollment using targeted community outreach and online media campaigns; Health Resources and Services Administration, 2011-2014; PI: James Rodrigue, PhD

A DMV-based intervention to increase donor registrations; HRSA, 2012-2014; PI: James Rodrigue, PhD

House calls and decision support: Increasing access to live donor transplantation; NIH, 2012-2017; PI: James Rodrigue, PhD

Cognitive function in dialysis patients: Ancillary study to FHN trial; NIH, 2009-2013; Co-Investigator: James Rodrigue, PhD (PI: Bradley Dixon, MD)

Pegylated interferon +/- Ribavirin for children with HCV (Peds-C); Hoffmann-La Roche, 2011-2013; Co-Investigator: James Rodrigue, PhD (PI: Kathleen Schwarz, MD)

Positive psychotherapy to improve autonomic function and mood in ICD Patients; NIH, 2013-2015; Co-Investigator: James Rodrigue, PhD (PI: Eva Serber, PhD)

Selected Publications

Rodrigue JR, Pavlakis M, Egbuna O, Paek MJ, Waterman AD, Mandelbrot DA. The "House Calls" trial: A randomized controlled trial to reduce racial disparities in live donor kidney transplantation: Rationale and design. *Contemp Clin Trials* 2012;33:811-8.

Rodrigue JR, Paek MJ, Egbuna O, Waterman AD, Pavlakis M, Mandelbrot DA. Willingness to pursue live donor kidney transplantation among wait-listed patients with human immunodeficiency virus (HIV): A preliminary investigation. *Transplantation* 2013;95:787-90.

Abt PL, Marsh CL, Dunn TB, Hewitt WR, Rodrigue JR, Ham JM, Feng S. Challenges to research and innovation to optimize deceased donor organ quality and quantity. *Am J Transplant*. 2013;13:1400-4.

Rodrigue JR, Schold JD, Mandelbrot DA. The decline in living kidney donation in the United States: Random variation or cause for concern? *Transplantation*; in press.

Schold JD, Goldfarb DA, Buccini LD, Rodrigue JR, Mandelbrot DA, Heaphy ELG, Fatica R, Poggio ED. Hospitalizations following living donor nephrectomy in the United States. *Clin J Am Soc Nephrol*; in press.

Rodrigue JR, Hanto DW, Curry, MP. The Alcohol Relapse Risk Assessment: A scoring system to predict the risk of relapse to any alcohol use after liver transplantation. *Prog Transplant*; in press.

A complete list of publications begins on page 17

Barbara Wegiel, PhD, MSc

Assistant Professor of Surgery



Research Group

Zsuzsanna Nemeth, PhD
Kavita Bisht, MSc
Mailin Li
Julia Blanter

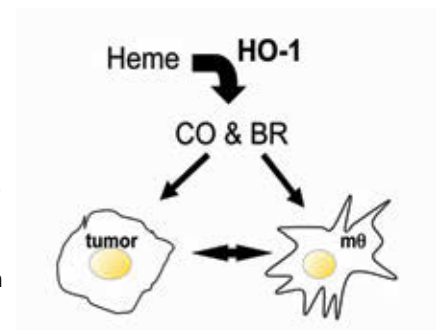
Research Focus

A major interest of our laboratory is the heme degradation pathway and cytoprotective protein, heme oxygenase-1 (HO-1), which during heme catalysis generates carbon monoxide (CO), iron, and biliverdin (BV). HO-1 acts in concert with biliverdin reductase (BVR) to form one of the strongest antioxidants, bilirubin (BR). We focus on the role of HO-1 and BVR in inflammation and tumor biology. Together with Leo Otterbein, PhD, we have demonstrated that HO-1 is a critical regulator of DNA repair pathways and hypothesized its contribution in cancer, premature aging, and other diseases. Further, we have uncovered novel properties of BVR to act as a signaling molecule and mediate anti-inflammatory effects of BV. We continue to explore the role of BVR using our newly generated *BVR-fl/fl* conditional knockout mice as well as transgenic models of carcinogenesis.

A role of HO-1 and carbon monoxide in cancer

One of our projects is focused on the characterization of molecular mechanisms and the role of HO-1 and heme degradation products, carbon monoxide and bile pigments in cancer, with an emphasis on the microenvironment and metabolic status of the cells. Our data suggest that cancer cells maintain low levels of enzymatically active nuclear HO-1, which contributes to the malignancy, while application of heme degradation products or introduction of enzymatic activity of HO-1 will drive cancer cell death. CO at low, safe concentrations inhibits prostate cancer growth in a tumor xenograft model in nude mice via accelerating apoptosis and inducing growth arrest, in part through restoration of mitochondrial respiration. Further, CO sensitizes cancer cells to doxorubicin treatment while preserving normal tissues, making it an ideal candidate for regulation of toxicity to mitochondria. Moreover, we are currently exploring how a balance between the innate immune response to eliminate cancerous cells and the promotion of cancer growth is regulated by HO-1 and polarization of tumor-associated macrophages (TAM). (Figure 1).

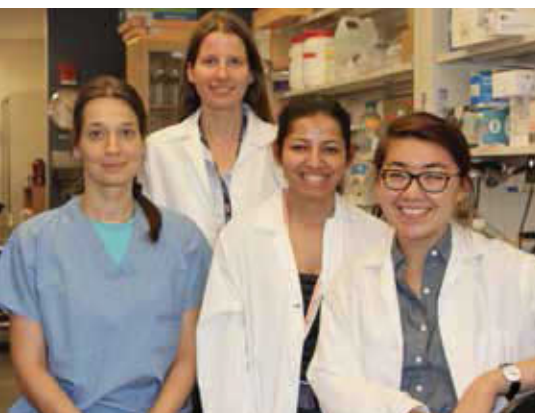
▼ Figure 1



We are currently working with HO-1 conditional knockout mice to specifically delete HO-1 expression in prostate epithelial cells as well as stroma cells (i.e., inflammatory cells) in the TRAMP and *PTEN/p53-fl/fl*-Cre-probasin transgenic mice to test the role of HO-1 in cancer development and progression.

Biliverdin reductase and bile pigments signaling during the inflammatory responses

We are studying the role of bile pigments, which act specifically via BVR during the inflammatory responses. We showed that BVR is acting as a receptor for BV and mediates its effects through Akt-IL-10 signaling pathway and direct inhibition of TLR4 expression. Our hypothesis is that BVR is a major signaling molecule that is activated upon conversion of BV to BR and has potent anti-inflammatory effects in the innate immune system. We have generated *BVR-fl/fl* conditional knockout mice and are currently testing the effects of tissues-specific deletion of BVR in mice models of inflammatory disorders.



▲ Members of Dr. Wegiel's laboratory

Accomplishments 2012-2013

- Invited speaker and new investigator plenary session speaker (top five abstracts) at the International Meeting on Heme Oxygenases and Related Enzymes, Edinburgh, UK, 2012
- 2013-2014 Eleanor and Miles Shore 50th Anniversary Fellow
- Cover of *Trends in Molecular Medicine*; "The social network of carbon monoxide in medicine," 2013;19:3-11.
- A study of Mailin Li, a research student in the lab, was selected for oral presentation (15 out of more than 150 abstracts) at the Harvard Medical School Surgery Research Day, May 11, 2013. (Li M, Gallo D, Csizmadia E, Otterbein LE, Wegiel B. Carbon monoxide induces chromatin remodeling to facilitate endothelial cell migration.)
- Ad hoc reviewer for the following journals: *European Urology*, *Molecular and Cellular Biochemistry*, *Respiratory Care*, *Current Chemical Biology*, *Radiation Oncology*, *Neurological Research*, *Antioxidant Redox Signaling*
- Reviewer of Harvard Catalyst grant applications, April 2012
- Reviewer of Polish National Academy grants, 2013
- Member of American Heart Association
- Judge at the 17th Annual ASBMB Undergraduate Student Research Poster Competition, Experimental Biology Conference, April 20, 2013, Boston, MA

Invited Presentations

- Go green: Antiinflammatory role of biliverdin reductase, International Meeting on Heme Oxygenases and Related Enzymes, Edinburgh, UK, 2012
- Carbon monoxide as a host immune sensor, International Meeting on Heme Oxygenases and Related Enzymes, Edinburgh, UK, 2012
- Heme degradation pathway and sterile inflammation, Department of Medical Biotechnology, Jagiellonian University, Krakow, Poland, 2013

Teaching, Training, and Education

I have been training research fellows, summer students, and research assistants in the laboratory for the past five years. During the last two years, I have been a supervisor for one post-doctoral fellow, two summer students, one visiting PhD student, and one research assistant. I am involved in teaching experimental design, molecular and biochemical techniques, data acquisition and analysis, as well as manuscript preparation.

Selected Research Support

Role of biliverdin reductase in sterile inflammation; Eleanor and Miles Shore 50th Anniversary Fellowship, 2013-2014; PI: Barbara Wegiel, PhD

Heme degradation pathway and immunomodulation in prostate cancer; NIH, 2013-2015; PI: Barbara Wegiel, PhD

The role of heme oxygenase-1 derived-carbon monoxide in vascular injury and repair; NCRP Scientist Development Grant, American Heart Association, 2009-2013; PI: Barbara Wegiel, PhD

Department of Surgery start-up package, 2011-2014; PI: Barbara Wegiel, PhD

Cancer and metabolism; Department of Surgery Affinity Research Collaborative (ARC), 2012-2014; Co-PI: Barbara Wegiel, PhD (PI: Leo E. Otterbein, PhD)

Selected Publications

Banerjee P, Basu A, Wegiel B, Otterbein LE, Mizumura K, Gasser M, Waaga-Gasser AM, Choi AM, Pal S; Heme oxygenase-1 promotes survival of renal cancer cells through modulation of apoptosis- and autophagy-regulating molecules. *J Biol Chem* 2012; 287 (38):32113-23.

Wegiel B, Otterbein LE. Go green: The anti-inflammatory effects of biliverdin reductase. *Front Pharmacol* 2013;3:47.

Wegiel B, Hanto DW, Otterbein LE. The social network of carbon monoxide in medicine. *Trends Mol Med* 2013; 19(1):3-11.

Wegiel B, Otterbein LE: Heme-originated gas molecule in DNA repair and cancer. Concept Press, *The Research and Biology of Cancer*, 2013.

Wegiel B, Nemeth Z, Costa M, Bulmer A, Otterbein LE. Heme oxygenase-1: A metabolic Nike. *Antioxidant Redox Signaling*, Forum Issue 2003; in press.

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Research Group

Laura Dunn
Haydn Kissick, PhD
Daniel McManus
Chris Seungtae On

Research Focus

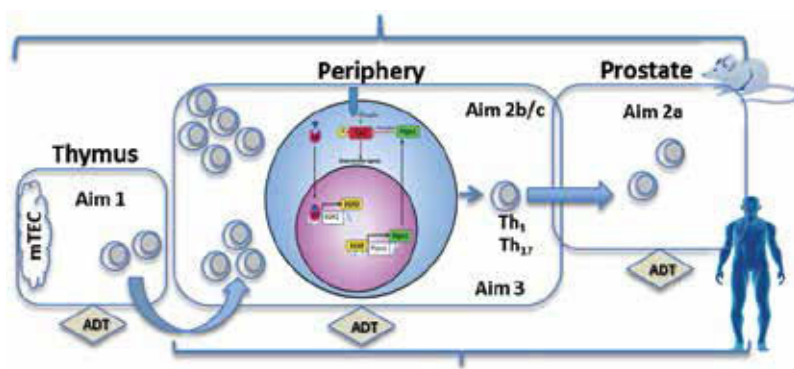
My research revolves around immunology and immunotherapy of prostate cancer with a special emphasis on exploring mechanisms driving immune tolerance to tumor antigens and pre-clinically implementing novel cancer immunotherapy platforms. I am especially interested in the concept of combinatorial immunotherapy, which tests the translation potential of new breakthroughs in immune tolerance into efficient immunotherapeutic strategies in conjunction with cancer vaccines. My recent efforts represent a transition that has allowed me to establish my abilities as an independent investigator. I have developed a set of related projects that reflect the vision I have for my future scientific career. Three representative projects are described below.

Androgen regulation of T cell responses to cognate antigen (Figure 1)

The ultimate goal is to understand how hormone therapy can be best combined with prostate cancer immunotherapy, and to discover new molecules that could be targeted clinically. A comprehensive gene expression profiling of castrated CD4+ T lymphocytes

revealed major dysregulations in key signaling pathways such as T cell differentiation, IFN- γ , and IL-10. We have shown that testosterone affects T cell differentiation through modulation of the phosphorylation state of several key signaling components, including Tyk, JAK2, and EGR2, as a result of PTPN1 gene upregulation through a direct binding of the androgen receptor to the PTPN1 gene. This phenomenon was also found to take place in peripheral blood lymphocytes in prostate cancer patients undergoing hormone therapy. Further experiments using specific inhibitors corroborated the implication of PTPN1, suggesting that targeting PTPN1 could be a viable strategy to replace hormone therapy in prostate cancer patients who are given immunotherapy, but also as immune-enhancer in the context of cancer vaccine therapy overall.

Recent data suggest ERG2 could be of similar importance as a therapeutic target for immunopotentialization of cancer vaccines.



▲ Figure 1: Outline of the objectives of the androgen induced immunoregulation project.

Personalized vaccine design for cancer immunotherapy

This project explores the possibility of using immunogenic epitopes that arise from patients' tumor-specific coding mutations in personalized cancer vaccine design. Peptide-based vaccines are identified *in silico* from genome-wide sequencing data, and tested *in vitro* and *in vivo* using an array of bioinformatics tools, binding assays, humanized mice, and human peripheral blood. Using laser capture micro-dissection to selectively harvest malignant epithelial cells of human prostate tumors, we have been able to identify numerous novel, distinct coding mutations, many of which are predicted or confirmed to react with the patient's own HLA alleles, as demonstrated in humanized mice for HLA-A*0201 haplotype.

Listeria-based vaccine delivery platform for the treatment of cancer

This effort consists of a multi-institutional collaboration involving BIDMC, Aduro Biotech, Johns Hopkins University, and Emory University, with the goal of starting a phase I clinical trial as soon as preclinical testing is completed. The live-attenuated *Listeria* platform provides an efficient antigen delivery system achieving high immunogenicity, and offers the possibility to insert a full or partial antigen sequence, or even a single immunogenic epitope. This platform has been carried through clinical trials in pancreatic cancer by my partners at Aduro Biotech and has demonstrated efficacy and safety.

Accomplishments 2012-2013

Research

- In the last two years, I have completed a number of research projects that were funded by the Department of Defense (DoD, New Investigator Award) and the Prostate Cancer Foundation (Young Investigator Award). Specifically, I completed the preclinical phase of development of peptide-based vaccines for the treatment of prostate cancer. In the process of bringing this work closer to the clinic, I have two ongoing collaborations with Liquidia Technologies (Morrisville, NC) and Aduro Biotech (Berkeley, CA), addressing the applicability of nanoparticle and live-attenuated *Listeria* platforms for tumor antigen delivery. The two platforms are being tested in clinical trials in the context of infectious disease and pancreatic cancer, providing safe and efficient means for our translational work. My contributions to these new collaborations are funded by an ongoing challenge grant from the Prostate Cancer Foundation and a recently awarded Hypothesis Idea Development grant from the DoD. We anticipate that this work will result in applications for NIH SBIR/STTR grants and DoD laboratory-to-clinical transition grants, ultimately leading to IND filing and phase I clinical trials.
- In addition, I have contributed to the success of several collaborative projects. These include: the α -GalCer-based vaccine for prostate cancer (a collaboration with Dr. Balk at BIDMC and Dr. Exley at Brigham and Women's Hospital); CD21-driven EBV infection of B lymphocytes (a collaboration with Dr. Fingerth at BIDMC); and reversing autoimmune disease in mice through metabolic manipulation of T lymphocyte differentiation (a collaboration with Dr. Elkhail at Brigham and Women's Hospital).

Administrative

- Member, DF/HCC CURE Advisory Board Member and Selection Committee
- Reviewer, Qatar Foundation Annual Research Conference
- Reviewer, DoD CDMRP PRPC Review Panel
- Assessor, PhD thesis, Graduate School of Health and Medical Sciences, University of Copenhagen, Denmark

Teaching, Training, and Education

I contributed to the Harvard Medical School cancer vaccine nanocourse in the spring of 2012 with two BIDMC Cancer Center faculty members. In addition, I hosted students participating in the Dana-Farber/Harvard Cancer Center Continuing Umbrella of Research Experience (CURE) program in the summer of 2012. I regularly participate in the BIDMC Exploration Program and the Red Sox Scholars Shadow Day by hosting groups of middle and high school students to briefly introduce them to the cancer research environment in my lab and the BIDMC Cancer Center. In addition, I am supervising two undergraduate students from UMass Boston and Massachusetts College of Pharmacy and Health Sciences who are conducting small research projects in my laboratory.

Selected Research Support

Nanoparticle-targeted peptide vaccines for prostate cancer; Prostate Cancer Foundation Challenge Grant, 2011-2013; PI: Mohamed Arredouani, PhD

Live-attenuated *Listeria* expressing an HLA-A2.1-restricted, ERG-derived immunogenic epitope for prostate cancer immunotherapy; Department of Defense Exploration Hypothesis Development Award, 2013-2014; PI: Mohamed Arredouani, PhD

Peptide immunization against ERG and immunogenic mutations to treat prostate cancer; Department of Defense Postdoctoral Fellowship, 2013-2015; Mentor: Mohamed Arredouani, PhD (PI: Haydn Kissick, PhD)

Selected Publications

Kissick H, Sanda MG, Dunn LK, Arredouani MS. Development of a peptide-based vaccine targeting TMPRSS2:ERG fusion positive prostate cancer. *Cancer Immunol Immunother* 2013; in press.

Heinbokel T, Li S, Trachenberger AJ, Rodriguez H, Biefer C, Mounayar M, Chabtini L, Edtinger K, Young MHH, Arredouani MS, Kuo WP, Ghiran I, Vasudevan A, Tullius SG, Elkhail A. Reversing autoimmune disease in mice through metabolic manipulation of T lymphocyte differentiation. (Revised manuscript in preparation for resubmission to *Cell*).

Arredouani MS, Bhasin M, Sage D, Gill MB, Libermann T, Fingerth J. Novel and distinct roles of CD21 in B-cell maturation and initiation of EBV infection revealed by a comprehensive transcriptome analysis. (Submitted to *Journal of Virology*, September 2013).

Kissick H, Finke J, Dunn L, Asara J, Sanda M, Arredouani MS. Metabolic profiling of T-cell differentiation and tolerance. *J Immunol* 2012;188:115.5.

Arredouani MS, Haydn Kissick, Laura Dunn, and Martin Sanda. Distinct transcriptome of regulatory T cells in prostate cancer. *J Immunol* 2012;188:162.18.

Arredouani MS. Personalized, peptide-based vaccine design for prostate cancer. Qatar Foundation Annual Research Forum, Doha, Qatar; November 2012.

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William C. DeWolf, MD

Professor of Surgery
Chief, Division of Urology



Research Focus

Basic research

Using the embryonal carcinoma model in the form of human cancer stem cell lines derived from human germ cell tumors, we have discovered a novel cancer stem cell marker called podocalyxin. When found in stem cells and cancer, it is associated with TRA antigens that are known stem cell markers. The TRA markers have also been identified as potential serum markers for testes cancers. With the identification of podocalyxin as the carrier of the TRA molecules, studies can now be done to further the initial findings of TRA antigens in human cancers and stem cells.

Our current studies on podocalyxin are now focused in two directions. The first is to determine the function of podocalyxin in human stem cells by identifying other molecules in stem cells that interact with podocalyxin. Thus far we have identified six podocalyxin interacting proteins that include the glucose transporter — the molecules responsible for supplying energy to all cells. This would represent the first characterized interaction between a glucose transporter and a cell adhesion protein. In almost all human cancers glucose transporters are highly over-expressed but very little is known about the molecular mechanisms that drive the process.

The second direction with our studies of podocalyxin is more clinically associated. 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 serum cancer marker.

Clinical research

Clinical research is quite active and deals with active surveillance in the management of prostate cancer. Currently we have over 150 patients enrolled over a 10-year period and followed by a strict active surveillance protocol refereed by a 20 core saturation biopsy technique performed every 12-18 months as a restaging process. We have published our first manuscript, which characterizes the criteria that predict odds to progression for patients in the process of being monitored. The three key factors involve PSA density, family history, and PSA progression. We are currently working on the outcomes of patients on the active surveillance program, with specific attention paid to those that progressed and underwent surgery. We are trying to answer the question, "Is it safe to withhold treatment under the active surveillance program, or should patients be treated immediately?" The results thus far are favorable to waiting because none of the patients subsequently operated on (n=22) had positive margins or Gleason 8 (high grade) pattern of prostate cancer.

Basic science

We have previously confirmed that the stem cell/cancer cell adhesion protein podocalyxin forms a specific complex with the glucose 3 transporter in human cancer stem cells. We currently have preliminary evidence that podocalyxin reacts and identifies selectively metastatic prostate cancer cells.

Clinical

Our manuscript describing the outcome of the 150 patients followed by active surveillance enrolled over 10 years is currently underway ("Preliminary Outcome of Primary vs. Deferred Therapy in Men with Low Risk Prostate Cancer Diagnosed and Followed with 20 Core Biopsy Technique"). The results are promising in that of the 22 patients who progressed and went to surgery, none had positive margins or were node positive, and only one patient had extracapsular extension, which is far below the norm.

Administrative

This has been a big year. We have started two new fellowships to fill in two clinical gaps. The first is the Minimally Invasive Surgery Fellowship; our fellow, Peter Chang, MD, is in his second year of the fellowship, learning robotic surgery under the leadership Andrew Wagner, MD, and Peter Steinberg, MD. Dr. Chang will also obtain an MPH degree from the Harvard School of Public Health. He is adding to our already growing minimally invasive program, which was topped off last year by an instructional course directed by Andrew Wagner, MD, and sponsored by Intuitive, Inc., which was held at BIDMC for residents. The course was so successful that a second, daylong course for faculty and residents took place in the fall of 2013. The second fellowship is in Sexual Dysfunction and Infertility, with Abraham Morgentaler, MD, and myself as directors. Ravi Kacker, MD, already began his first clinic, which was filled with six patients, demonstrating the need for this service.

Another administrative landmark was the hiring of Peter Steinberg, MD, as an expert in minimally invasive surgery for urinary stone disease. Dr. Steinberg did his fellowship training at Albert Einstein School of Medicine in Bronx, NY, which he completed in 2010. The division now has fellowship-trained expertise in oncology, minimally invasive surgery, neurourology/urodynamics, sexual dysfunction and infertility, and urolithiasis.

Finally, plans have been approved to increase the space of our division by 50% to accommodate new fellows, staff, and research personnel.

Teaching, Training, and Education

The division sponsors a CME course biannually on Men's Health; the next is April 2014 in Boston. Dr. Michael Kearney and I are preceptors for a general HMS course in urologic science for Harvard Medical School students, which includes a rotation on the Urology service and clinical and didactic experience. Our training focuses on our three Urology residents programmed from Brigham and Women's Hospital, as well as our two fellowship programs in Minimally Invasive Surgery (Directors: Andrew Wagner, MD, and Peter Steinberg, MD) and Sexual Dysfunction and Infertility (Directors: myself and Abraham Morgentaler, MD).

I also present numerous lectures and participate in national organizations, including: AUA Program Co-Chair for Basic Research in Prostate Cancer; Medical Advisory Board, Boston Prostate Cancer Walk; Invited Speaker, Boston Coalition for Prostate Cancer; and the editorial boards of *Urology*, *Harvard Men's Health Watch*, and *Harvard Perspectives in Prostate Disease*.

Selected Research Support

Harvard/Michigan prostate cancer biomarker clinical center; NIH, 2010-2012; Co-Investigator: William DeWolf, MD (PI: Martin Sanda, MD)

Intramural funding, Division of Urology, BIDMC

Delto JC, Kacker R, Bubley G, DeWolf WC. Intravesical mitomycin therapy for stage T1 and Tis high grade squamous cell carcinoma of the bladder. Clin CU Cancer 2013; in press.

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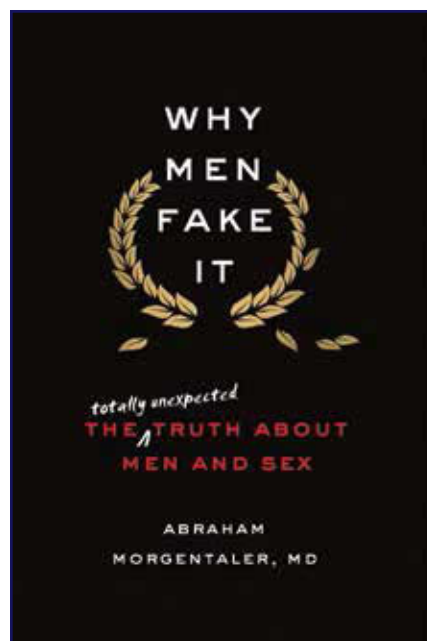
Abraham Morgentaler, MD

Associate Clinical Professor of Surgery
Director, Men's Health Boston

Research Focus

My research focus is on the impact of testosterone deficiency on various aspects of health, and the relationship of testosterone and prostate cancer.

Testosterone deficiency is a major issue in men's health and has been a focus of my clinical and academic activities for 20 years. This issue fits nicely into my practice, Men's Health Boston, which is affiliated with BIDMC and its Department of Surgery. Men's Health Boston was the first center in the US providing comprehensive evaluation and management of male-specific health issues, including erectile dysfunction and other sexual issues, male infertility, prostate health, and hormonal issues, especially testosterone deficiency. Research performed at Men's Health Boston has contributed significantly to a re-evaluation of the previously axiomatic concept that higher serum testosterone causes more rapid prostate cancer growth and is therefore a risk factor for prostate cancer. Current data from our own center and others indicates that this concept is incorrect. Reduced concerns regarding prostate cancer have allowed expansion of testosterone therapy into areas that could not be imagined just a decade ago.



Accomplishments 2012-2013

- In April 2013 I published my fourth book, entitled “Why Men Fake It: The Totally Unexpected Truth About Men And Sex”
- My group was awarded first prize in the localized prostate cancer section at the national meeting of the American Urological Association (AUA) for our abstract reporting a low rate of cancer progression in 33 men with untreated prostate cancer who received testosterone therapy for a median of 2.5 years. I was course director for a new postgraduate course on testosterone therapy at that same meeting, which received high evaluations from the 200+ attendees.
- I was an invited lecturer in six foreign countries, was course director at the meeting of the International Society for Sexual Medicine, and was lecturer and moderator at an international meeting on androgens and the prostate in Berlin, Germany.
- I have authored nine articles that have appeared in medical journals since the beginning of 2012.

Teaching, Training, and Education

I teach medical students about male reproduction and sexuality in the classroom each year in the HST course on Human Reproduction. I provide teaching and training of urology residents in the operating room, on the wards, and in conferences. I run an Andrology Journal club on a bimonthly basis. Beginning in July 2013, with Dr. William DeWolf I co-direct the Andrology Fellowship at BIDMC and Men's Health Boston.

Abstracts, Posters, and Exhibits

Clinical efficacy of collagenase clostridium histolyticum in the treatment of Peyronie's disease by baseline penile curvature severity stratum: Results from two large double-blind, randomized, placebo-controlled phase 3 studies. AUA, May 2013, San Diego, CA

Testosterone therapy in men with untreated prostate cancer. Mariam Hult, William P. Conners, III, Abraham Morgentaler, MD

Selected Publications

Kacker R, Hornstein A, Morgentaler A. Free testosterone by direct and calculated measurement versus equilibrium dialysis in a clinical population. Epub 2013 Oct 3.

Kacker R, Traish AM, Morgentaler A. Estrogens in men: Clinical implications for sexual function and the treatment of testosterone deficiency. J Sex Med 2012 9:1681-96.

Morgentaler A. Goodbye androgen hypothesis, hello saturation model. Eur Urol 2012;62:765-7.

Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: From physiology to clinical implications. Eur Urol. Epub 2013 Aug 16.

Conners WP 3rd, Morgentaler A. The evaluation and management of testosterone deficiency: The new frontier in urology and men's health. Curr Urol Rep. Epub Sep 3, 2013.

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Andrew A. Wagner, MD

Assistant Professor of Surgery
Director, Minimally Invasive Urologic Surgery



Research Group

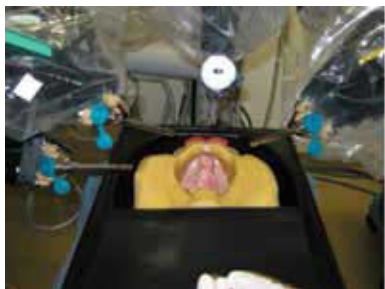
Peter Chang, MD
Catrina Crociani, MPH
Kimberly Taylor
Srikanth Vedachalam

Research Focus

Kidney cancer

We are interested in evaluating recovery trends after both open and minimally invasive kidney surgery by prospectively collecting patient-reported quality of life data. Our pilot data was published in *Urology* in 2012. Our goal is for this to become multi-center study, so we recently began accruing patients at Brigham and Women's and Faulkner hospitals. We are working to include other New England institutions within the next year. This data will be used to define recovery trends after various approaches to kidney surgery (including open, laparoscopic, and robotic surgery), compare recovery after radical and partial nephrectomy, and evaluate optimal situations for cytoreductive nephrectomy. We also aim to define the costs of kidney surgery, including hospital costs and societal costs — by incorporating patient-reported data about leave from work, salary lost, and family leave taken to help care for the patient. Our work comparing hospital costs of open, laparoscopic, and robotic partial nephrectomy was recently published in the *Journal of Endourology* (2013).

Our team has helped refine minimally invasive surgical approaches for kidney cancer. We were the first to describe an “early unclamping” technique for robotic partial nephrectomy (*Journal of Endourology*, 2011). We have also put together a large (700 patient) retrospective database with French investigators to further evaluate the utility of this technique. In addition, we described a method of robotic partial nephrectomy for hard-to-reach upper pole tumors. Our video describing this “kidney transposition technique” was awarded the first prize at the World Congress of Endourology in Turkey in 2012.



▲ Robotic prostatectomy simulator using porcine tissue.



We are also interested in surveillance for small renal masses. Many of these patients do not require treatment because competing comorbidities outweigh the significance of the indolent small renal mass. We are an active member of the DISSRM study (Delayed Intervention and Surveillance for Small Renal Masses), and are prospectively following patients who choose surveillance. This study, led by investigators at Johns Hopkins University, evaluates the natural history of these masses and will help improve our decision-making about treatment vs. surveillance in this population.

Prostate cancer

We are the only Northeast center to be a member of the Prostate Cancer Active Surveillance Study (PASS). This is a multi-center study with over 1,000 patients enrolled. We are collecting clinical data, as well as urine and serum, from patients in an effort to identify important biomarkers that could distinguish which patients have more aggressive prostate cancer that eventually requires treatment.

Bladder cancer

We are the first robotic team in Boston to complete a radical cystectomy and urinary diversion completely robotically. We would like to objectively compare this approach to traditional open surgery and are gathering prospective data with a focus on clinical outcomes and validated quality of life data. We also recently joined the IRCC (International Radical Cystectomy Consortium) for radical cystectomy, a large (150 center) database project aimed at evaluating trends in cystectomy treatment over time.

Accomplishments 2012-2013

We continue to accrue patients from BIDMC, Brigham and Women's and Faulkner hospitals to our prospective study evaluating health-related quality of life following kidney surgery. At the EAU in Paris, 2012 we presented our data on cytoreductive nephrectomy and found most patients recovered to near baseline by four weeks.

We also accrue patients to the Prostate Cancer Active Surveillance Study (PASS), perhaps the largest multi-center study following men with low-risk prostate cancer. We published our work on the costs of open, laparoscopic, and robotic partial nephrectomy. We demonstrated similar variable costs for all three approaches but increased fixed costs related to robotic equipment.

We submitted our work on a new robotic prostatectomy simulator that uses inanimate porcine tissue (Figure 1). Our simulator allows trainees to practice robotic surgery in a safe environment prior to operating on patients. We validated this simulator by comparing performance among novice and expert robotic surgeons.

In other accomplishments, I was elected to the AUA leadership program 2012-2013; I represented New England at this year-long program, which helps foster innovation among young urologists. I attended multiple leadership conferences, participated in the UROPAC advocacy conference in Washington, DC, and helped develop a team project for urology advocacy. I was also nominated as a member of the AUA Robotics, Laparoscopy and New Technology Committee, a national committee to examine technology in urologic surgery. In addition, our video "Renal transposition in robotic partial nephrectomy: A novel technique for excision of upper pole tumors," received the first prize at the 2012 World Congress of Endourology in Istanbul, Turkey.

Invited Presentations

- Surgery in the setting of metastatic disease, International Kidney Cancer Symposium, Chicago, IL, 2012
- Kidney cancer take-home messages, American Association of Urology annual meeting, San Diego, CA 2012
- Is robotic prostatectomy the new gold standard? Cancer of the Prostate Symposium, Catolica Universidad de Chile, Santiago, 2012
- Developing a robotic surgery program, Hospital Grand Rounds, Catolica Universidad de Chile, Santiago, 2012

Teaching, Training, and Education

We are one of the primary teaching institutions for the Harvard/Longwood combined Urology Residency Program.

In July 2010, we launched a Urologic Fellowship Program. Fellows spend one to two years at BIDMC pursuing minimally invasive surgical techniques and urologic research. Fellows also have the option of training in clinical effectiveness through the Harvard School of Public Health. Our current fellow is Peter Chang, MD.

In May 2012, we hosted the first ever New England Urologic Robotic Training Course. This two-day course attracted residents, fellows, and attending surgeons from New England and beyond. The second annual course was held October 18-19, 2013.

Abstracts, Posters, and Exhibits

Percy AG, Jacobus SJ, Kaplan JR, Kim SB, Wagner AA. Patient-reported health related quality of life outcomes following cytoreductive nephrectomy. EAU, Paris, 2012

Kaplan J, Percy A, Chang P, Wagner AA. Robot-assisted partial nephrectomy: Early unclamping technique. WCE, Istanbul, Turkey, 2012

Alemozaffar M, Narayan R, Minnillo B, Matthes K, Wagner AA. A novel tissue-based simulator for robotic assisted radical prostatectomy: Validation and stepwise instructions for creation of model. WCE, Istanbul, Turkey, 2012

Selected Publications

Pedrosa I, Rafatzand K, Robson P, Wagner AA, Atkins MB, Rofsky NM, Alsop DC. Arterial spin labeling MR imaging for characterization of renal masses in patients with impaired renal function: Initial experience. *Eur Radiol* 2012;22:484.

Pedrosa I, Sun ME, Wagner AA, Rofsky NM et al. Arterial spin labeling MR imaging of renal masses: Correlation with histopathology findings. *Radiology* 2012; Epub Oct 9.

Sun ME, Wagner AA, San Francisco I, Brook A et al. Need for intraoperative ultrasound and surgical recommendation for partial nephrectomy: Correlation with tumor imaging features and urologist practice patterns. *Ultrasound Quart* 2012;28:21.

Kim SB, Williams SB, Cheng SC, Sanda MG, Wagner AA. Evaluation of patient-reported quality of life outcomes after renal surgery. *Urology* 2012;79:1268.

Alemozaffar M, Chang SL, Kacker R, Sun ME, DeWolf WC, Wagner AA. Comparing costs of robotic, laparoscopic, and open partial nephrectomy. *J Endourol* 2013;27:560.

Kaplan JR, Chang P, Percy AG, Wagner AA. Renal transposition during minimally invasive partial nephrectomy: A safe technique for excision of upper pole tumors. *J Endourol* 2013; in press.

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Elliot L. Chaikof, MD, PhD

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

Research Group

Julianty Angsana
Perla Ayala, PhD
Jiaxuan Chen
Erbin Dai, MD
Vicki Dydek
Jennifer Gagner, PhD
Stephanie Grainger, PhD
Carolyn A. Haller, PhD
Oki Ham
Donny Hanjaya-Putra
Wookhyun Kim, PhD
Venkata R. Krishnamurthy, PhD
Liyang Liu, MD
Mohammed Sardar, PhD

Research Focus

Our laboratory (chaikoflab.org) is focused on the development of biologically inspired materials, devices, and pharmacotherapeutics based upon the principles of molecular engineering and nanofabrication technologies. Ongoing research is directed at the following areas.

Tissue engineering and regenerative medicine

Engineering blood vessels

Synthetic blood vessels for cardiac surgery do not exist. Ongoing efforts in our group seek to design new synthetic collagen and elastin analogues and to assemble them along with vascular wall cells derived from stem cells to engineer a living artery.

Materials for soft tissue repair

Current synthetic materials cannot be used for surgical reconstruction in the setting of bacterial contamination or infection. As a test bed, we are investigating the application of new materials, stem cells, and fabrication techniques to design abdominal wall patches to facilitate normal healing and local tissue repair in the setting of bacterial contamination.

Cell transplantation

A major obstacle in islet transplantation for the treatment of diabetes is the high rate of early islet destruction. Synthetic cell coatings, anti-thrombotic fusion proteins, and carbohydrate mimics that limit inflammatory responses are being explored to enhance the effectiveness of islet transplantation.

Vascular biology

Targeted therapies to promote vascular wall healing

Restenosis remains a major cause of failure after angioplasty and stenting for treatment of lower extremity peripheral arterial disease. New approaches are being developed that target thrombotic and inflammatory events at the site of vessel wall injury through antibody directed targeting of activated platelets.

Preventing and treating aortic aneurysms

Medical therapy that prevents the growth or induces the regression of aortic aneurysms does not exist. Current investigations in our laboratory are directed at harnessing the innate immune system to turn off proteolytic or inflammatory events and promote local tissue repair at sites of early aneurysm formation.

Chemical biology and materials science

Design of anti-thrombogenic surfaces

The development of artificial organs remains limited by the propensity of all synthetic surfaces to induce thrombus formation despite systemic anticoagulation. Current studies are designing surfaces, which present molecules that resist clotting, along with computational models that describe surface-induced coagulation events under conditions of flow.

Chemoenzymatic synthesis of P-Selectin Glycoprotein-1

Selectins play an important role in the recruitment of leukocytes to inflamed tissue. We are currently synthesizing P-Selectin Glycoprotein-1 (PSGL-1) mimics to block inflammatory responses.



▲ Members of Dr. Chaikof's laboratory

Accomplishments 2012-2013

Through new collaborations with David Liu, PhD (Chemistry, Harvard), and Jian Liu, PhD (Chemistry, UNC), we have expanded our efforts directed at identifying and harnessing biologically inspired designs to limit blood clotting on artificial surfaces. In 2013, we were awarded continued support under R01 HL56819: “*In situ* regeneration of bioactive surfaces: Rechargeable anti-thrombogenic films.” The project narrative follows:

The fabrication of a small diameter vascular prosthesis (< 6 mm) remains unsolved due to the absence of a surface coating that reliably resists thrombus formation over clinically relevant time scales. We hypothesize that engineered thin films designed with the capacity for rapid and repeatable covalent recharging of selective molecular constituents, which block thrombin and purinergic pathways, will display sustained resistance to thrombus formation *in vivo*. In the process, the lifetime of bioactive “anti-thrombogenic” films will be extended with enhanced patency of synthetic small diameter arterial substitutes.

Teaching, Training, and Education

Bioengineering PhD candidates Vivek Kumar, Adam Martinez, John Zheng Qu, and Julianty Angsana (primary advisor: Elliot L. Chaikof, MD, PhD) successfully completed degree requirements from the Georgia Institute of Technology, Atlanta, GA.

Selected Research Support

In situ regeneration of bioactive surfaces: Rechargeable anti-thrombogenic films; NIH, 2013-2017; PI: Elliot L. Chaikof, MD, PhD

Site-specific therapies to prevent intimal hyperplasia; NIH, 2011-2016; PI: Elliot L. Chaikof, MD, PhD

Molecularly engineered blockade of islet induced inflammatory responses; NIH, 2010-2015; PI: Elliot L. Chaikof, MD, PhD

Engineered fascia for stem cell therapy in hernia repair; Harvard Stem Cell Institute, 2011-2013; PI: Elliot L. Chaikof, MD, PhD

Selected Publications

Kim W, Brady C, Chaikof EL. Amphiphilic protein micelles for targeted *in vivo* imaging. *Acta Biomater* 2012;8(7):2476-2482.

Ravi S, Caves JM, Martinez AW, Xiao J, Wen J, Haller CA, et al. Effect of bone marrow-derived extracellular matrix on cardiac function after ischemic injury. *Biomaterials* 2012;33(31):7736-7745.

Xiao J, Angsana J, Wen J, Smith SV, Park PW, Ford ML, et al. Syndecan-1 displays a protective role in aortic aneurysm formation by modulating T cell-mediated responses. *Arterioscler Thromb Vasc Biol* 2012;32(2):386-396.

Qu Z, Krishnamurthy V, Haller CA, Dorr BM, Marzec UM, Hurst S, Hinds MT, Hanson SR, Liu DR, Chaikof EL. Immobilization of actively thromboresistant assemblies on sterile blood-contacting surfaces. *Adv Healthc Mater* 2014;3(1):30-5.



◀ Fellow Mohammed Sardar, PhD

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Research Focus

Our research has focused on three main areas of vascular biology: 1) Evaluating mechanisms responsible for prosthetic graft failure, 2) preventing intimal hyperplasia (IH) in vein grafts, and 3) developing novel biomaterials, as well as surface modification.

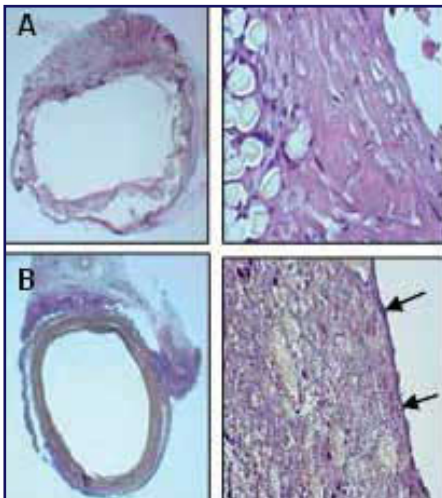
In close collaboration with Matthew D. Phaneuf (Biosurfaces, Inc.), we have developed, through electrospinning, a polyester (Dacron) prosthetic vascular graft with unique structural properties. We have the ability to either modify the vascular graft luminal surface with thrombolytic agents, growth factors, or antibiotics or incorporate them into the prosthetic graft material during the manufacturing process.

Presently we have two ongoing projects. We have created a 4mm ID Dacron prosthetic vascular graft, where the luminal surface has been modified with Activated Protein C (APC), a natural anticoagulant that inactivates factors Va and VIIa, attenuates fibrin deposition, and reduces neutrophil activation. APC also induces endothelial cell (EC) proliferation and migration. Thus, APC decreases thrombosis while fostering cellular EC healing on the graft's luminal surface.

Grafts were implanted in a common carotid artery (CCA) bypass canine model and harvested at different time points: 14, 30, and 60 days. APC grafts had higher patency compared to control plain Dacron grafts (CPG). Overall, APC grafts were $\geq 50\%$ patent, while CPG were $\leq 25\%$. Clopidogrel (Plavix) treatment further improved patency of APC grafts from 50% to 100%, and had no apparent significant effect on CPG.

Histology results are ongoing, H&E and immune markers for CD31, α -Actin and Ki67 are being performed. Quantitative analysis (Velocity program) will be performed between both groups — APC and CPG. Morphometric analysis will also be performed. We are looking forward to these results as they may show significant differences in healing (EC and SMC) that could potentially help in the bioengineering design of small-diameter vascular grafts ≤ 5 mm ID for arterial reconstruction.

The second project we are working on is the *in vivo* (canine) arterio-venous fistula evaluation of our new 6mm ID nanofibrous bioactive hemodialysis access graft (BHAG) which was designed with anti-thrombin, anti-proliferative, and antimicrobial properties by incorporating recombinant Hirudin (rHir), paclitaxel (Pac) and moxifloxacin (Moxi) dissolved in an organic solvent prior to electrospinning. We will be comparing our BHAG to the clinically used ePTFE A-V prosthetic graft. Surgical implants are ongoing and we will harvest our grafts at 30 and 60 days; in addition, grafts are being punctured twice a week to challenge both our BHAG and ePTFE-G to duplicate dialysis needle puncture. We will assess graft patency and overall healing and will perform the same histological, immunohistochemistry, markers and morphometric studies previously described.



▲ H&E cross-section of the mid-portion of a 6mm ID woven Dacron graft (WDG) (A) and a nanofibrous bioactive graft (NBG) (B) at 60 days revealed that the NBG had significant cellular penetration supported by neo-vascularization without thrombus formation. An EC cell layer (arrows) CD31 positive was also evident. In contrast, the WDG had increased luminal thrombus formation and poor cellular infiltration and neo-vascularization. (10X & 40X)

Accomplishments 2012-2013

Our first generation nanofibrous bioactive graft design demonstrated that a combinatorial approach using rHir and VEGF (Figure 1) directly released from the nanofibrous matrix over an extended period of time prevented acute thrombosis and promoted EC migration and proliferation throughout the graft upon implantation in our canine carotid arterial grafting model. Observation of this unique type of cellular healing was exciting and encouraging, since spontaneous endothelialization does not occur in this animal model and in humans. Unfortunately, anastomotic intimal hyperplasia (AIH) occurred at the anastomotic sites (60 days). We are currently considering different methodologies to prevent SMC increased proliferation, either by incorporating antiproliferative agents or gene-specific SiRNA use.

In addition to vascular graft development we have been able to use our electrospinning technology to design and manufacture different products such as a bioengineered combinatorial approach to prevent indwelling catheter-related infections. The total of patients acquiring nosocomial infections continues to increase at an alarming rate. Our catheter coating incorporates an anti-biofilm naturally occurring peptide with an antimicrobial agent. In addition, we have developed a nanofibrous coating for stents that will specifically target genes via SiRNA methodology that are involved in SMC proliferation in an attempt to prevent re-stenosis.

Finally, one very exciting project has been the development of a nanofibrous suture specific for vascular arterial reconstruction with very unique properties that will specifically target IH at the anastomosis. We have submitted SBIR/STTR NIH/NHLBI grant applications for testing and evaluating these new products and are currently under review.

Teaching, Training, and Education

I have been training our T32 surgical residents on microsurgical techniques so they become proficient and comfortable performing microvascular procedures (rat model) on their own and could work independently on our ongoing research projects. They also have the opportunity to assist in our vascular surgery procedures (canine model) to improve their skills ranging from venous harvest, prosthetic or venous bypass grafting, and vascular anastomosis reconstruction. They enjoy scrubbing in and often see this opportunity as the highlight of their vascular surgical research experience. In addition, they are trained in tissue harvest and processing, histology, and immunohistochemistry technique as well as data acquisition and analysis for oral or poster presentation and manuscript preparation.

Selected Research Support

A bio-active prosthetic vascular graft; NIH, 2010-2013; Co-PI: Mauricio A. Contreras, MD (PI: Matthew D. Phaneuf)

A nanofibrous bioactive hemodialysis access graft; NIH, 2012-2014; Co-PI: Mauricio A. Contreras, MD (PI: Saif Pathan)

Mechanisms of prosthetic graft failure; NIH, 2010-2014; Co-Investigator: Mauricio A. Contreras, MD (PI: Frank W. LoGerfo, MD)

Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery; NIH, 2013-2017; Co-Investigator: Mauricio A. Contreras, MD (PI: Frank W. LoGerfo, MD)

Selected Publications

Bhasin M, Huang Z, Pradhan-Nabzdyk L, Malek JY, LoGerfo PJ, Contreras MA, Guthrie P, Csizmadia E, Andersen N, Kocher O, Ferran C, LoGerfo FW. Temporal network based analysis of cell specific vein graft transcriptome defines key pathways and hub genes in implantation injury. PLoS One 2012;7(6):e39123.

Vissapragada R, Contreras M, DaSilva C, Kumar V, Ochoa A, Vasudevan A, Selim M, Ferran C, Thomas A. Reciprocal relationship between embryonic brain endothelial cells and neural progenitor cells promotes proliferation and angiogenesis. Manuscript submitted to BRes, currently under review.

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Research Group

Maria Beatriz Arvelo, MD
Victor Chien, MD
Cleide Gonçalves Da Silva, PhD
Eva Csizmadia, MS
Andrew El-Hayek
Philip LoGerfo
Alessandra Mele, MD
Herwig Moll, PhD
Jesus Revuelta-Cervantes, PhD

Research Focus

My laboratory focuses on:

- Defining the molecular signature of what “return to homeostasis” entails in the face of injury, whether inflammatory, immune, infectious, metabolic, or mechanical;
- Identifying the culprits that hinder “return to homeostasis,” resulting in pathology; and
- Validating signature molecules in animal models of human disease for potential clinical translation as diagnostic, prognostic, and therapeutic tools.

This line of research was triggered by our seminal discovery that up-regulation of the ubiquitin-editing protein A20 or the anti-apoptotic Bcl member, A1, in endothelial cells in response to inflammatory stimuli, serves a general “protective” function by shutting down inflammation through inhibition of the transcription factor NF- κ B, and modulation of apoptotic responses (JBC 1996, 271:18068). Subsequent studies confirmed A20 as one of humans’ most potent physiologic anti-inflammatory molecules. We have since expanded the work to different cell types and animal models of human diseases that share inflammation as a central pathogenic component. We mostly focus on three areas of research.

Vascular diseases

Our data qualifies a potent “atheroprotective” and novel anti-angiogenic functions of A20 in animal models of:

- neointimal hyperplasia post-balloon angioplasty
- transplant arteriosclerosis, the main cause of failure of vascularized allografts
- accelerated atherosclerosis of diabetes
- proliferative retinopathies, namely retinopathy of prematurity and diabetic retinopathy

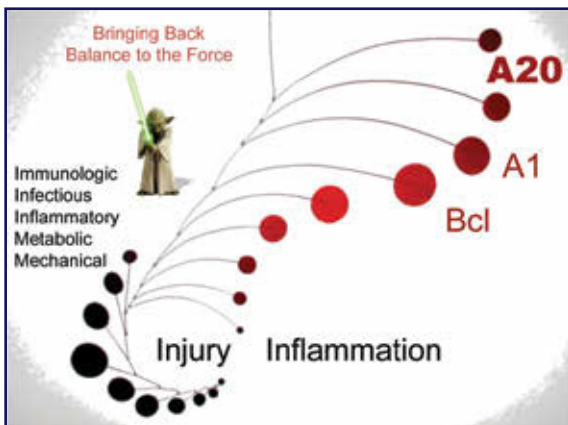
Liver regeneration and repair

We have also extensively established a potent “hepatoprotective” role for A20 in the liver, stemming from combined anti-inflammatory, anti-apoptotic, and pro-proliferative functions of A20 in hepatocytes. Accordingly, A20-based therapies protect mice from lethality in models of acute chemically-induced toxic hepatitis, lethal radical hepatectomy where more than 87% of the liver is resected, prolonged warm liver ischemia, and orthotopic liver transplantation using marginal livers.

Recently, we uncovered an unsuspected phenotype in A20 heterozygous mice, whereby a benign 2/3 hepatectomy causes a staggering 42% lethality. These data have important clinical implications. Indeed, recently discovered single nucleotide polymorphisms that negatively impact A20 expression and/or function should be recognized in order to gauge safety of extensive liver resections for donation or tumor. We are currently conducting an NIH-funded pilot study analyzing the impact of A20 SNPs on liver regeneration in recipients and donors of living donor liver transplantation.

Islet transplantation and regeneration

A20 retained its anti-apoptotic and anti-inflammatory functions in β -cells, thus was an ideal candidate to genetically engineer islet grafts for the treatment of diabetes. Recently, we explored novel means to generate neo-islets for the treatment of diabetes. This line of research could overcome limitations of islet transplantation including organ shortage and side effects of immunosuppression.



- ▲ The molecular response to injury and inflammation. A20, A1, and Bcl-2 as signature molecules of “return to homeostasis.”

Novel scientific findings

- *Vascular field:* We determined that A20 maintains vascular homeostasis by increasing expression and activity of endothelial nitric oxide synthase. We also discovered that A20 inhibits interferon- γ signaling in smooth muscle cells to contain pathological vascular remodeling.
- *Liver field:* Based on our data suggesting a significant role for A20 in lipid and glucose metabolism (PLoS One 2011;6: e17715), we undertook dietary manipulations to rescue A20 heterozygous mice from death after partial hepatectomy. These results are finalized for publication and could form the basis of clinical trials.
- *Diabetes field:* We uncovered means to cure diabetes by generating neo-islets.

Funding (also see "Selected Research Support")

- Iacocca Family Foundation Grant (title not disclosed for reason of IP). This grant sponsors the fellowship of Alessandra Mele, MD. PI: Christiane Ferran, MD, PhD
- Harvard Trauma Inflammation Training Program, NIH; 2013-2018; Faculty: Christiane Ferran, MD, PhD (Director: Wolfgang Junger, PhD)
- Austrian Science Foundation fellowship grant awarded to Herwig Moll, PhD, for his work on A20 and interferon- γ signaling

Awards and honors

- Herwig Moll, PhD: Best poster award at the American Transplant Congress 2012, and the CVBR annual retreat for his work on A20 and interferon- γ signaling
- Alessandra Mele, MD: Best abstract at the annual residents and post-doctoral fellows competition 2013 for her work on islet neogenesis
- Andy Lee, MD: Best data club presentation, the Center for Vascular Biology Research, 2013
- Cleide da Silva, PhD: Selected for oral presentation at the Harvard Surgery Research Day 2013 for her work on dietary manipulation and liver regeneration

Departmental contributions

I was Chair and a member of the organizing committee for the Harvard Surgery Research days, 2012, 2013; Chair of the Affinity Research Collaborative (ARC) initiative, BIDMC Surgery; and member of Harvard Search Committees for several division chiefs at BIDMC, Mass General, and Boston Children's Hospital.

Teaching, Training, and Education

For the past 20 years I have been training post-doctoral research fellows, surgical residents, graduate and medical students, undergraduate students, and research associates who rotate in my laboratory. As the co-director of the T32 training grant in Vascular Surgery, headed by Frank LoGerfo, MD, I also provide support and feedback for all T32 trainees. I also mentor junior faculty in the Department of Surgery and the Center for Vascular Biology Research.

Selected Research Support

Improved liver function and regeneration with A20; NIH, 2003-2014; PI: Christiane Ferran, MD, PhD

Vascular remodeling in transplant arteriosclerosis; NIH, 2006-2013; PI: Christiane Ferran, MD, PhD

A20 gene polymorphisms in living donor liver transplantation; NIH, 2011-2014; PI: Christiane Ferran, MD, PhD

Transdifferentiation of liver resident cells into glucose-sensitive insulin producing cells to cure diabetes; Iacocca Family Foundation, 2013-2014; PI: Christiane Ferran, MD, PhD

Mechanisms of prosthetic graft failure; NIH, 1987-2015; Co-PI: Christiane Ferran, MD, PhD (PI: Frank LoGerfo, MD)

Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery; NIH, 2007-2017; Co-PI: Christiane Ferran, MD, PhD (PI: Frank LoGerfo, MD)

Living donor liver transplantation: Diagnostic markers of liver regeneration to predict outcomes; NIH, 2009-2014; Subcontract: Christiane Ferran MD, PhD (PI: Elizabeth Pomfret, MD, PhD)

Da Silva CG, Maccariello ER, Wilson SW, Putheti P, Daniel S, Damrauer SD, Peterson C, Siracuse JJ, Kaczmarek E, Ferran C. Hepatocyte growth factor preferentially activates the anti-inflammatory arm of NF-kappaB signaling to induce A20 and protect renal proximal tubular epithelial cells from inflammation. *J Cell Physiology* 2012;227:1382-1390.

Siracuse JJ, Fisher MD, da Silva CG, Peterson CR, Csizmadia E, Moll HP, Damrauer SM, Studer P, Choi LY, Essayagh S, Kaczmarek E, Macariello ER, Lee A, Daniel S, Ferran C. A20-mediated modulation of the inflammatory and immune responses in aortic allografts and development of transplant arteriosclerosis. *Transplantation* 2012;93:373-382.

Da Silva CG, Studer P, Skroch M, Mahiou J, Peterson CR, Wilson SW, Patel VI, Ma A, Csizmadia E, Ferran C. A20 promotes liver regeneration by decreasing SOCS-3 expression to enhance IL-6/STAT3 proliferative signals. *Hepatology* 2013;5:2014-2025.

Guedes RP, Rocha E, Mahiou J, Moll H, Arvelo MB, Taube JM, Peterson CR, Kaczmarek E, Longo CR, da Silva CG, Ferran C. The C-terminal domain of A1/Bfl-1 regulates its anti-inflammatory function in human endothelial cells. *Biochimica Biophysica Acta* 2013;1833:1553-1561.

Studer P, da Silva CG, Csizmadia E, Siracuse JJ, Damrauer SM, Peterson CR, Essayagh S, Kaczmarek E, Candinas D, Stroka DM, Ma A, Bhasin M, Ferran C. Lethality in A20 heterozygous mice after partial hepatectomy establishes A20's key role in liver regeneration. *Am J Transplant* 2013; in review.

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Research Group

Tonghui Lin, PhD
Susan Wang

Raul J. Guzman, MD

Visiting Associate Professor

Research Focus

My research focuses on the role of arterial calcification in lower extremity vascular disease. We are interested in the mechanisms by which smooth muscle cells in the arterial wall become phenotypically transformed into bone-like cells. This primarily occurs in patients with diabetes and renal failure.

In previous studies using cell culture systems and rodents, we showed that the matrix-degrading enzymes known as MMPs were critical factors in the development of medial artery calcification and that reducing MMP activity could prevent medial calcification *in vitro* and *in vivo*. We have been working to better understand how MMPs promote calcification and whether these inhibitors can be used in the clinical setting to prevent vascular calcification in patients. During our work on MMPs, we found that a class of bone-related factors known as bone morphogenetic proteins, or BMPs, are up-regulated during arterial calcification. Through collaborations with several investigators, we have begun to study the potential role of new synthetic small-molecule BMP inhibitors in our calcification models. The ultimate goal of our basic studies is to gain insight into mechanisms that control calcification so we can develop clinically relevant therapies for use in our patients with critical limb ischemia.

Through clinical studies we have undertaken over the last eight years, we have learned that the amount of calcification in lower extremity arteries is a better predictor of long-term amputation risk than demographic and vascular risk factors. More recently, our research has focused on the finding that extensive arterial calcium is associated with poor limb outcomes in a manner that is independent of occlusive disease. This finding is contrary to previous notions of how vascular disease affects lower extremity blood flow. Currently, we are evaluating the hypothesis that arterial calcification, perhaps by affecting vessel wall compliance, contributes to limb ischemia and increases amputation risk in vascular patients. Our ultimate goal is to develop pharmacologic therapies to decrease calcium accumulation, improve arterial wall compliance, and thus reduce amputations in patients with diabetic vascular disease.

Accomplishments 2012-2013

My lab has recently moved to Boston from our previous home in Nashville, Tenn. Over the past several months, we have set up our new lab space while re-establishing our research and experimental protocols. Most importantly, we have begun new and exciting research collaborations with several investigators on campus. We are particularly fortunate to be entering into a new collaboration with Aristidis Veves, MD, from our Division of Podiatry, Research Director of the Microcirculation Lab. We are working together to initiate studies aimed at understanding the relationship between arterial calcification and ischemia in patients with diabetes. We have recently demonstrated that the association between calcification and foot ulcers is independent of arterial occlusion. Because this association remains undefined, however, we hope to develop a large clinical dataset on diabetic patients with and without foot ulcers to study this problem. We are also currently initiating new protocols that quantify arterial calcification in patients undergoing endovascular interventions. Our hope is that we can use this unique data set to gain a more precise understanding of why calcification predicts increased amputation risk.

Our basic investigations have also been stimulated by a new collaboration with Christiane Ferran, MD, PhD, of the Department of Surgery. Through this collaborative effort, we hope to better understand the role of inflammation-mediating proteins in smooth muscle cell transformation during the arterial calcification process. These studies, planned for the upcoming months, will allow us to analyze the mechanisms that connect inflammation and arterial calcification using organ culture, *in vivo*, and *in vitro* models. Our hope is that through such collaborations, we can begin to develop novel therapeutic agents that can reduce arterial calcification and prevent amputation in our patients with diabetes and renal disease.

Teaching, Education, and Training

My educational contributions have primarily been in the teaching of general and vascular surgery residents in the operating room and on the inpatient wards. I also have been fortunate to mentor and supervise young surgery residents during their basic research experience. While much of my teaching is clinically oriented, I have also enjoyed teaching in the laboratory and, in particular, enjoyed training our residents in methods of careful experimental design, execution, and interpretation of research results.

Selected Research Support

Role of arterial calcification in restenosis; NIH, 2010-2015; PI: Raul Guzman, MD

Methods to reduce vein harvest injury; NIH, 2013-2016; Co-investigator: Raul Guzman, MD (PI: Joyce Chueng-Flynn, PhD)

Selected Publications

Guzman RJ, Bian A, Shintani A, Stein CM. Association of foot ulcer with tibial artery calcification is independent of peripheral occlusive disease in type 2 diabetes. *Diabetes Res Clin Pract* 2013;99(3):281-6.

Woo KV, Qu X, Babaev VR, Linton MF, Guzman RJ, Fazio S, Baldwin HS. Tie1 attenuation reduces murine atherosclerosis in a dose-dependent and shear stress-specific manner. *J Clin Invest* 2011;121(4):1624-35.

Powell RJ, Comerota AJ, Berceli SA, Guzman R, Henry TD, Tzeng E, Velazquez O, Marston WA, Bartel RL, Longcore A, Stern T, Watling S. Interim analysis results from the RESTORE-CLI, a randomized, double-blind multicenter phase II trial comparing expanded autologous bone marrow-derived tissue repair cells and placebo in patients with critical limb ischemia. *J Vasc Surg* 2011;54(4):1032-41.

Guzman RJ, Brinkley DM, Schumacher PM, Donahue RM, Beavers H, Qin X. Tibial artery calcification as a marker of amputation risk in patients with peripheral arterial disease. *JACC* 2008;51:1967-74.

Corriere, MA, Rogers, CM, Eliason, JL, Faulk JB, Kume T, Hogan, BLM, Guzman, RJ. Endothelial Bmp4 is induced during arterial remodeling: Effects on smooth muscle cell migration and proliferation. *J Surg Res* 2008;145(1):142-149.

Qin X, Corriere MA, Matrisian LM, Guzman RJ. Matrix metalloproteinase inhibition attenuates aortic calcification. *Arterioscler Thromb Vasc Biol* 2006;26(7):1510-6.

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Frank W. LoGerfo, MD

William McDermott Professor of Surgery

Leena Pradhan-Nabzdyk, PhD

Assistant Professor of Surgery

Research Focus

Our group has been extensively involved in different areas of vascular biology, diabetes, and neuropeptide research: 1) evaluating mechanisms responsible for development of intimal hyperplasia (IH) in vein grafts and prosthetic grafts, 2) developing novel techniques to prevent IH in both vein grafts and prosthetic grafts using bioengineering methodologies, 3) wound-healing in diabetes, and 4) the role of neuropeptides in heart failure and inflammatory bowel disease.

IH 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. The LoGerfo lab studies 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 vein graft IH and anastomotic IH (AIH).

Dr. Pradhan-Nabzdyk's main research focus is in diabetic neuropathic complications. 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 diabetic foot ulcers (DFU).

To achieve this goal, Dr. Pradhan-Nabzdyk has successfully developed an *in vivo* diabetic rabbit model of ischemic and neuroischemic wound healing. She is conducting studies in rabbit models of wound healing aimed at understanding the role of neuropeptides in diabetic wound healing. Dr. Pradhan-Nabzdyk also collaborates with Aristidis Veves, MD, where they use knock-out mice models to further understand the mechanisms underlying diabetic wound-healing complication.

In addition to investigating the role of neuropeptides in wound healing, Dr. Pradhan-Nabzdyk is also investigating their role in diabetic heart failure. In collaboration with Vitaliy Poylin, MD, Dr. Pradhan-Nabzdyk is now investigating the role of neuropeptides in colorectal diseases including Crohn's disease and ulcerative colitis.

Accomplishments 2012-2013

Based on their previous work, the LoGerfo group has identified gene targets that are upregulated in both vein graft IH and AIH. Current work is focused on understanding the biology of these molecules, including Thrombospondin-2 (TSP-2), interleukin (IL)-6, and IL-8 and developing techniques to deliver silencing RNA (siRNA) to the vessel wall to silence those targets and thereby mitigate the development of IH. Results from these projects have been presented at several national and international meetings and have resulted in manuscripts.

In collaboration with Biosurfaces, Inc., they are developing electrospun (e) prosthetic grafts made of polyethylene terephthalate (PET) polymer to which siRNA could be adsorbed. Our preliminary experiments show that we are able to deliver siRNA to a rat carotid artery from the ePET graft. Similarly we were successful with the direct intraluminal delivery of TSP-2 siRNA in presence of transfection reagent Polyethylimine (PEI). This resulted in TSP-2 gene and protein knock-down in the carotid artery of the rat. The goal is to silence multiple genes at a time to prevent IH development.

Research Group

Maggie Chun
Mauricio Contreras, MD
Sarah Dougherty
Aniket Gurav, MS
Joel Johnson
Elliot Kramer
Priya Patel
Wande Pratt, MD, MPH
Nurazhani Raof, PhD
Natasha Resendes
David Allen Weisst hose



▲ Representative section of carotid artery and ePET graft dip-coated in control siRNA (no fluorophore label) at 24 hours. Immunofluorescence is absent within wall of denuded artery or within graft material.



▲ Representative section of carotid artery and ePET graft dip-coated in siRNA tagged with red fluorophore (siGLO-Red) at 24 hours. Fluorophore-labeled siRNA is observed throughout wall of denuded artery.

Dr. Pradhan-Nabzdyk's recent manuscript in *Journal of Vascular Surgery* suggests that diabetes significantly delays wound healing, and neuroischemia, a common complication of diabetes, further aggravates the problem. Furthermore, there is a macrophage activation dysregulation, with higher activation of the M1 macrophages (pro-inflammatory), and unchanged activation of M2 macrophages (reparative macrophages). Moreover, there is higher neutrophil infiltration in the diabetic and neuroischemic wounds. The diabetic rabbit model is being used not only to understand the mechanisms of this devastating problem, but is also being used to test therapies directed to improve wound healing. In collaboration with Harvard's Wyss Institute for Biologically Inspired Engineering, Dr. Pradhan-Nabzdyk tested the efficacy of the neuropeptide Substance P that was encapsulated in modified alginate gel in neuroischemic wound healing. The goal was to deliver Substance P in a continuous manner for a period of 10 days using the alginate gel. The results are very encouraging, suggesting that the most beneficial effect of Substance P in improving wound healing using the alginate gel is the treatment of diabetic neuropathic wounds in diabetic wound healing. The next goal in this project is to use a bandage form of alginate gel and test its efficacy in this model.

Our individual accomplishments include receiving the Lifetime Achievement Award from the Society of Vascular Surgery (Frank LoGerfo, MD, 2013) and being promoted to Assistant Professor of Surgery (Leena Pradhan-Nabzdyk, PhD, 2013).

Teaching, Training, and Education

We have mentored several students and post-docs in the lab. Additionally Dr. LoGerfo is the Program Director of the Harvard-Longwood Research Training Program in Vascular Surgery NIH-T32 program. Currently there are eight post-doctoral fellows in this program mentored in different labs in the Longwood Medical Area. Based on the success of the T-32 program and the past William J. von Liebig Summer Research in Vascular Surgery Fellowship program for medical students, we (Dr. LoGerfo as the Director; Dr. Pradhan-Nabzdyk as Co-Director) received NIH T-35 funding. The goal of this T-35 program is to train medical students in vascular surgery research for a short (10-12 weeks) period.

Present and past research students and fellows:

Maggie Chun (2009-2012)
Sarah Dougherty (2013-present)
Joel Johnson (2012-present)
Priya Patel (2012-2013)
Wande B. Pratt, MD, MPH (2011-2013)
Nurazhani Raof, PhD (2012-present)
Natasha Resendes (2010-2013)
David Allen Weiss (2013-present)

Selected Research Support

Mechanisms of prosthetic arterial graft failure; NIH, 2010-2015; PI: Frank W. LoGerfo, MD

Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery; NIH, 2013-2017; PI: Frank W. LoGerfo, MD; Co-Investigator: Leena Pradhan-Nabzdyk, PhD

Role of neuropeptides in diabetic foot problems; NIH, 2010-2015; Multiple Principal Investigators: Leena Pradhan-Nabzdyk, PhD, Aristidis Veves, MD; Co-Investigator: Frank W. LoGerfo, MD

Novel therapeutic approaches for the management of diabetic foot ulceration; NIH, 2012-2014; Multiple Principal Investigators: Frank W. LoGerfo, MD, David Mooney, PhD, William Shih, PhD, Aristidis Veves, MD; Co-Investigator: Pradhan-Nabzdyk, PhD

Harvard-Longwood Research Training in Vascular Surgery; NIH, 2009-2014; PI: Frank W. LoGerfo, MD; Mentor/Coordinator: Leena Pradhan-Nabzdyk, PhD

Harvard-Longwood Short-Term Research Training in Vascular Surgery; NIH, 2013-2018; Program Director: Frank W. LoGerfo, MD; Program Co-Director: Leena Pradhan-Nabzdyk, PhD

Mechanisms of neuropeptides action in diabetes; NIH, 2011-2016; Co-investigators: Frank W. LoGerfo, MD, Leena Pradhan-Nabzdyk, PhD

Pradhan-Nabzdyk L, Kuchibhotla S, Guthrie PJ, Chun M, Deso S, Andersen ND, Nabzdyk C, Gnardellis G, LoGerfo FW, Veves A. Expression of neuropeptides and cytokines in a novel rabbit model of diabetic neuroischemic wound healing. *J Vasc Surg* 2013; Jun 4. (Epub ahead of print).

Nabzdyk CS, Chun M, Pradhan-Nabzdyk L, Yoshida S, LoGerfo FW. Differential susceptibility of human primary aortic and coronary artery vascular cells to RNA interference. *Biochem Biophys Res Commun* 2012;425(2):261-5.

Bhasin M, Huang Z, Pradhan-Nabzdyk L, Malek JY, LoGerfo PJ, Contreras M, Guthrie P, Csizmadia E, Andersen N, Kocher O, Ferran C, LoGerfo FW. Temporal network based analysis of cell specific vein graft transcriptome defines key pathways and hub genes in implantation injury. *PLoS One* 2012;7(6):e39123.

Dinh T, Tecilazich F, Kafanas A, Doupis J, Gnardellis C, Leal E, Tellechea A, Pradhan L, Lyons TE, Giurini JM, Veves A. Mechanisms involved in the development and healing of diabetic foot ulceration. *Diabetes* 2012;61(11):2937-47.

Pradhan L, Veves A. Neuropeptides and Diabetic Wound-Healing. In: *The Diabetic Foot: Medical and Surgical Management*, 3rd Edition. Eds: Veves A, Giurini JM, LoGerfo FW. New York, NY: Springer; 2012.

Pradhan-Nabzdyk L, Nabzdyk C. Neuropeptides and Angiogenesis. In: *Biochemical Basis and Therapeutic Implications of Angiogenesis*, 1st Edition. Eds: Dhalla N, Mehta JL. New York, NY: Springer; 2013.

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Research Group

Rodney Bensley, MD
Dominique Buck, MD
Mark Burns
Eduardo Cabral
Thomas Curran, MD
Jeremy Darling
Christina Feng, MD
Margriet Fokkema, MD
Jeremy Herman
Ruby Lo, MD
John McCallum, MD
Borami Shin, MD
Li Wang
Jennifer Zhang, MD

Research Focus

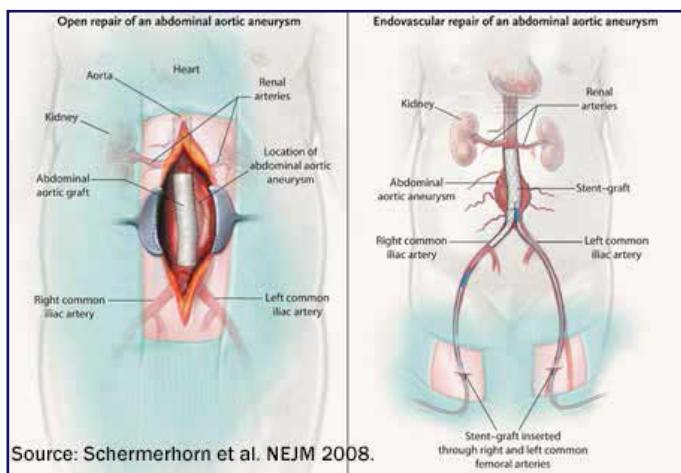
My clinical research group has an active interest in outcomes research in vascular surgery on a local and national level. As the surgical armamentarium evolves to include emerging technologies in a variety of clinical settings, comparative effectiveness research has been instrumental in the identification of best practices from among an increasingly complex set of therapeutic options. Our main interest is to compare outcomes after open surgery and endovascular surgery for a variety of vascular diseases, including aortic aneurysm, carotid disease, and lower extremity arterial disease, to help guide patient selection for each type of procedure. In order to understand the comparative effectiveness of various interventions, we have extended our inquiries beyond small, randomized controlled trials of ideal populations to study interventions in real-world settings using observational data, as discussed below.

We have utilized a wide range of data sources to better understand the treatment of vascular disease processes with each data source providing unique insight. Our local experience at BIDMC, boasting the world's largest series of distal bypass and tibial angioplasty, has provided rich data from which we have published on the effectiveness of primary endovascular therapy for critical limb ischemia and the benefit of ultrasound-guided femoral access for totally percutaneous endovascular AAA repair. Joining with other institutions in the region and nationally, we have been active in the utilization of data from the Vascular Study Group of New England (VSGNE) and the Vascular Quality Initiative (VQI) to investigate risk factors for stroke following carotid endarterectomy and gender differences in abdominal aortic aneurysm (AAA) management among other things. Similarly, our institution's involvement with the National Surgical Quality Improvement Project (NSQIP) has afforded us access to a large set of prospectively collected clinical

data from which we have published a contemporary reappraisal of outcomes following open thoracoabdominal aortic aneurysm (TAAA) repair; a series against which newly developed endovascular treatments may be measured.

Administrative data such as the Nationwide Inpatient Sample (NIS), a 20% sampling of all hospital inpatient admissions, and the State Ambulatory Surgery Databases (SASD), a database of all ambulatory surgical encounters in a given state, have been invaluable in addressing population-based clinical questions, including the epidemiologic trends in the diagnosis and treatment of acute and chronic mesenteric ischemia. Importantly, we have cultivated partnerships with the Centers for Medicaid and Medicare Services (CMS) to obtain Medicare data for the study of open versus endovascular AAA management including, most recently, the risk of long-term laparotomy-related complications associated with open AAA repair. We have also demonstrated a decline in national deaths due to AAA after the introduction of endovascular repair. Finally,

we have also combined data from several of these sources to comment on data quality, as in our review of the accuracy of administrative data versus clinical data for assignment of neurologic symptom status in patients undergoing carotid revascularization. Expertise in the use of these data sets against the backdrop of our busy clinical practice has allowed our group to take ownership of a number of clinical questions to produce tangible improvements in the management of vascular disease.



- ▲ Open repair and endovascular repair of an infrarenal abdominal aortic aneurysm.

Accomplishments 2012-2013

With 22 peer-reviewed publications and 26 presentations* at national society meetings in the last two years, my research group has continued to make significant contributions to vascular surgery in the area of comparative effectiveness research. Our robust clinical volume in vascular surgery at BIDMC has allowed us to publish extensively on our institutional experience in both open and endovascular management of vascular pathology, including our experience with tibial angioplasty, one of the largest such series in the world. This rich clinical activity has also facilitated our participation in multi-center clinical trials in the areas of endovascular abdominal aortic aneurysm repair and management of carotid artery atherosclerotic disease. Such activity has kept our Division of Vascular and Endovascular Surgery at the cutting edge of new advances in endovascular surgery and positioned us well to report on the effectiveness of these techniques in the literature.

Beyond our institution, I have taken on leadership positions in the Vascular Study Group of New England (VSGNE) and the Vascular Quality Initiative (VQI), innovative quality improvement initiatives at the regional and national level, respectively. The VSGNE, a consortium of over 30 regional hospitals, collects granular clinical data across institutions that has allowed us and others to publish novel insights on the management of vascular disease. The success of the VSGNE has provided a model for quality-improvement efforts nationally through the formation of the VQI, a cooperative of over 12 regional quality groups nationwide endorsed by the Society for Vascular Surgery. As a member of the Executive and Research Advisory Committees for both organizations, I have worked with our research group to develop projects utilizing these data, resulting in several peer-reviewed publications.

* *Vascular Annual Meeting for the Society for Vascular Surgery (seven presentations in 2012 and seven presentations in 2013), and the Society for Clinical Vascular Surgery Annual Symposium (five presentations in 2012 and seven presentations in 2013).*

Teaching, Training, and Education

Under my mentorship, our research group has welcomed a number of tremendously productive clinical research fellows and PhD candidates in vascular surgery over the last two years. Research fellows have come from our own general surgery residency as well as prestigious residency programs around the country. PhD candidates have come through an exciting international research exchange relationship with the University Medical Center Utrecht in the Netherlands, now in its third year of existence. All research fellows receive formal instruction in research methods and statistics through the Harvard School of Public Health and have gone on to present our work at national meetings in vascular surgery.

Selected Research Support

Long term outcomes of open versus endovascular abdominal aortic aneurysm repair; NIH, 2010-2014; Co-PI: Bruce Landon, MD; PI: Marc L. Schermerhorn, MD

Harvard/Longwood Training Grant in Vascular Surgery, NIH; Co-Investigator: Marc L. Schermerhorn, MD (PI: Frank LoGerfo, MD)

Post-approval study evaluating the long term safety and effectiveness of the Endurant stent graft system (clinical trial), ENGAGE PAS, 2011-2016; National PI: Marc L. Schermerhorn, MD

Selected Publications

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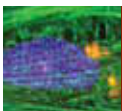
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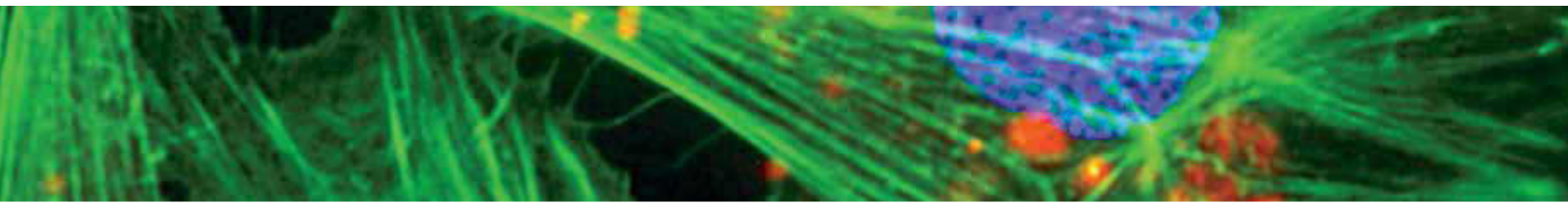


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