



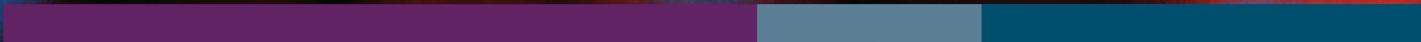
Beth Israel Deaconess
Medical Center



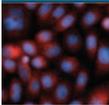
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Roberta and Stephen R. Weiner Department of Surgery

SURGERY RESEARCH REPORT

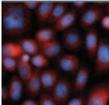


◀ COVER IMAGE: The Otterbein research group (page 92) was selected to provide the cover image for the December 2013 issue of *Cancer Research* (Carbon monoxide expedites metabolic exhaustion to inhibit tumor growth. *Cancer Res* 2013;73:7009-21.) The article reported on the Otterbein group's research findings, led by first author Barbara Wegiel, PhD, MSc (page 96), which demonstrated that administering carbon monoxide (CO) to cancer cells (on cover) sensitized the cells to chemotherapy while protecting normal cells. In mouse models of prostate and lung cancer, CO inhibited tumor growth. This research drew national media attention.



Contents

From the Chairman	4	Plastic and Reconstructive Surgery	70
Overview of Surgical Research	5	Bernard T. Lee, MD, MBA	70
Bibliography	15	Samuel J. Lin, MD	72
Acute Care Surgery, Trauma, and Surgical Critical Care	34	Joseph Upton, MD	74
Carl J. Hauser, MD	34	Podiatry	76
Wolfgang G. Junger, PhD	36	Aristidis Veves, MD, DSc	76
Teresa Sanchez, PhD	38	Surgical Oncology	78
Michael B. Yaffe, MD, PhD	40	Per-Olof Hasselgren, MD, PhD	78
Cardiac Surgery	42	A. James Moser, MD	80
Kamal R. Khabbaz, MD	42	Ranjna Sharma, MD	82
Sidney Levitsky, MD, and James D. McCully, PhD	44	Jennifer F. Tseng, MD, MPH	84
Center for Drug Discovery and Translational Research	46	Thoracic Surgery and Interventional Pulmonology	86
Lijun Sun, PhD	46	Erik Folch, MD, MSc	86
Colon and Rectal Surgery	48	Sidharta P. Gangadharan, MD	88
Deborah A. Nagle, MD	48	Adnan Majid, MD	90
Vitaliy Y. Poylin, MD	50	Transplant Surgery	92
General Surgery	52	Leo E. Otterbein, PhD	92
George L. Blackburn, MD, PhD	52	James R. Rodrigue, PhD	94
Mark P. Callery, MD	54	Barbara Wegiel, PhD, MSc	96
Susan J. Hagen, PhD	56	Urology	98
Daniel B. Jones, MD, MS	58	Mohamed Simo Arredouani, PhD	98
Tara S. Kent, MD, MS	60	Peter Chang, MD, MPH	100
Jin-Rong Zhou, PhD	62	William C. DeWolf, MD	102
Neurosurgery	64	Abraham Morgentaler, MD	104
Jeffrey Arle, MD, PhD	64	Andrew A. Wagner, MD	106
Ophthalmology	66	Vascular and Endovascular Surgery	108
Jorge G. Arroyo, MD, MPH	66	Elliot L. Chaikof, MD, PhD	108
Otolaryngology/Head and Neck Surgery	68	Mauricio A. Contreras, MD	110
Selena E. Heman-Ackah, MD, MBA	68	Christiane J. Ferran, MD, PhD	112
		Raul J. Guzman, MD	114
		Frank W. LoGerfo, MD, and Leena Pradhan-Nabzdyk, PhD	116
		Marc L. Schermerhorn, MD	118
		Index	120



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 \$14 million dollars in funding as well as some 490 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



To accomplish great things we must dream as well as act.”

— Anatole France, French writer and recipient of the 1921 Nobel Prize in Literature

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.

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, organizes many of the research activities. In fiscal year (FY) 2014, activities of Surgical Research were supported by a half-time administrative assistant with others in the department contributing administrative support for specific functions.

Surgical Research has the following responsibilities within the Department of Surgery:

- Pre-award approval of all grant submissions. This includes assisting in the preparation of 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 (publications, grant submissions, grant funding, etc.)
- 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
- Preparing applications for Harvard Medical School appointments for research fellows and instructors in Surgical Research
- Making recommendations concerning research faculty appointments and reappointments in Surgery (working with the Department of Surgery Appointments, Reappointments, and Promotions 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 FY2014, 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 on 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, honors, and appointments in FY2014 including, among many others:

- Election to the Institute of Medicine of the National Academies (Elliot L. Chaikof, MD, PhD)
- Harvard Medical School Eleanor and Miles Shore Fellowship (Martina Stipler, MD, Neurosurgery; Barbara Wegiel, PhD, Transplant Surgery)
- Election as President of the Association for Surgical Education (ASE) and 2014 ASE Distinguished Educator Award (Daniel B. Jones, MD, MS, General Surgery)

- Academic Scholar Award, American Association of Plastic Surgeons (Samuel J. Lin, MD, Plastic and Reconstructive Surgery)

Surgery faculty continued to travel and lecture worldwide. Their contributions included invited speaking engagements at international meetings in: Norway (Susan J. Hagen, PhD); China (Jin-Rong Zhou, PhD); Australia, France, and the United Kingdom (Leo E. Otterbein, PhD); Austria and Sweden (Wolfgang G. Junger, PhD), Italy and Switzerland (James R. Rodrigue, PhD); Sweden, Poland, and the United Kingdom (Barbara Wegiel, PhD); and the Netherlands and Japan (Jeffrey Arle, MD, PhD).

Research Funding

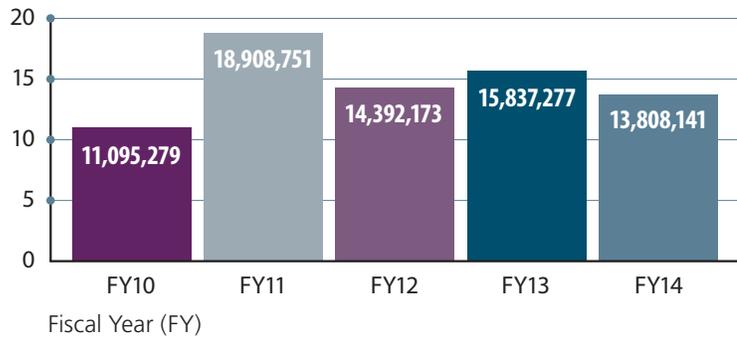
All research — both basic and clinical — in the Department of Surgery is supported by external funding, with more than one quarter of this funding in the form of NIH grants.

In FY2014, Surgery held numerous (quantities follow grant type) NIH investigator-initiated grants: R01 (28), R21 (3), R24 (1), R43 (2), R44 (1), P30 (1), U01 (1), D71 (2), and additional other federal grants (2) for a total of 42 federally funded grants. There were also 124 non-federal awards, two NIH T32 grants, and one NIH T35 training grant. Overall, total research funding was more than \$13.8 million dollars for FY2014 (Figure 1).

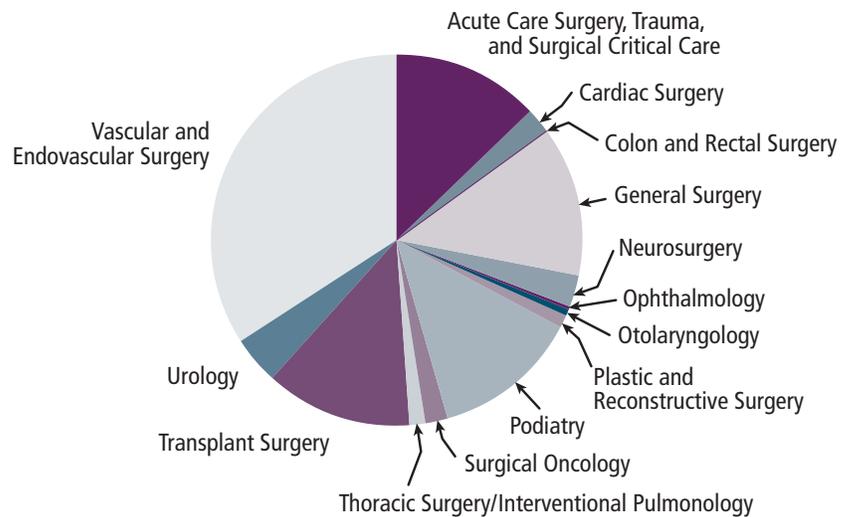
It should be noted that Surgery funding levels have been inconsistent over the past five years because of the considerable budget restraints imposed on the NIH, with many meritorious grant applications not meeting the pay line. Surgery investigators continue to resubmit these meritorious applications until they are successful.

The distribution of external funding among the divisions in the Department of Surgery for FY2014 is illustrated in Figure 2. Most notable is the growth of research funding in Vascular and Endovascular Surgery, which now comprises more than 30% of total funding in the Department of Surgery. For the first time in recent history, all divisions in the Department of Surgery have at least one research grant (Figure 3). Vascular and Endovascular Surgery holds the majority of research grants (Figure 3). Of special note is the Division of Podiatry, with 11 research grants totaling more than 1.7 million dollars (Figure 3), all of which were awarded to a single investigator, Aristidis Veves, MD, DSc.

▼ FIGURE 1: Total (federal, non-federal, other federal, and training) research dollars awarded per year during the five-year period 2010-2014



▼ FIGURE 2: Total (federal, non-federal, other-federal, and training) research dollars awarded in fiscal year 2014, by division



▼ FIGURE 3: Number and amounts of research awards in fiscal year 2014, by division

Division	Number of Awards	Amount of Awards
Acute Care Surgery, Trauma, and Surgical Critical Care	16	\$1,780,868
Cardiac Surgery	8	\$298,815
Colon and Rectal Surgery	2	\$9,016
General Surgery	25	\$1,800,424
Neurosurgery	9	\$372,661
Ophthalmology	5	\$53,531
Otolaryngology	1	\$50,000
Plastic and Reconstructive Surgery	5	\$188,779
Podiatry	11	\$1,741,045
Surgical Oncology	7	\$277,548
Thoracic Surgery/Interventional Pulmonology	7	\$176,391
Transplant Surgery	20	\$1,752,504
Urology	15	\$601,468
Vascular and Endovascular Surgery	52	\$4,670,559

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 FY2014, numerous members of the Department of Surgery utilized the 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 R. 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 FY2014, the Department of Surgery continued its longstanding NIH Training Grant in Vascular Surgery Research (PI: Frank W. LoGerfo, MD). This group also ran a successful NIH T35-funded program in Vascular Surgery for summer students. Investigators in Surgery actively participated in the GI Surgery Research Training Grant, which is a joint NIH-funded T32 training grant among the three Harvard Medical School teaching hospitals (PI: Richard Hodin, MD, at Massachusetts General Hospital). In FY2014 the newly established NIH-funded T32 training grant in Inflammation and Trauma (PI: Wolfgang G. Junger, PhD) hosted its first research fellows.

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 R. Rodrigue, PhD, Marc L. Schermerhorn, MD, and Jennifer F. 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.

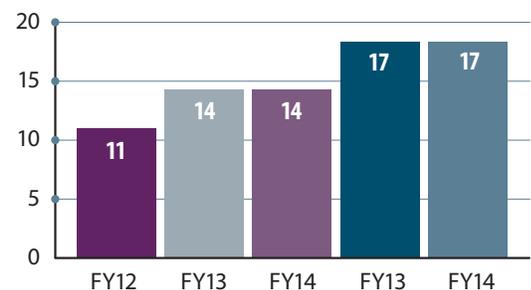
Within the structure of the Clinical Scholarship Program, residents meet regularly with research mentor(s), participate in the Surgical Outcomes Analysis & Research (SOAR) meetings, receive informal and formal feedback from faculty on project proposals, and are provided with readings. They also attend 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 14 residents per year elected to spend time in a basic or clinical research laboratory as part of their surgical training. In FY2014, 17 residents elected to do research (Figure 4). 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 second or third clinical years.

▼ FIGURE 4: Number of surgical residents per fiscal year spending time (2-3 years) in a research elective.





◀ FIGURE 5: “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 Massachusetts Institute of Technology, 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 72-page booklet entitled “Funding Sources for Surgical Residents,” which describes various funding sources, deadlines, financial support available, and application forms (see Figure 5). This booklet is updated annually. It is also available electronically at: bidmc.org/surgery>surgical_education>training_programs>general_surgery_residency.

Research Abstract Competition for Surgical Trainees

The annual Research Abstract Competition was held again in November 2013 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 2013 were truly outstanding. Peer-review grading by faculty of the Department of Surgery identified five basic science and five clinical abstracts as semi-finalists for the competition, which were presented to a judging panel that included the Clowes Visiting Professor, B. Mark Evers, MD.

The semi-finalists in 2013 were:

Basic Science

Denis Gilmore, MD

“Prevention of Nodal Metastases in Breast Cancer Following the Lymphatic Migration of Paclitaxel-Loaded Expansile Nanoparticles”

Mentor: Yolanda Colson, MD, PhD (Boston Children’s Hospital)

Gab S. Kim, PhD

“Critical Role of Sphingosine-1-Phosphate Receptor 2 in Blood Brain Barrier Disruption, Intracerebral Hemorrhage and Neurovascular Injury in Experimental Stroke”

Mentor: Teresa Sanchez, PhD

Nicola Sandler, MD

“Mitochondrial DAMPS from Fracture Injury Modulate Pulmonary Immune Responses via FPR-1 and FPR-2”

Mentor: Carl J. Hauser, MD

Nils Schallner, MD

“Carbon Monoxide Derived from Heme Oxygenase-1 Prevents Neuronal Injury and Memory Loss Resulting from Subarachnoid Hemorrhage in Mice”

Mentor: Leo E. Otterbein, PhD

Ana Tellechea, PhD student

“Mast Cell Stabilization in Diabetes: A Potential Treatment for Diabetic Foot Ulcers”

Mentor: Aristidis Veves, MD, DSc

Clinical Research

Christopher Barrett, MD

“Surgeon Performed Ultrasound (SPUS) Can Predict Surgical Wound Infections”

Mentor: Carl J. Hauser, MD

Dominique Buck, MD

“Isolated Iliac Artery Aneurysms: Management and Outcomes in the Endovascular Era”

Mentor: Marc L. Schermerhorn, MD

Eliza Lee, MD

“Renal Autotransplantation: An Alternative to Renal Artery Bypass in the Management of Complex Pediatric Renovascular Disease”

Mentor: Heung Bae Kim, MD

Prathima Nandivada, MD

“Cirrhosis Due to Parenteral Nutrition-Associated Liver Disease: No Longer an Indication for Transplantation?”

Mentor: Mark Puder, MD, PhD

Omair Shakir, MD

“The Effects of Preemptive Ultrasound Guided Paravertebral Block on Immediate Postoperative Lung Function as Compared to Direct Vision Intercostal Block: A Prospective Randomized Study”

Mentor: Sidhu P. Gangadharan, MD

* FIRST PLACE PRIZES:

Basic Science:

Ana Tellechea, PhD student

Clinical Research:

Prathima Nandivada, MD

Surgical Outcomes Analysis & Research (SOAR)

Led by James R. Rodrigue, PhD, Director of the Center for Transplant Outcomes and Quality Improvement and Vice Chair, Clinical Research; Marc L. Schermerhorn, MD, Chief of Vascular and Endovascular Surgery; and Jennifer F. 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 third year of 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 initiated by Christiane C. Ferran, MD, PhD, and is assisted by Susan J. Hagen, PhD, Associate Vice Chair for Surgical Research, and Leo E. Otterbein, PhD, Associate Professor of Surgery in the Division of Transplant Surgery.

Progress reports from funded ARC projects in year two 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 “ARC Seminars Series” beginning on the next page).

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 G. Junger, PhD, a faculty member of the “Activation of Innate Immunity by Surgery and Injury” ARC (Carl J. Hauser, MD, Director). Additionally, another new T32 training grant application, led by Aristidis Veves, MD, DSc, 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 second year, 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 years, 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"

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

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

Samuel J. Lin, MD: "Electrochemical Activation and Inhibition of Neuromuscular Systems with Modulation of Ion Concentrations Using Ion-Selective Membranes"

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

ARC Seminar Series

ACTIVATION OF INNATE IMMUNITY BY SURGERY AND INJURY

Director: **Carl J. Hauser, MD**

- January 14, 2014 Andrew D. Luster, MD, PhD
Persis, Cyrus and Marlow B. Harrison Professor of Medicine
Chief, Division of Rheumatology, Allergy and Immunology
Director, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital
"Lipid-Cytokine-Chemokine Cascades Control Leukocyte Trafficking in Inflammation"
- September 4, 2014 John C. Alverdy MD
Professor of Surgery and Executive Vice-Chair for Academic Affairs
Department of Surgery, University of Chicago
"Creating Molecular Détente between Host and Pathogen to Prevent Sepsis"

METABOLISM AND CANCER

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

- October 9, 2013 Sumsumu Kobayashi, MD, PhD
Assistant Professor of Medicine, Beth Israel Deaconess Medical Center
"Mechanisms of Response and Resistance to EGFR Kinase Inhibitors in Lung Cancer"
- October 16, 2013 David A. Zaharoff, PhD
Assistant Professor, Department of Biomedical Engineering
Winthrop P. Rockefeller Cancer Institute, University of Arkansas
"Engineering Immunotherapies for Bladder and Breast Cancers"
- October 30, 2013 Marcia C. Haigis, PhD
Associate Professor, Department of Cell Biology, Harvard Medical School
"Sirtuins – A New Direction for Tumor Metabolism"
- November 6, 2013 Steven Balk, MD, PhD
Professor of Medicine, Beth Israel Deaconess Medical Center
"Androgen Receptor in Prostate Cancer Development"

December 4, 2013	Pankaj Seth, PhD Assistant Professor of Medicine, Beth Israel Deaconess Medical Center "Modulating LDH-A Results in Therapeutic Efficacy in Highly Glycolytic Tumors"
January 21, 2014	Jennifer Tseng, MD, MPH Chief, Surgical Oncology, Department of Surgery, Beth Israel Deaconess Medical Center "Predictive Modeling in Pancreatic Cancer"
February 12, 2014	David M. Sabatini, MD, PhD Member, Whitehead Institute, Professor of Biology, Massachusetts Institute of Technology Investigator of the Howard Hughes Medical Institute, Senior Associate Member; Broad Institute Member, David H. Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology "Regulation of Growth and Metabolism"
March 12, 2014	Peter Sicinski, MD, PhD Professor of Genetics, Harvard Medical School, Dana-Farber Cancer Institute "Cell Cycle Machinery in Development and in Cancer"
March 19, 2014	Tak Mak, PhD Professor, Department of Medical Biophysics, and Department of Immunology, University of Toronto Director, The Campbell Family Institute for Breast Cancer Research Senior Scientist, Stem Cell and Developmental Biology Advanced Medical Discovery Institute/Ontario Cancer Institute, Canada "Future Anti-Cancer Targets: Put the Cart Before the Horses"
April 16, 2014	M. Simo Arredouani, PhD Assistant Professor of Surgery, Harvard Medical School, Beth Israel Deaconess Medical Center "The ETS Transcription Factor ERG Confers a Nerve-like Phenotype to Prostate Cancer Cells and Enhances Responsiveness to Neurotransmitters"
May 21, 2014	James W. Mier, PhD Associate Professor, Department of Medicine, Harvard Medical School Beth Israel Deaconess Medical Center "HDM2/HDMX as a Therapeutic Target in RCC and Melanoma"
June 18, 2014	A. James Moser, MD Associate Professor of Surgery, Harvard Medical School, Division of Surgical Oncology, Beth Israel Deaconess Medical Center "Identifying Molecular Targets for Pancreatic Cancer Therapy "
September 15, 2014	Jenny Liao Persson, PhD Associate Professor, Clinical Research Center, Lund University, Sweden "Target PI3K/AKT-related Lipid Kinase Pathways for Treatment of Advanced Cancer"
September 24, 2014	Stuart Calderwood, PhD Associate Professor of Radiation Oncology, Harvard Medical School, Beth Israel Deaconess Medical Center "Transcriptional Elongation, Molecular Chaperones and Cancer"

NEUROPEPTIDES IN WOUND HEALING, HEALTH, AND DISEASE

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

- October 18, 2013 Harold Brem, MD
Chief of Wound Healing and Regenerative Medicine, Winthrop University Hospital
“Biological Basis for Treatment of Diabetic Foot Ulcers”
- November 8, 2013 Irene Georgakoudi, PhD
Associate Professor, Department of Biomedical Engineering, Tufts School of Engineering
“Non-invasive Assessment of Cellular Metabolic and Biosynthetic Status in Three-dimensional Tissues”
- March 28, 2014 Jeffrey M. Davidson, PhD
Professor of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine
“Translating Regenerative Biology into Therapeutic Strategies and Materials”
- June 4, 2014 Paula Shireman, MD
Professor and Vice Dean For Research, Dielmann Chair in Surgery,
University of Texas School of Medicine at San Antonio
“Macrophage Plasticity, Muscle Regeneration and Battlefield Injury”

ELECTROCHEMICAL ACTIVATION AND INHIBITION OF NEUROMUSCULAR SYSTEMS WITH MODULATION OF ION CONCENTRATIONS USING ION-SELECTIVE MEMBRANES

Director: Samuel J. Lin, MD

- December 6, 2013 Stephen Helms Tillery, PhD
Associate Professor, Department of Psychology and School of Biological and Health Systems Engineering
Director, Sensorimotor Research Group, Arizona State University
“Towards a Tactile Neuroprosthesis”

DEVELOPMENT OF NOVEL THERAPEUTIC AND DIAGNOSTIC APPROACHES FOR STROKE

Director: Teresa Sanchez, PhD

- December 9, 2013 Magdy H. Selim, MD, PhD
Associate Professor of Neurology, Harvard Medical School
Chief, Division of Stroke and Cerebrovascular Diseases, Beth Israel Deaconess Medical Center
“Translational Research in Intracerebral Hemorrhage: From Google to Bench to HI-DEF”
- March 24, 2014 Costantino Iadecola, MD
Anne Parrish Titzell Professor of Neurology, Weill Cornell Medical College
Director, Brain and Mind Research Institute
“Neurovascular Coupling in Health and Disease: Mechanisms and Implications for Brain Function”
- April 1, 2014 Lee Rubin, PhD
Professor, Stem Cell and Regenerative Biology, Harvard University
Director of Translational Medicine, Harvard Stem Cell Institute
“Human Disease in a Dish: Advantages and Disadvantages”
- August 5, 2014 Jonathan Edlow, MD
Professor of Medicine, Harvard Medical School
Vice-Chairman, Department of Emergency Medicine, Beth Israel Deaconess Medical Center
Acute Dizziness: When is It Stroke and How Do We Best Diagnose It?”

Surgical Horizons Seminars Series

In FY2014, the major seminar series for research in the Department of Surgery was the Surgical Horizons Seminars Series, which hosted outstanding seminars by young emerging leaders and senior leaders from both surgical and non-surgical disciplines. These included individuals who work in the engineering, physical, and social sciences and whose endeavors promise to dramatically alter the landscape of care for the surgical patient.

The Surgical Horizons Seminars Series include refreshments and a lecture from the invited speaker. External speakers were invited to dinner with a small group of faculty and residents. The speakers for this series in FY2014 follow:

October 21, 2013	Eric Sugalski, MBA Founder and CEO of Boston Device Development "Medical Device Launchpad"
November 4, 2013	Wolfgang G. Junger, PhD Professor of Surgery, Harvard Medical School Acute Care Surgery, Beth Israel Deaconess Medical Center "ATP and Adenosine Receptors in Immune Cell Activation"
December 10, 2013	Barbara Wegiel, PhD Assistant Professor of Surgery, Harvard Medical School Transplant Surgery, Beth Israel Deaconess Medical Center "The Crosstalk between Metabolism and Inflammation in Cancer"
January 6, 2014	James S. Allan, MD Assistant Professor of Surgery, Harvard Medical School Division of Thoracic Surgery, Massachusetts General Hospital "Immunologic Tolerance in Large-Animal Models of Lung Transplantation"
February 3, 2014	Roger D. Kamm, PhD Cecil and Ida Green Distinguished Professor of Biological and Mechanical Engineering Associate Chair of Mechanical Engineering, Massachusetts Institute of Technology "Microfluidics: A Powerful Tool to Study Multi-cell Interactions in Metastatic Cancer"
March 3, 2014	Raphael Bueno, MD Professor of Surgery, Harvard Medical School Associate Chief of Thoracic Surgery, Brigham and Women's Hospital "New Paradigms in Genomic Surgery: Development and Clinical Implementation of Molecular Tests for Selecting Surgical Therapies in Cancer"
May 19, 2014	William C. Aird, MD Professor of Medicine, Harvard Medical School Director of Vascular Biology, Massachusetts General Hospital "Endothelium in Health and Disease"

Appointments, Reappointments, and Promotions Committee

Surgical Research is involved in the Appointments, Reappointments, and Promotions 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.

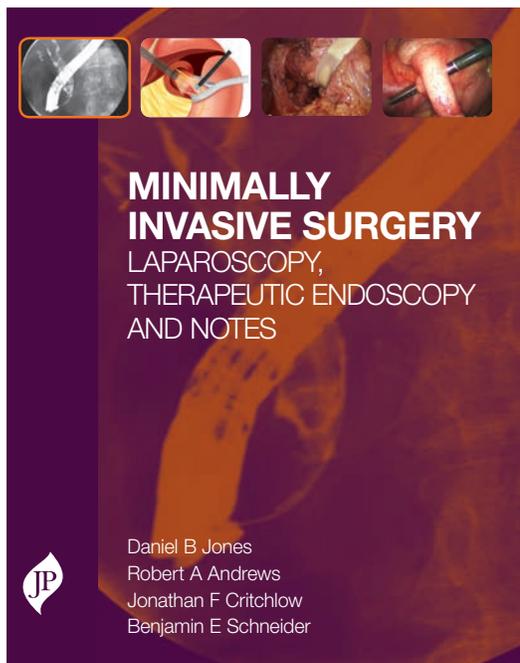
Research Facilities and Space

In FY2014, research in the Department of Surgery occupied approximately 22,000 square feet (sf) of space, including wet labs, special purpose rooms (cold rooms, tissue culture rooms, shared equipment rooms), clinical research space, 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 (9,864 sf), Surgery also has research space in several other locations. These spaces include the Center for Life Sciences (6,259 sf), Research North (2,403 sf), Palmer (583 sf), Feldberg (963 sf), Deaconess (779 sf), and Stoneman (706). The overall dollar density in FY2014 for research space in the Department of Surgery was approximately \$230 per square foot.

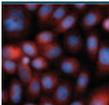
Tracking Academic Performance

In addition to a strong performance in obtaining external research grant funding in this challenging environment (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 FY2014, many of which were in high-impact journals such as *PNAS*, *Nature*, *PLoS One*, *Journal of Immunology*, *JAMA*, *Journal of Biological Chemistry*, etc. In addition, there was one book/textbook from FY2014 that is now in press (below) and will be published in January of 2015. This book was edited by Daniel B. Jones, MD, MS, Robert A. Andrews, MD, Jonathan F. Critchlow, MD, and Benjamin E. Schneider, MD, of the Division of General Surgery.

On the following pages is the integrated bibliography for FY2014; BIDMC faculty and trainees during FY2014 are list in bold type.



◀ Jones F. DB, Andrews R, Critchlow J, Schneider B. *Minimally Invasive Surgery: Laparoscopy, Therapeutic Endoscopy and NOTES*. London: JP Medical Publishers 2014; in press.



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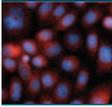
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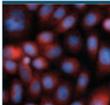
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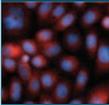
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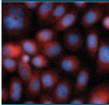
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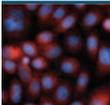
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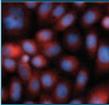
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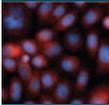
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Carl J. Hauser, MD

Visiting Professor of Surgery
Trauma Medical Director

RESEARCH FOCUS

The major basic science research focus of my research is clinical inflammation biology and the mechanisms and management of infection after injury and surgery. My lab is especially interested in the role of cellular “Danger” molecules, or “damage-associated molecular patterns” (aka “DAMPs” or “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). It has been widely cited as a groundbreaking conceptual advance in sepsis and inflammation research, and has been cited more than 500 times. The known mitochondrial DAMPs include mitochondrial DNA, formyl peptides, and some of the mitochondrial lipids. Our most recent work has identified at least three novel non-formylated peptide DAMPs. Mitochondrial DNA is a potent activator of toll-like receptor 9 (TLR-9) and we have recently found that it is also a potent activator of neutrophil (PMN) extracellular traps (“NETs”). Signaling downstream from this receptor, however, may result in tolerance and so plays a critical role in suppression of immune function after injury.

Formyl peptides (FPs) derived from mitochondria can act as potent chemoattractants. As such, they are critically important activators of immune responses to damaged tissue, including phagocytic wound debridement and thus the initiation of healing. On the other hand, these molecules may compete for the immune system’s “attention” in systemically injured patients. In work presented at this year’s American Association for the Surgery of Trauma (AAST) we showed that innate responses to FPs released by injury render the host susceptible to infection by suppressing PMN surveillance of the lung after bacterial inoculation. In further work, we have now shown that only five of the 13 native mitochondrial FPs are active at the formyl peptide receptors. Having now raised novel antibodies to these specific species, we are now ready to initiate studies using this information for diagnosis and therapeutic intervention.

Our current work, therefore, centers on modulating inflammation in a way that balances the need for inflammation after injury and the susceptibility to infection that inflammation incurs. Molecular aspects of these problems that we study (and which participants can become expert in) include neutrophil signaling, chemokine biology (and intracellular calcium flux signaling), the regulation of endothelial permeability in SIRS, and the study of neutrophil 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.

We believe that these central innate immune 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 submitted multi-PI grants with Leo Otterbein, PhD, and plan to extend this collaboration into a P50 Center Grant in collaboration with three other inflammation laboratories (Wolfgang Junger, PhD, Michael Yaffe, MD, PhD, and Danny Talmor, MD), all powerhouses on the Longwood campus.

In addition, we have begun a clinical research program investigating global use of ultrasound technology to guide wound care and management. This work led to a podium presentation at the AAST and a publication in the *Journal of Trauma* for one of our surgical residents. It is expected to be the basis of a large multicenter trial that will change the way clinical postoperative wounds are managed.

RESEARCH GROUP

Kiyoshi Itagaki, PhD
Elzbieta Kaczmarek, PhD
Nicola Sandler, MD

ACCOMPLISHMENTS 2013-2014

- Served as Medical Director of Trauma Services, BIDMC
- Achieved re-verification of BIDMC as an ACS Level 1 Trauma Center
- Served as Vice President of the Western Trauma Association
- Mentored Nicola Sandler, MD, National Trauma Research Institute, Melbourne, Australia
- Mentored Haipeng Li, MD, Orthopedic Department, Beijing Army General Hospital

Visiting Professorships and Invited Presentations

- Visiting Professor, University of Chicago, Chicago, IL
- Distinguished Visiting Scientists Seminar, University of Southern Alabama, Mobile, AL
- Lecturer, Cottage Hospital Trauma Symposium, Santa Barbara, CA
- Lecturer, Medical World Americas Conference, Houston, TX
- Virendra B. Mahesh Memorial Lecturer, Department of Physiology, Georgia Regents University, Augusta, GA
- Keynote speaker, University of Arizona Southwest Regional Trauma Conference, Tucson, AZ
- Podium presentation, American Association for the Surgery of Trauma and Clinical Congress of Acute Care Surgery, Philadelphia, PA
- Visiting Scientist Lecturer, NIH/NIAID Twinbrook Lecture Series, Rockville, MD
- Distinguished Visiting Professor, Seoul National University Hospital, Seoul, Korea
- Visiting Professor, Royal British Legion Center for Blast Injury Studies, Birmingham, UK
- Lecturer, BioMerieux Foundation Conference, Annecy, France

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 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

SELECTED PUBLICATIONS

Lefering R, Zielske D, Bouillon B, Hauser CJ, Levy H. Lactic acidosis is associated with multi-organ failure and need for ventilator support in patients with severe hemorrhage from trauma. *Eur J Trauma Emerg Surg* 2013; in press.

Li H, Itagaki K, Sandler N, Gallo D, Galenkamp a, Kaczmarek E, Livingston DH, Zeng Y, Lee YT, Tang IT, Isal B, Otterbein LD, Hauser CJ. Mitochondrial DAMPs from fractures suppress pulmonary immune responses via formyl peptide receptors 1 and 2. *J Trauma Acute Care Surg* 2014; in press.

Barrett CD, Celestin A, Eskander MF, Fish E, Glass CC, Gospodinov G, Gupta A, Hauser CJ. surgeon performed ultrasound in predicting wound infections: No collection, no infection. *J Trauma Acute Care Surg* 2014; in press.

A complete list of publications begins on page 15.



RESEARCH FOCUS

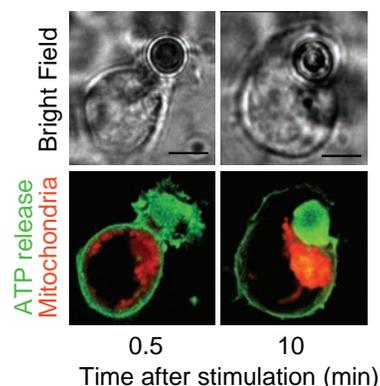
Immune cell stimulation causes the release of cellular ATP via pannexin-1. We found that the released ATP has an important role in regulating immune cell activation and function through a process termed autocrine purinergic signaling (Junger 2011). This process involves P2X-, P2Y-, and P1-type purinergic receptors and ectonucleotidases (ENTPDs, e.g., CD39 and CD73) that convert ATP, ADP, and AMP to adenosine. The focus of my laboratory has been to define these purinergic signaling mechanisms under normal physiological conditions and in pathological conditions following severe injury, burns, and sepsis.

Our overarching research goal is to use our research results for the development of novel strategies to improve clinical outcomes in critical care patients. In these patients, inflammation and immune dysfunction are particularly problematic. Excessive neutrophil activation is a common problem that results in host tissue damage and the failure of organs such as the liver, kidney, and the lungs. In addition, T cells become impaired and fail to protect critical care patients from infections, resulting in sepsis, a leading cause of death. The underlying mechanisms leading to these complications are poorly understood. Therefore, we study the cellular and molecular mechanisms by which immune cell function is regulated and how trauma impairs these mechanisms.

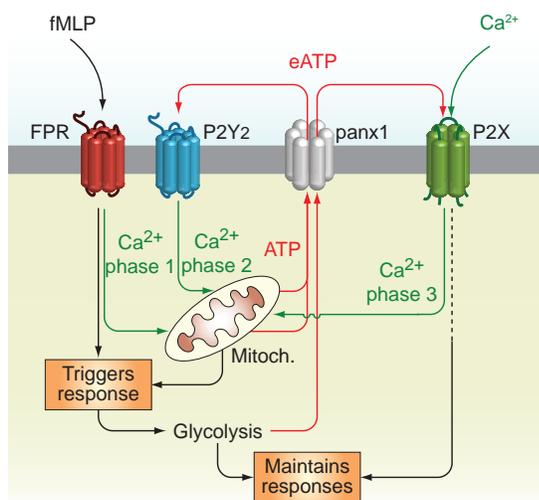
Our work has shown that autocrine purinergic signaling is a refined endogenous signaling mechanism that regulates neutrophil and T cell functions (Junger 2010). We could show that mitochondria deliver the ATP that is required for autocrine purinergic signaling in these cells (Figure 1). We also found that at least two different phases of purinergic signaling and mitochondrial activation are required to regulate intracellular calcium signaling and subsequent functional responses of immune cells (Figures 2 and 3). Excessive amounts of external ATP can interfere with these endogenous purinergic signaling mechanisms, resulting in impaired immune cell function. We found that sepsis causes the release of large amounts of ATP from damaged cells and injured tissues, which promotes inflammation and exacerbates neutrophil-mediated host organ damage. Recently, we found that mitochondrial ATP production in T cells is markedly reduced in critical care patients with sepsis compared to control patients without sepsis and healthy subjects. Reduced mitochondrial activity is associated with impaired autocrine purinergic signaling, severely suppressed T cell function, and an increased risk of infections and sepsis.

RESEARCH GROUP

- Yi Bao, PhD
- Christian Bergmayr, PhD
- Bianca Brix, BSc
- Amelie Graf
- Albert Lee, PhD
- Carola Ledderose, PhD
- Linglin Li, MD
- Xiaoou Diana Li, MD
- Maria Reinisch
- Laura Staudenmaier, BSc
- Katharina Strasser, BSc
- Tiecheng Yu, MD
- Jingping Zhang, MD
- Johannes Zipperle



▲ FIGURE 1: Mitochondrial accumulation at the immune synapse of T cells drives localized ATP release. Jurkat cells were loaded with MitoTracker Red CM-H2XRos to visualize activated mitochondria and stained with 2-Zn(II) to assess ATP release. Then cells were stimulated with anti-CD3/CD28 antibody-coated beads to simulate T cell activation by antigen presenting cells and translocation of activated mitochondria to the immune synapse and a concomitant increase in ATP release were observed by multichannel fluorescence microscopy (from Ledderose et al. 2014, with modifications).



◀ FIGURE 2: Proposed role of mitochondria in neutrophil activation. Stimulation of formyl peptide receptors (FPR) triggers a first phase of Ca²⁺ mobilization, mitochondrial activation, and ATP production followed by rapid ATP release via panx1 channels. This initial burst in ATP release promotes a second round of Ca²⁺ signaling triggered by P2Y2 receptor activation. A switch to ATP production via glycolysis results in further ATP release, activating P2X receptors that contribute to a third phase of Ca²⁺ signaling due to influx of Ca²⁺ from the extracellular space. This second ATP signaling phase sustains intracellular Ca²⁺ levels and maintains functional neutrophil responses following FPR stimulation (from Bao et al. 2014, with modifications).

ACCOMPLISHMENTS 2013-2014

- Reviewer for journals including *Nature*, *Science*, *Nature Reviews*, *Nature Biotechnology*, *Nature Communications*, *Nature Medicine*, *Science Signaling*, *PLoS ONE*, *EMBO Journal*
- 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
- Chiring 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
- Invited Lecture; 150th Anniversary of the Department of Physiology of Uppsala University; Uppsala, Sweden

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, Maria Reinisch, Amelie Graf, and Marcus Lidicky, who performed thesis projects in my laboratory for their MD degrees from the Paracelsus Medical University, Salzburg, Austria
- Thesis advisor of Severin Muehleider, Bianca Brix, and Katharina Strasser, who performed their master's thesis projects in my laboratory and received their master's degrees from the Fachhochschule Technikum, Vienna, Austria
- Faculty mentor of Jamaji Chilaka Nwanaji-Enwerem, who enrolled in the MD/PhD program of Harvard Medical School
- Thesis advisor of Laura Staudenmaier, who performed her master's thesis projects in my laboratory and who will receive a master's degree from the University of Ulm, Ulm, Germany
- Faculty advisor for Xiaoou Diana Li, MD, who has been working on her PhD thesis and received a grant from the Chinese government to carry out research in my laboratory
- Faculty advisor for Tiecheng Yu, MD, who received a full fellowship from the Chinese government and began to carry out research in my laboratory
- Advisor to junior faculty and fellows

SELECTED RESEARCH SUPPORT

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

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

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

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

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

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

Chronic subdural hematoma and inflammation; Eleanor and Miles Shore Fellowship Program; 2014-2016; Co-Investigator: Wolfgang G. Junger, PhD (PI: Martina Stippler, MD)

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.

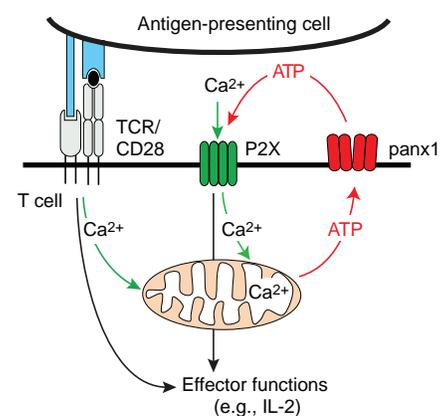
Bao Y, Ledderose C, Seier T, Graf AF, Brix B, Chong E, Junger WG. Mitochondria regulate neutrophil activation by generating ATP for autocrine purinergic signaling. *J Biol Chem* 2014; 289(39):26794-803.

Junger WG, Rhind SG, Rizoli SB, Cuschieri J, Baker AJ, Shek PN, Hoyt DB, Bulger EM. Prehospital hypertonic saline resuscitation attenuates the activation and promotes apoptosis of neutrophils in patients with severe traumatic brain injury. *Shock* 2013;40(5): 366-74.

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

Ledderose C, Bao Y, Lidicky M, Zipperle J, Li L, Strasser K, Shapiro NI, Junger WG. Mitochondria are gate-keepers of T cell function by producing the ATP that drives purinergic signaling. *J Biol Chem* 2014;12;289(37):25936-45.

Sumi Y, Woehrle T, Chen Y, Bao Y, Li X, Yao Y, Inoue Y, Tanaka H, Junger WG. Plasma ATP is required for neutrophil activation in a mouse sepsis model. *Shock* 2014;42(2):142-7.



▲ FIGURE 3: Proposed model of regulation of T cell activation by Ca^{2+} and purinergic signaling and by mitochondrial ATP firing. T cell receptor/CD28 co-receptor (TCR/CD28) stimulation triggers Ca^{2+} release from intracellular stores, resulting in mitochondrial Ca^{2+} firing and ATP production that feeds autocrine purinergic signaling and prolonged Ca^{2+} influx via P2X1 and P2X4 receptors at the immune synapse (from Ledderose et al. 2014, with modifications).

A complete list of publications begins on page 15.

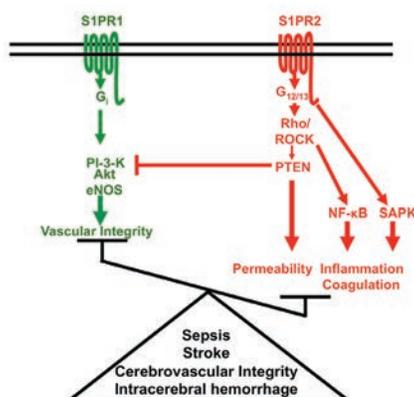


RESEARCH GROUP

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 κB (NFκB) 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 metalloproteinases. Altogether our data indicate that S1PR2 receptor could be pharmacologically targeted to promote cerebrovascular integrity at the time of reperfusion in stroke patients.

▲ 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.

ACCOMPLISHMENTS 2013-2014

- Invitation to serve on NIH study section, Special Emphasis Panel/Scientific Review Group, HLBP
- Session chair, abstract reviewer, and poster grader in the 10th Center for Vascular Biology Research Annual Summer Retreat in North Falmouth, MA, June 2014

Invited Presentations

- Novel targets for acute cerebrovascular protection in stroke; Center for Vascular Biology Research Seminar Series, BIDMC, February 2014
- Critical role of sphingosine-1-phosphate receptor 2 in sepsis morbidity and mortality; Society for Academic Emergency Medicine National Meeting, Dallas, TX, May 2014
- Sphingosine-1-phosphate receptor-2 as a novel target for acute vasoprotection; Center for Vascular Biology, Department of Pathology, Weill Cornell Medical College, New York, NY, June 2014
- Translational research in vascular biology: Novel targets for acute vascular protection; Center for Vascular Biology Research Summer Student Seminar Series, BIDMC, July 2014
- Sphingosine-1-phosphate receptor 2 as a novel therapeutic target for acute cerebrovascular protection; Gordon Research Conference: Endothelial Cell Phenotypes in Health and Disease, Girona, Spain, July 2014
- Sphingosine-1-phosphate receptor-2 as a novel target for acute vascular protection, Department of Brain Ischemia and Neurodegeneration. Spanish Research Council, Institute for Biomedical Research August Pi i Sunyer (IDIBAPS), Barcelona, Spain, July 2014

Administrative

- I have continued to be a member of the committee in charge of organizing the Center for Vascular Biology Research Annual Summer Retreat, which was held in North Falmouth, MA, in June 2014.
- 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 Club and Data Club.

TEACHING, TRAINING, AND EDUCATION

I have continued to train research fellows and research assistants in the lab. 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 Journal and Data clubs 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, 2009-2015; 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 Affinity Research Collaborative (ARC), 2014; 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.

A complete list of publications begins on page 15.



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, MSS
Susanne Swartout, PhD

Dr. Yaffe also has a joint appointment
in Surgical Oncology at BIDMC.

Michael B. Yaffe, MD, PhD

David H. Koch Professor of Biology and Biological Engineering,
Massachusetts Institute of Technology

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.

- 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
- 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, 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 B. Yaffe, MD, PhD

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

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

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

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

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, Fydrych 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, Ogirodowicz 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.

Morton SW, Lee MJ, Deng ZJ, Dreaden EC, Siouwe E, Shopsowitz KE, Shah NJ, Yaffe MB, Hammond PT. A nanoparticle-based combination chemotherapy delivery system for enhanced tumor killing by dynamic rewiring of signaling pathways. *Sci Signal* 2014;7(325):ra44.

Kamal R. Khabbaz, MD

Associate Professor of Surgery
Chief, 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 engaged in devising new methods of interrogating valvular structures using 3D echocardiography. We are continuing our collaboration with Cardiology and Vascular and Endovascular Surgery on multiple projects, including clinical trials that 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.

Echocardiography to predict recurrent ischemic mitral regurgitation after surgical mitral valve repair: This NIH-funded study seeks to develop echocardiographic techniques to predict, preoperatively, the degree of recurrent ischemic mitral regurgitation (IMR) that can be expected for an individual patient within the first year after surgery. The anticipated results of the proposed study will allow surgeons to determine which IMR patients are best treated with standard MV repair (i.e. ring annuloplasty) and which are better served by valve replacement.

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.

Evaluation of the GORE Conformable TAG® thoracic endoprosthesis for treatment of acute complicated Type B aortic dissection (TAG 08-01)

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 19 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. Our 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, Society of Cardiovascular Anesthesiologists Annual Meeting 2012, Boston MA (poster)

Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis; U.S. CoreValve Clinical Investigators. *N Engl J Med* 2014; 370(19):1790-8.

Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J Jr, Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK; CoreValve U.S. Clinical Investigators. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 2014;63(19):1972-81.

Owais K, Kim H, Khabbaz KR, Bergman R, Matyal R, Gorman RC, Gorman JH 3rd, Hess PE, Mahmood F. In-vivo analysis of selectively flexible mitral annuloplasty rings using three-dimensional echocardiography. *Ann Thorac Surg* 2014;97(6):2005-10.

Subramaniam B, Khabbaz KR, Heldt T, Lerner AB, Mittelman MA, Davis RB, Goldberger AL, Costa MD. Blood pressure variability: Can nonlinear dynamics enhance risk assessment during cardiovascular surgery? *J Cardiothorac Vasc Anesth* 2014;28(2):392-7.

Subramaniam B, Lerner A, Novack V, Khabbaz K, Paryente-Wiesmann M, Hess P, Talmor D. Increased glycemic variability in patients with elevated preoperative HbA1C predicts adverse outcomes following coronary artery bypass grafting surgery. *Anesth Analg* 2014;118(2):277-87.

Black KM, Masuzawa A, Hagberg RC, Khabbaz KR, Trovato ME, Rettagliati VM, Bhasin MK, Dillon ST, Libermann TA, Toumpoulis IK, Levitsky S, McCully JD. Preliminary biomarkers for identification of human ascending thoracic aortic aneurysm. *J Am Heart Assoc* 2013;2(6):e000138.

Sidney Levitsky, MD

Cheever Professor of Surgery

James D. McCully, PhD

Associate Professor of Surgery



RESEARCH GROUP

Hiroshi Kondo, MD
Janine Preble, MS

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.

Autogenic 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 autogenic 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.

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

ACCOMPLISHMENTS 2013-2014

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.

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

Friehs 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

Levitsky S, Chitwood WR, Orringer MB, Mack MJ: Education above and beyond: Innovative STS educational initiatives. *Ann Thorac Surg* 2014;97:S29-S33.

Preble JM, Kondo H, Levitsky S, McCully JD: Quality control parameters for mitochondria transplant in cardiac tissue. *JSM Biochemistry and Molecular Biology*; in press.

A complete list of publications begins on page 15.



Lijun Sun, PhD

Associate Professor of Surgery

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.

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 to chemotherapies.

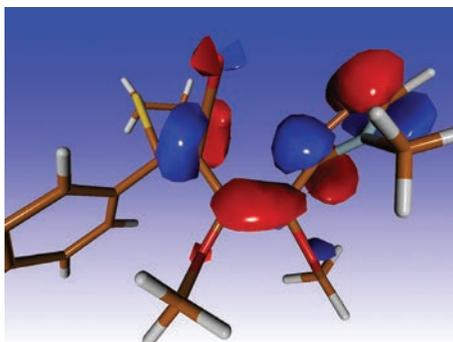
Anti-inflammatory drug discovery

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.

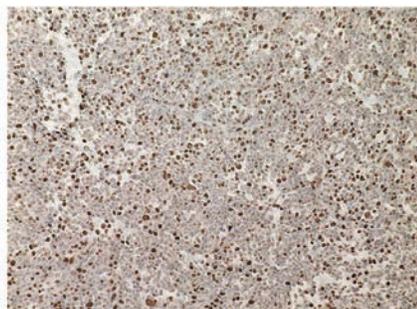
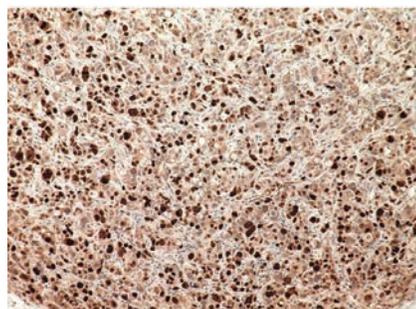
We aim to develop novel drug-like small-molecule AhR ligands that will help validate AhR as a novel target for treating human diseases.

RESEARCH GROUP

Sha Bai, PhD
Finith Jernigan, PhD
Steffi Koerner, PhD
Hiyoku Nakata, MS
Yiqiang Wang, PhD



▲ FIGURE 1: Quantum mechanics simulation of a reaction transition state predicting selectivity



◀ FIGURE 2: *In vivo* inhibition of prostate cancer cell proliferation by CDD-026

ACCOMPLISHMENTS 2013-2014

We discovered a series of novel, synthetic AhR agonists that are shown to potently modulate the expression of key mediators implicated in inflammatory disorders such as atherosclerosis and Crohn's disease (in collaboration with Dr. Elliot Chaikof, BIDMC). We are currently evaluating the lead molecules in disease models and improving their pharmaceutical properties.

We made significant progress in the synthesis of an ATP selective chemosensor that has been applied to real-time monitoring of ATP levels in immune cells (in collaboration with Dr. Wolfgang Junger, BIDMC). Our current focus is to reengineer the ATP probe with a red-shifted fluorescein-based chromophore for improved biocompatibility. Furthermore, we plan to conjugate the chemosensor to a lipid, which enables cell surfacing anchoring of the sensor for detection of extracellular ATP.

We initiated the synthesis and optimization of small molecule inhibitors of mast cell degranulation. The optimized inhibitor will be evaluated in preclinical models of diabetic wound healing (in collaboration with Dr. Aristidis Veves, BIDMC).

We have synthesized 30 novel compounds targeting a pivotal enzyme implicated in lipogenesis of cancer cells. From these set of compounds we are developing the structure-activity relationship (SAR) that will guide the development of novel anticancer agents (in collaboration with Dr. Vikas Sukhatme, BIDMC).

In collaboration with Dr. Barbara Wegiel (BIDMC), we have identified a series of novel indolyl-chalcone type of anticancer agents that target the STMN1 pathway and selectively induce mitotic catastrophe. The most potent compound, CDD-026, demonstrated cytotoxicity in prostate cancer cells with an IC50 of 100 nM. The objectives of this research are to delineate the mechanism of actions and to develop mechanism-guided anticancer therapies.

By applying the principles of bioisotere-/property-guided drug designs, we were able to improve the potency (by >10-fold) and solubility of an HTS hit that was extremely difficult to deliver systemically. The novel lead OBD-09 is shown to be equally active in metastatic prostate cancer cells (in collaboration with Dr. Bruce Zetter, Boston Children's Hospital).

Honors and Awards

I was promoted to Associate Professor of Surgery at Harvard Medical School, effective January 2014.

I was elected as co-chair of the prostate cancer section in the 17th International Symposium on Molecular Medicine, Athens, Greece, October, 2014.

TEACHING, TRAINING, AND EDUCATION

The Center is committed to providing a platform for educating the next-generation of research scientists, who will gain broad knowledge and experience in drug discovery and translational research. In the BIDMC Affinity Research Collaborative (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 promote 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.

ABSTRACTS, POSTERS, AND EXHIBITS

Wang Y, Jernigan F, Zetter B, Sun L. Novel strategy for the treatment of metastatic and castrate resistant prostate cancer. 19th World Congress on Advances in Oncology and 17th International Symposium on Molecular Medicine, Athens, Greece, 2014

Wegiel B, Wang Y, Jernigan F, Sun L. The indolyl-chalcone CDD-026 induces cancer cell death through targeting of STMN1 and mitotic catastrophe. 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Barcelona, Spain, 2014

SELECTED RESEARCH SUPPORT

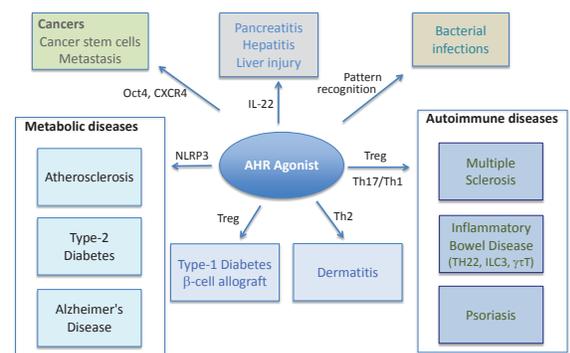
BIDMC Department of Surgery start-up package, 2012-2017; PI: Lijun Sun, PhD

Development of anticancer agents; Fujifilm, 2014-2016; PI: Lijun Sun, PhD (Co-PI: Vikas Sukhatme, MD, PhD)

Development of anticancer agents (Visiting Scientist Supplement); Fujifilm, 2014-2016; PI: Lijun Sun, PhD

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

Mechanisms of neuropeptides action in diabetes; NIH, 2014-2015; Co-Investigator: Lijun Sun (Co-PI/Contact PI: Aristidis Veves, MD, DSc)



▲ FIGURE 3: The central role of AhR in human diseases



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
- Management of pathways and algorithms to maintain improved results in perioperative care

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

- Evaluation of the impact of a 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 2013-2014

This year, we published our research on the reduction of urinary tract infections in colorectal surgery patients. We continue to develop our pathways for patient education in the prevention of dehydration after creation of a new ileostomy. This work has been shared in national and international settings and has prompted collaborative efforts with other institutions in training and research. Based on this work, Dr. Vitaliy Poylin was honored with a traveling visiting fellowship from the American Society of Colon and Rectal Surgeons (ASCRS). We have extended these efforts to include perioperative anesthesia pathways for colorectal surgery patients and management of infection.

Our administrative achievements include:

- Program growth has been achieved through expansion to two new suburban locations. This increases patient access to our services in the community setting.
- A new program has been developed in sacral nerve stimulation therapy for the treatment of bowel incontinence.
- We have extended our multidisciplinary clinic model for colorectal cancer management to the community at the Beth Israel Deaconess Cancer Center & Surgical Pavilion adjacent to Beth Israel Deaconess–Needham.

Invited Presentations

- Best practices for the management of rectal cancer; Visiting Professor at Stony Brook University, Stony Brook, NY, December 2013
- Integrating robotic surgery into a busy laparoscopic colorectal surgery practice; ASCRS, 2014
- Perioperative use of tamsulosin significantly decreases rates of urinary tract infection in men undergoing pelvic surgery; ASCRS, 2014 (poster)
- Myocutaneous flap closure increases wound dehiscence in patients undergoing abdominoperineal resection in the National Surgical Quality Improvement Project; ASCRS, 2014 (poster)
- Gabapentin significantly decreases posthemorrhoidectomy pain: A prospective study; Tripartite meeting, Birmingham, UK, 2014

TEACHING, TRAINING, AND EDUCATION

A medical student rotation in Colon and Rectal Surgery was added to the Core Surgery Clerkship in the last academic year. We developed and maintain 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 a special focus on advanced minimally invasive surgery. We also provide outpatient education in the clinics where residents can participate in independent evaluation and decision-making. Our service initiated the training of residents in robotic colon and rectal surgery at BIDMC and will extend this training to console work in the near future.

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

SELECTED PUBLICATIONS

Poylin V, Bensley R, Nagle D. Changing approaches to rectal prolapse repair in the elderly. *Gastroenterol Rep (Oxf)* 2013;1(3):198-202.

Nagle D, Curran T, Anez-Bustillos L, Poylin V. Reducing urinary tract infections in colon and rectal surgery. *Dis Colon Rectum* 2014;57(1):91-7.

Nandivada P, Nagle D. Surgical therapies for fecal incontinence. *Curr Opin Gastroenterol* 2014 Jan;30(1):69-74.

Poylin V, Curran T, Lee E, Nagle D. Laparoscopic colectomy decreases the time to administration of chemotherapy compared with open colectomy. *Ann Surg Oncol* 2014;21(11):3587-91.

Poylin V, Quinn J, Messer K, Nagle D. Gabapentin significantly decreases post-hemorrhoidectomy pain: A prospective study. *Int J Colorectal Dis* 2014; in press.

A complete list of publications begins on page 15.



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
- Decision making in the approach to pelvic surgery
- Relationship of obesity and diverticulitis

ACCOMPLISHMENTS 2013-2014

Since 2012, I completed a prospective trial on the effects of gabapentin on recovery after anorectal surgery that was awarded the Traveling Fellowship of the American Society for Colon and Rectal Surgeons (ASCRS). I went on a tour of hospitals in Ireland and England and presented the outcomes of this project at the Tripartite meeting in Birmingham, UK.

Administratively, I became a Fellow of the ASCRS. I am also a member of the Awards Committee and Young Surgeons Committee of ASCRS. In addition, at BIDMC I participated in the First Case Start Committee, the Operating Room Code Response Faculty Hour, and the Utilization Review Pathology Advisory Committee.

Invited Presentations

- Gabapentin significantly decreases posthemorrhoidectomy pain: A prospective study; Tripartite meeting, Birmingham, UK, 2014
- Myocutaneous flap closure increases wound dehiscence in patients undergoing abdominoperineal resection in the National Surgical Quality Improvement Project; Tripartite meeting, Birmingham, UK, 2014 (poster)
- Getting off the island – approach to comprehensive postoperative care; St. Vincent Hospital, University College of Dublin, Ireland, 2014
- Reducing urinary tract infections in colon and rectal surgery may be easier than you think!; Plenary Talk, ASCRS Annual Meeting, 2013
- Anal fissures; Harvard Medical School, 2013
- Bright red blood per rectum; Harvard Medical School, 2013
- Evaluation and treatment of benign pruritus ani; Harvard Medical School, 2013
- Anal plug procedure: Yes, it does work!; Harvard Medical School, 2013

TEACHING, TRAINING, AND EDUCATION

This year I participated in Harvard combined courses on colorectal surgery for primary care physicians and surgeons. 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. I also give lectures to GI and oncology fellows on common anorectal conditions and surgical approaches to rectal cancer.

SELECTED PUBLICATIONS

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.

Poylin V, Bensley R, Nagle D. Changing approaches to rectal prolapse repair in the elderly. *Gastroenterol Rep (Oxf)* 2013;1(3):198-202.

Nagle D, Curran T, Anez-Bustillos L, Poylin V. Reducing urinary tract infections in colon and rectal surgery. *Dis Colon Rectum* 2014;57(1):91-7.

Poylin V, Curran T, Lee E, Nagle D. Laparoscopic colectomy decreases the time to administration of chemotherapy compared with open colectomy. *Ann Surg Oncol* 2014;21(11):3587-91.



RESEARCH GROUP

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

RESEARCH FOCUS

My current research encompasses several different areas in the field of nutrition medicine. I am one of the original (2004) principle investigators on the NIDDK Look AHEAD clinical trial to study intense lifestyle intervention in overweight/obese type 2 diabetes mellitus (T2DM). We are now in the second year of the Look AHEAD Continuation (Look AHEAD-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 in the

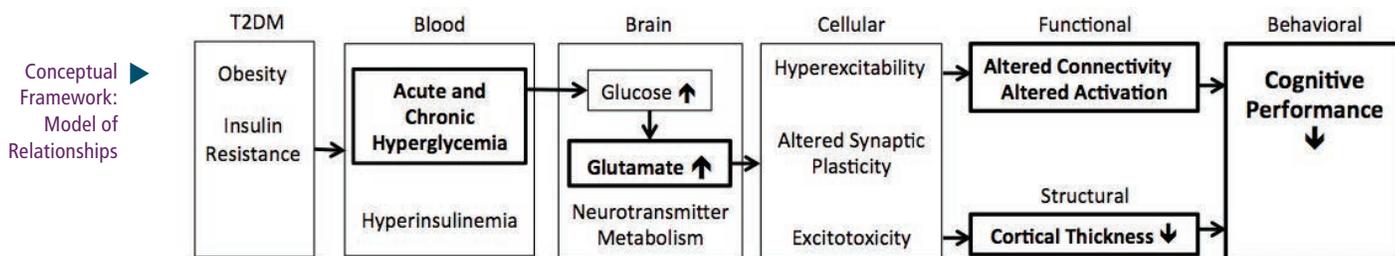
neurocognitive basis of inter-individual differences in this area, and the development of new brain- and cognition-based therapies to enhance eating control in pathological situations, such as obesity. These efforts are interdisciplinary, innovative, and have clinical relevance. We feel confident that 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, diabetologists, and neuroscientist, and brought them together to submit an R01 grant entitled Look AHEAD Cognitive Fitness Ancillary Study.

The public health implications of cognitive dysfunction and deterioration in type 2 diabetes mellitus are of great consequence to the U.S. health care system. This research project will use advanced neuroimaging techniques to investigate the biochemical mechanisms underlying alterations of brain function that impact cognition in a well-characterized group of people from 70 to 86 years old with type 2 diabetes. It will provide novel targets for neuroprotective treatments that preserve cognition and help design better complementary cognitive-enhancing treatments.

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 sub-cohort 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 2013-2014

As the S. Daniel Abraham Professor in Nutrition Medicine I actively work to promote Mr. Abraham's philosophy on healthy living. Mr. Abraham is interested in developing collaborations between the Mayo Clinic and Harvard Medical School in this area.

I continue to be an ad hoc reviewer for several journals (2013 acknowledgement from *Annals of Internal Medicine*) and participate in grant reviews (NIH Loan Repayment Grant review/Harvard Catalyst).

I am on a Data Safety Monitoring Board for new obesity technology to ensure patient safety.

I also serve as a board member for Food Research Action Center (FRAC), the leading national organization working to improve public policy to eradicate hunger and under-nutrition in the United States. FRAC engages in research, analysis, training, technical assistance, advocacy, and public education to improve public nutrition programs and broaden their reach.

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 for our medical students. I am a member of the HMS Nutrition Education sub-committee. 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 for Grand Rounds. 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

Lifestyle intervention study in adjuvant treatment of early breast cancer (LISA); DFCI/Novartis Pharmaceuticals, 2008-2016; Site PI: George L. Blackburn, MD, PhD (DFCI PI: Jennifer Ligibel, MD; PI: Pamela Goodwin, MD)

Look AHEAD Cognitive Fitness Ancillary Study NIH (Pending); PI: George L. Blackburn, MD, PhD

SELECTED PUBLICATIONS

Foltz JL, Belay B, Blackburn GL. Improving the weight of the nation by engaging the medical setting in obesity prevention and control. *J Law Med Ethics* 2013;41(Suppl 2):19-26.

Apovian CM, Huskey KW, Chiodi S, Hess DT, Schneider BE, Blackburn GL, Jones DB, Wee CC. Patient factors associated with undergoing laparoscopic adjustable gastric banding vs Roux-en-Y gastric bypass for weight loss. *J Am Coll Surg* 2013;217:1118-25.

Wadden TA, Bantel JP, Blackburn G, Bolin P, Bracati FL, Bray GA, et al. Eight-year weight losses with an intensive lifestyle intervention: The look AHEAD study. *Obesity* 2014;22(1): 5-13.

Wee CC, Mukamal KJ, Huskey KW, Davis RB, Colten ME, Bolcic-Jankovic D, Apovian C, Jones DB, Blackburn GL. High-risk alcohol use after weight loss surgery. *Surg Obes Relat Dis* 2014;10:508-13.

Mason C, Xiao L, Imayama I, Duggan CR, Campbell KL, Kong A, Wang CY, Alfano CM, Blackburn GL, Foster-Schubert KE, McTiernan A. The effects of separate and combined dietary weight loss and exercise on fasting ghrelin concentrations in overweight and obese women: A randomized controlled trial. *Clin Endocrinol* 2014; in press.

Goodwin PJ, Segal RJ, Vallis M, Ligibel JA, Pond GR, Robidoux A, Blackburn GL, Findlay B, Galow JR, Mukherjee S, Levine M, Pritchard KI. Randomized trial of a telephone-based weight loss intervention in postmenopausal women with breast cancer receiving Letrozole: The LISA Trial. *J Clin Oncol* 2014;32:2231-9.

A complete list of publications begins on page 15.



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 more than 200 major pancreaticobiliary operations per year.

A prospective database of more than 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. Now we are 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 2013-2014

- Elected to the Gastrointestinal Surgery Advisory Council, American Board of Surgery, 2014
- Nobility in Science Award, National Pancreas Foundation, 2014
- Editor, *HPB*
- Executive Council, International Hepato-Pancreato-Biliary Association
- Treasurer, Executive Committee, Society for Surgery of the Alimentary Tract, 2013
- Kenneth Warren Award, New England Baptist Hospital, 2013
- S. Robert Stone Award, Excellence in Teaching, Beth Israel Deaconess Medical Center/Harvard Medical School, 2013
- Masters of Arts (Honorary), Harvard University, 2013

Invited Presentations

The promotion and tenure process; Career Development Symposium, SAGES, 2014

Evaluation and approaches for borderline resectable pancreas cancer, Combined Clinical Symposium, Annual SSAT/DDW Meeting, 2014 (co-moderator)

Chair, Best Video Session, International Hepato-Pancreato-Biliary Association World Congress, 2014

Tips to avoid open conversion during laparoscopic HPB surgery symposium, IHPBA World Congress, 2014 (moderator)

Invited Professor, New surgical techniques in the resection of the pancreatic head, Joint Meeting of the Americas HPB, 2014

Invited Professor, Prevention and management of pancreatic fistula, Joint Meeting of the Americas HPB, 2014

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

McMillan MT, Christein JD, Callery MP, Behrman SW, Kent TS, Drebin JA, Miller BC, Lewis RS, Vollmer CM. Prophylactic octreotide for pancreatoduodenectomy: More harm than good? 11th World Congress of the International Hepato-Pancreato-Biliary Association (IHPBA), Seoul, Korea, 2014 (oral plenary presentation)

Abbasi A, Lo R, Moser AJ, Tseng JF, Vollmer CM, Callery MP, Kent TS. Role of surgical palliation in patients with pancreatic ductal adenocarcinoma (PDAC). AHPBA Annual Congress, Miami, FL, 2014 (oral poster presentation)

SELECTED PUBLICATIONS

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.

Glass CC, Gondek SP, Vollmer CM, Callery MP, Kent TS. Readmission following pancreatectomy: What can we do better? *HPB* 2013;15:703-708.

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.

Miller BC, Christein JD, Behrman SW, Drebin JA, Pratt WB, Callery MP, Vollmer CM Jr. A multi-institutional external validation of the fistula risk score for pancreatoduodenectomy. *J Gastrointest Surg* 2014;18:172-80.

Vollmer CM Jr, Lewis RS, Hall BL, Allendorf JD, Beane JD, Behrman SW, Callery MP, Christein JD, Drebin JA, Epelboym I, He J, Pitt HA, Winslow A, Wolfgang C, Strasberg SM. Establishing a quantitative benchmark for morbidity in pancreatoduodenectomy using ACS-NSQIP, the accordion severity grading system, and the postoperative morbidity index. *Ann Surg* 2014; in press.

A complete list of publications begins on page 15.

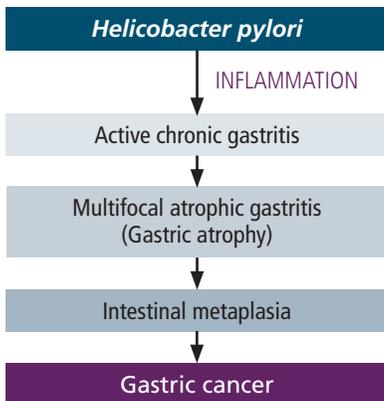
Susan J. Hagen, PhD

Associate Professor of Surgery
Associate Vice Chair, Research



RESEARCH GROUP

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



▲ FIGURE 1: Schematic diagram of the gastric cancer cascade

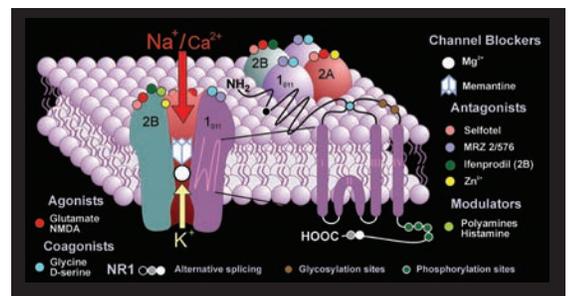
RESEARCH FOCUS

The focus of my laboratory is to understand how barrier dysfunction facilitates gastric cancer development during *Helicobacter pylori* infection; in particular, the relationship between barrier dysfunction and atrophy, 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. Atrophy occurs when the protective barrier, formed by a confluent monolayer of epithelial cells, is disrupted during infection. Loss of epithelial barrier function increases mucosal permeability, initiates inflammation, and affects the cell survival/death mechanisms of epithelial cells. We approach our work by studying the details of gastric barrier function in general, and its disruption during infection and cancer development, using advanced microscopy and genomic approaches. Our aims have two important goals: one is to understand basic science principles and the other is translational.

Despite expressing a specific subset of the 27 types of tight junction claudins, which are proteins that confer barrier properties to epithelial cells, the stomach expresses one main tight junction claudin, claudin-18. Claudin-18 is a cation-specific tight junction protein that is transcriptionally down-regulated in *H. pylori* infection in mice as well as in patients with gastric cancer. We have shown this to occur, at least in part, by pro-inflammatory cytokines, particularly IL-1 β . Because claudin-18 is attenuated in disease, we made claudin-18 knockout mice to study its role in mucosal barrier function in general and in gastric cancer pathogenesis in particular. Our recent work demonstrates that claudin-18 is: 1) not tight junction associated but is rather a basolateral membrane protein, 2) an important signaling molecule that regulates gastric homeostasis, 3) a key regulator of atrophy development if it is down-regulated during disease, and 4) a potent tumor suppressor in the stomach. We are currently creating cell-specific conditional knockout mice to genetically dissect the role of claudin-18 in gastric tumorigenesis. We complement the animal studies with *in vitro* work using primary cultured gastric epithelial cells that contain nearly pure parietal or chief cells.

We are beginning a new area of research in the laboratory that concerns the translation of results from our animal studies into biomarkers or therapeutics for early gastric cancer. For this we have partnered with Duan Chen, MD, PhD, who is a surgeon/scientist from the Norwegian University of Science and Technology, and Chunhui Lan, MD, PhD, who is a gastroenterologist/scientist from China. With both collaborators, we will be able to obtain human pathology samples from gastritis through gastric cancer (Figure 1). We will use these to evaluate gene-expression patterns for novel biomarkers related to claudin-18 that may inform patient management, drive biomarker development for early screening, and/or uncover therapeutic opportunities for novel drug development targeting gastric cancer.



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

Individual Accomplishments

One of 40 research teams to compete successfully for a Harvard Catalyst grant with the RFA entitled: "Advanced microscopy – Zooming in on the Big Idea in Pathology." Eleven teams were given one-year pilot grants from this program.

Committee member and opponent for the thesis defense of Helene Johannessen, a PhD candidate from the Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. The title of her thesis was "Translational research in obesity: Animal models of bariatric surgery and the underlying mechanisms." September 5, 2014.

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

Served as a mentor for Jessica Wu, who was in the Research Science Institute's (RSI) summer research program at MIT. Out of 100 top high school students from the U.S. and abroad, Ms. Wu was one of 10 students from the program invited to do an "encore presentation" of her summer project at the RSI Finale. In addition, her scientific paper entitled "Claudin-18 as a Potent Tumor Suppressor in Mice" won a Top 5 award in competition. The program ran from July 27-August 3, 2014.

Invited Presentations (selected)

Claudin-18 functions as a tumor suppressor in mouse stomach; Visiting Professor, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway, 2014

And why was HGF added to chief cell cultures?, Global GI meeting, San Diego, CA, 2014

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 Harvard Medical School Courses

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

Resident Courses

Module Leader in 2014 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

Evaluating gastric cancer pathogenesis using high-resolution microscopy and genomics; Harvard Clinical and Translational Science Center, NIH, Pilot project, 2014-2015; PI: Susan J. Hagen, PhD

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)

Pending Research Support

Them1-mediated metabolic regulation and pathogenic role in NAFLD; NIH, 2015-2020; Multi-PI R01: David E. Cohen, MD, PhD, Brigham and Women's Hospital; Susan J. Hagen, PhD; Eric Ortland, PhD, Emory University

Wohlwend high pressure freezer for the BIDMC EM core; NIH, 2015; PI: Susan J. Hagen, PhD

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;503(7475):272-6.

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;288(46):33376-86.

Hagen SJ. Glutamine supplementation in *H. pylori* infection. In: Rajendram R, Preedy VR, and Patel VB, editors. *Glutamine in Health and Disease*. London: Springer; 2013; in press.

Tashima K, Kabashima M, Matsumoto K, Yano S, Hagen SJ, Horie S. Allyl isothiocyanate, a pungent ingredient of wasabi and mustard oil, impairs gastric paracellular barrier in primary cultures from the rat stomach via an TRPA1-independent pathway. In: Mozsik G, Abdel-Salam OME, Takeuchi K, editors. *Capsaicin-Sensitive Neural Afferentation and the Gastrointestinal Tract: From Bench to Bedside*. Chapter 3. InTech 2014. p. 77-99.



Daniel B. Jones, MD, MS

Professor of Surgery

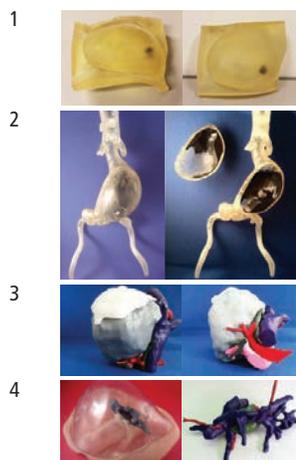
Vice Chair, Surgery, Technology and Innovation

Chief, Section of Minimally Invasive Surgery

Director, Bariatric Surgery Program

RESEARCH GROUP

Chris Awtrey, MD
 George Blackburn, MD, PhD
 Caroline Cao, PhD
 Suvranu De, PhD
 David Fobert
 Abe Frech, MD
 Steve Henriques, MD
 Stephanie Jones, MD
 Michael McBride, RN
 Marcos Mollina, MD
 Jaisa Olasky, MD
 Caroline Park, MD
 Ganesh Sankaranarayanan, PhD
 Benjamin Schneider, MD
 Steven Schwartzberg, MD
 Robert Sung, MD
 Darren Tavernelli, RN
 Linda Trainor, RN
 Hussna Wakily, MD
 Christina Wee, MD, MPH



▲ FIGURES 1-4: Novel 3D models developed from digital imaging using a 3D jet printer.
 1. Breast with tumor
 2. Liver with vessels
 3. Lung with tumor
 4. Aorta

RESEARCH FOCUS

My education-based research has established a technical skills laboratory, validating new teaching tools and instituting curricula 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 five ongoing, NIH-funded collaborative projects among the Center for Modeling, Simulation and Imaging in Medicine (CeMSIM), Rensselaer Polytechnic Institute (RPI), the BIDMC Carl J. Shapiro Simulation and Skills 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 Airway Simulation Trainer (VAST)

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.

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 motions are captured by optical and gyroscope sensors was built to interface the VEST for testing.

Virtual Airway Simulation Trainer (VAST) is a simulator to teach difficult airway management as might be encountered in an obese patient. Cricothyroidotomy is also taught.

Bariatric surgery

My research also focuses on 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.

ACCOMPLISHMENTS 2013-2014

Accomplishments include being elected: President, Association for Surgical Education (ASE); Vice President, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES); Chair, FUSE Task Force (SAGES); Chair, Patient Safety Committee, American Society of Metabolic and Bariatric Surgery; and Chair, Public Policy and Advocacy Committee, Society for Surgery of the Alimentary Tract (SSAT)

Invited Presentations

Surgery for obesity: Facts, risks and results; HMS/BIDMC Mini-Medical School Lecture Series, Boston, MA, 2013

Simulation: Challenges of training surgical residents in the new millennium; CRICO-HMS, Boston, MA, 2013

Overview of guidelines and changes in the surgical management of the bariatric patient; AACE/ASMBS/TOS clinical guidelines: Multidisciplinary perspective. Obesity Week, Integrated Health Symposium, Atlanta, GA, 2013

Simulation, skills training, and on-line education: The US response to a shorter work week; 56th International Surgery Group Meeting, Belgium, 2013

Bariatric surgery in the 21st century. Dasman Diabetes Institute Seminar tele-broadcast, Kuwait, 2013

3D modeling may improve surgical teaching and clinical performance; International Surgery Group, Newport, RI, 2014 (see Figures 1-4)

Recognition and Awards

- Best Doctors in America; *Top Doctors*, *Boston Magazine*, *US News & World Report*; America's Top Surgeons, Consumers Research Council of America
- ASE Excellence in Innovation in Education Award; ASE Distinguished Educator Award

Editorial Roles

Editorial Board: *Surgical Endoscopy*, *Bariatric Times*, and *UpToDate*

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 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

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 B. Jones, MD, MS

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

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

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

Virtual airway simulation trainer (VAST); NIH, 2014-2018; PI: Stephanie B. Jones, MD

SELECTED PUBLICATIONS

Glass C, Acton RD, Blair PG, Campbell AR, Deutsch ES, Jones DB, Liscum KR, Sachdeva AK. ACS-ASE Simulation-based medical school curriculum needs assessment. *Am J Surg* 2013; 207(2):165-169.

Apovian CM, Huskey KW, Chiodi S, Hess DT, Schneider BE, Blackburn GL, Jones DB, Wee CC. Patient factors associated with undergoing laparoscopic adjustable gastric banding vs Roux-en-Y gastric bypass for weight loss. *JACS* 2013;217(6):1118-25.

Feldman LS, Brunt LM, Fuchshuber P, Jones DB, Jones SB, Mischna J, Munro MG, Rozner MA, Schwaartzberg SD, SAGES FUSE Committee. Rationale for the fundamental use of surgical energy (FUSE) curriculum assessment: Focus on safety. *Surg Endosc* 2013;27(11):4054-9.

Arriaga AF, Gawande AA, Raemer DB, Jones DB, Smink DS, Weinstock P, Dwyer K, Lipsitz SR, Peyre S, Pawlowski JB, Muret-Wagstaff S, Gee D, Gordon JA, Cooper JA, Berry WR. Pilot testing of a model for insurance-driven, large scale multicenter simulation training for operating room teams. *Ann Surg* 2013; 259(3):403-10.

Kudsi Y, Gagner M, Jones DB. Laparoscopic distal pancreatectomy. *Surg Oncol Clin N Am* 2013;22(1):59-73.

A complete list of publications begins on page 15.

Tara S. Kent, MD, MS

Assistant Professor of Surgery
Vice Chair, Education



RESEARCH GROUP

Manuel Castillo-Angeles, MD
Tovy Kamine, MD
Alessandra Storino, MD
Ammara A. Watkins, MD

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 more than 200 major pancreaticobiliary operations per year.

A prospective database of more than 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. Now we are 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, as well as with Ammara A. Watkins, MD, and Manuel Castillo-Angeles, MD, our current research fellows, 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 recently completed 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. The second phase of this project is now also underway.

ACCOMPLISHMENTS 2013-2014

- Member, International Hepato-Pancreato-Biliary Association (IHPBA) Education and Training Committee, as of 2014
- Co-chair, Americas Hepato-Pancreato-Biliary Association (AHPBA) Education and Training Committee, as of 2014
- Vice Chair for Education, BIDMC Department of Surgery, as of October 2014
- 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
- In October 2014, I became the BIDMC Department of Surgery's Vice Chair for Education
- Through my involvement with the AHPBA Education and Training Committee, I have developed an online curriculum for HPB fellows
- I am a BIDMC Rabkin Fellow for Medical Education for the academic year 2014-2015

SELECTED RESEARCH SUPPORT

Readability, suitability, and accuracy of patient-targeted online information on pancreatic cancer treatment; Alliance for Families Fighting Pancreatic Cancer (AFFPC), 2014-2015; PI: Tara S. Kent, MD, MS

Post-pancreatectomy discharge process improvement and patient satisfaction; Harvard Medical School Office for Faculty Affairs Eleanor and Miles Shore 50th Anniversary Fellowship for Scholars in Medicine, BIDMC Department of Surgery; PI: Tara S. Kent, MD, MS

SELECTED PUBLICATIONS

Goldberg RF, Reid-Lombardo KM, Hoyt D, Pellegrini C, Rattner DW, Kent T, Jones D; Public Policy & Advocacy Committee of the SSAT. Will there be a good general surgeon when you need one? *J Gastrointest Surg* 2014;18:1032-9.

Warner SG, Connor S, Christophi C, Azodo IA, Kent T, Pier D, Minter RM. Development of an international online learning platform for hepatopancreatobiliary surgical training: A needs assessment. *HPB* 2014;16:1127-1132.

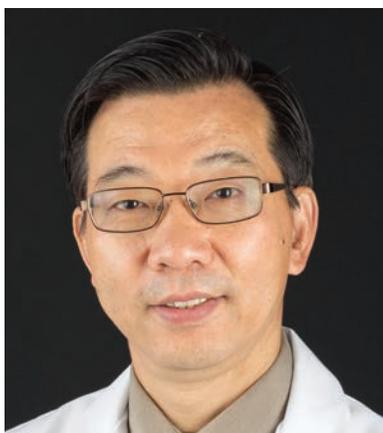
McKinley SK, Petrusa ER, Fiedeldej-van Dijk C, Mullen JT, Smink DS, Scott-Vernaglia SE, Kent TS, Stephen Black-Schaffer W, Phitayakorn R. Are there gender differences in the emotional intelligence of resident physicians? *J Surg Educ* 2014; in press.

McMillan MT, Christein JD, Callery MP, Behrman SW, Drebin JA, Kent TS, Miller BC, Lewis RS Jr, Vollmer CM Jr. Prophylactic octreotide for pancreatoduodenectomy: More harm than good? *HPB* 2014;16:954-962.

Kamine TH, Gondek S, Kent TS. Decrease in junior resident case volume after 2011 ACGME work hours. *J Surg Educ* 2014; in press.

Brook OR, Brook A, Vollmer CM, Kent TS, Sanchez N, Pedrosa I. Structured reporting of multiphasic CT for pancreatic cancer: Potential effect on staging and surgical planning. *Radiology* 2014; in press.

A complete list of publications begins on page 15.



Jin-Rong Zhou, PhD

Associate Professor of Surgery
Director, Nutrition/Metabolism Laboratory

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.

RESEARCH GROUP

Hamid Abdolmaleky, MD
Yi Gong, PhD

Ampelopsin (AMP) as a 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 greater 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.

Grant Review Activities

- Review panel, Key Programs, National Science Foundation of China, 2014
- Review panel, Super “Global Talent Recruitment” Program, National Science Foundation of China, 2014
- Reviewer, Innovative Research Team Program, National Science Foundation of China, 2014
- Review panel, Bedside and Bench Grant Review, National Medical Research Council of Singapore, 2014
- Ad hoc member, Cancer Etiology Omnibus SEP, NCI/NIH, 2014
- Ad hoc member, Cancer Marker Omnibus SEP, NCI/NIH, 2014
- Ad hoc member, Oncological Sciences AREA Grant Application Study Section, Center for Scientific Review/NIH, 2014
- Review panel, General Research Fund, Research Grant Council, Hong Kong, 2014

Editorial Services

- Ad hoc manuscript reviewer: 11 scientific journals
- Editor-in-Chief: *Nutrition and Metabolic Insights* (2012-present), *Journal of Health Sciences* (2013-present)

Invited Presentations

- Anti-cancer activities and mechanisms of action of bioactive tanshinones; Jiangsu Hospital of Traditional Chinese Medicine, Nanjing, China, 2013
- Research and commercialization of anti-recurrence and anti-metastasis functional products; North America Chinese Scholars International Exchange Center, Zhengzhou, China, 2014
- Advances in research and development of marine nutraceutical products; The 2nd International Forum of Chinese Overseas, Beijing, China, 2014

TEACHING, TRAINING, AND EDUCATION

I have been training post-doctoral fellows on a daily basis for the past year. In addition, I served as the graduate student thesis defense committee member in Suzhou Fangzhou R&D Center, Chinese Academy of Medical Sciences/Peking Union Medical College, China.

SELECTED RESEARCH SUPPORT

The herb (Jayeumganghwatang) and tamoxifen interaction on breast cancer; Korean CIMI Foundation, 2013-2015; PI: David Rosenthal, MD (Co-PI: Jin-Rong Zhou, PhD)

Effects of fermented soy germ bioactive components on prostate cancer stem cell self-renewal; Nichimo Co., Japan, 2014-2015; PI: Jin-Rong Zhou, PhD

Collaborative Innovation Center for Chinese Medicine for the Prevention and Treatment of Cancer; Chinese Government, 2014-2017; Collaborator (PI: Mianhua Wu, PhD)

CaNCURE: Cancer Nanomedicine Co-Ops for Undergraduate Research and Education; National Cancer Institute, 2014-2019; Collaborator (PI: Srinivas Sridhar, PhD)

Jeong JY, Zhou, JR, Gao C, Feldman L, Sytkowski AJ. Human selenium binding protein-1 (hSP56) is a negative regulator of HIF-1a and suppresses the malignant characteristics of prostate cancer cells. *BMB Rep* 2014;47(7):411-6.

Acharjee S, Zhou JR, Elajami TK, Welty FK. Effect of soy nuts and equol status on blood pressure, lipids and inflammation in postmenopausal women stratified by metabolic syndrome status. *Metabolism: Clinical and Experimental* 2014; in press.

Zhou J-R, Amami T. An overview on dietary soy consumption and prevention of breast and prostate cancer. (In Japanese) In: Yamori Y, editor. *The Soy Nutrition and Function – The Natural Supplement for “Health for All.”* Tokyo: CMC Publishing Co., Ltd, 2014; p. 198-207.

A complete list of publications begins on page 15.

Jeffrey Arle, MD, PhD

Associate Professor of Surgery
Associate Chief, Neurosurgery



RESEARCH GROUP

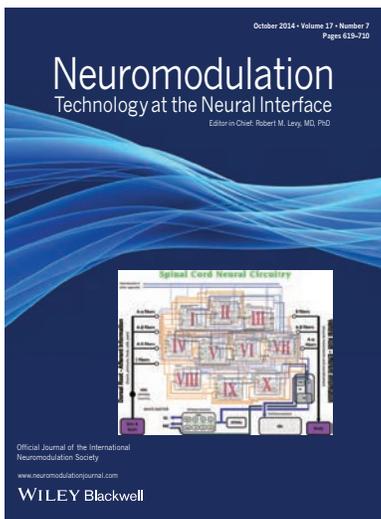
Kristen Carlson
LZ Mei, MS
Jay Shils, PhD

RESEARCH FOCUS

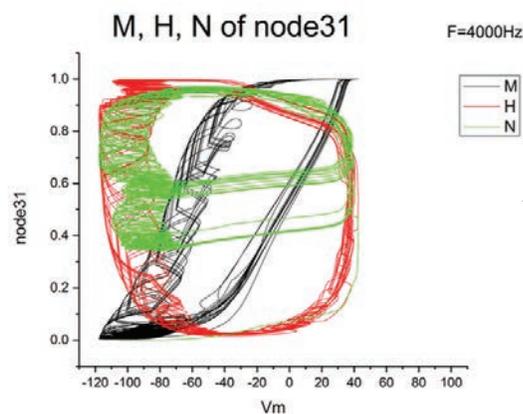
Our research efforts have focused on computational modeling of neural stimulation and circuitry related to devices and therapies used in neuromodulation. These therapies include deep brain stimulation (DBS), spinal cord stimulation (SCS), vagus nerve stimulation (VNS), motor cortex stimulation (MCS), 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.

More recently, with collaborative funding from both Boston Scientific and Cyberonics, we have created finite element models of the vagus nerve and examined how stimulation of the vagus nerve (used to control seizures and depression) interacts with the initial circuitry in the brainstem, as well as how high-frequency stimulation of the spinal cord axons in the dorsal column may be a new method for treating chronic pain disorders. Our work has been presented this past year at both the American Society for Stereotactic and Functional Neurosurgery (ASSFN) meeting in Washington, DC, as well as the European Society for Stereotactic and Functional Neurosurgery (ESSFN) meeting in Maastricht, Netherlands.

In these recent efforts, 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 was published in 2014 in *Neuromodulation*. We continue to examine the fundamental mechanisms of neuromodulation therapies, an area of rapidly developing technology and innovation. This work has also been, and continues to be, generously funded by the Sydney Family Foundation.



▲ The Arle research group was selected to provide cover images for the June and October 2014 (shown here) issues of *Neuromodulation*.



▲ Active model with detailed subanalysis of the ionic gate component dynamics. This graphic shows the phase plots of m, n, and h gates at 4kHz stimulation in a 14μm fiber diameter at a node distal to the activating function cathode peak and past the virtual anode, wherein an action potential is generated.

Organizational and Academic Work

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

Invited Presentations and Meetings

- Computational approaches toward device design and placement; ESSFN, Maastricht, Netherlands, 2014
- High frequency stimulation in the dorsal column: Relationship to gate subcomponent dynamics; ASSFN, Washington, DC, 2014
- World Society for Stereotactic and Functional Neurosurgery (WSSFN), moderated session, Tokyo, 2013
- American Society for Neurophysiological Monitoring (ASNM), moderated two sessions, Boston, 2013
- Spinal cord stimulation therapy and the circuitry of the spinal cord; ASNM, Boston, 2013
- The decision interface: Surgeon, neurophysiologist, and making the best decisions during surgery; American Clinical Neurophysiological Society (ACNS), Miami, FL, 2013
- Cortical and deep brain stimulation for pain; American Association of Neurological Surgeons (AANS), New Orleans, LA, 2013
- Neurostimulation for facial pain; invited talk, AANS-Pain Biennial Joint Section meeting, 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)

Arle JE, Carlson KW, Mei L, Shils JL. Modeling effects of scar on patterns of dorsal column stimulation. *Neuromodulation* 2014;17(4):320-33. Discussion, *Neuromodulation* 2014;17(4):333. (Cover)

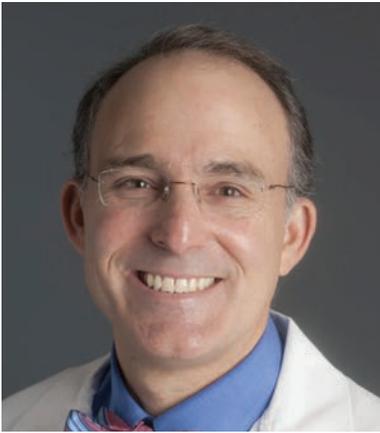
Arle JE, Carlson KW, Mei L, Iftimia N, Shils JL. Mechanism of therapeutic benefit with dorsal column stimulation using a computational model of the spinal cord. *Neuromodulation* 2014;17(7):642-55. (Cover)

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.

Jorge G. Arroyo, MD, MPH

Associate Professor of Ophthalmology



RESEARCH GROUP

Mark Kuperwaser, MD

Kyle V. Marra

Carole Uminski

Gina Yu

RESEARCH FOCUS

Our lab continues to research the efficacy and outcomes of novel ophthalmologic surgical techniques, intraocular cytokine levels of eyes as predictive measures for various ocular conditions, and novel risk factors for age-related macular degeneration (AMD).

Surgical techniques

Our research measuring visual outcomes following combined vitreoretinal surgery (specifically epiretinal membrane, ERM, peeling) and cataract surgery versus ERM peeling alone has been published and has implications for therapeutic decisions regarding these common eye surgeries. 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.

We also compared the efficacy of a novel procedure known as endocyclophoto-coagulation (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 of care” for NVG. This work has also recently been accepted and is awaiting publication in *Retina*.

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 in 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. We are also running analyses on bilirubin as a risk factor for AMD and have established a significant association.

Presentations

Our research team attended the annual meeting for the Association for Research in Vision and Ophthalmology (ARVO), where we presented statistically significant differences in the presence of various pro-inflammatory proteins, chemokines, cytokines, and growth factors compared to control patients, diabetic patients, proliferative diabetic retinopathic patients, and neovascular glaucoma patients, following eye surgery. I also presented at the Retina and Macula societies, and in June 2014 was invited to speak on a panel at the 5th Annual Mass Eye and Ear Vitrectomy Course.

Ongoing Projects

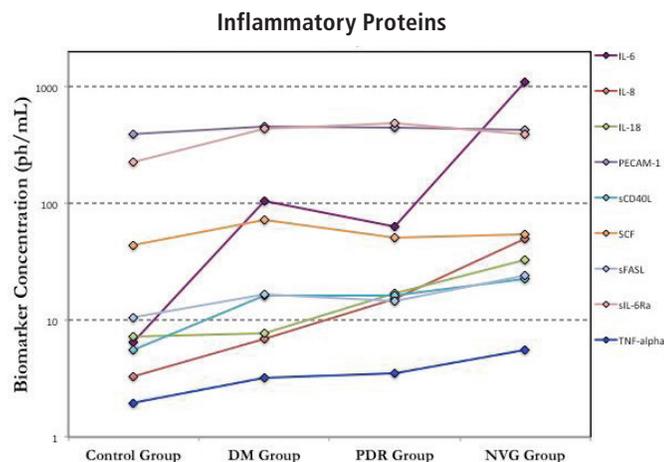
We are collaborating with MRI researchers on a study that, if successful, will be the first work to quantify blood flow changes in the choroid (the retina's underlying tissue for blood and nutrient delivery) at various stages of AMD. We expect to compare a total of 21 eyes among three groups: controls, 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 analyze the efficacy of possible treatment options for patients diagnosed with vitreomacular traction (VMT). Currently, there is significant debate on which of three main options – surgery, injection of FDA-approved Jetrea (ocriplasmin), or injection of an SF6 or C3F8 gas bubble – provides the highest efficacy and safety for treating VMT. We became particularly interested in safety after discovering photoreceptor damage post-ocriplasmin injection in one of our patients (published in *Retinal Cases & Brief Reports*, May 2014). By combining a comprehensive meta-analysis of VMT treatment with what is observed with our patients at the BIDMC clinic, our study will help illustrate how best to treat patients diagnosed with VMT.

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. Gina Yu, who graduated from Harvard University in 2013, is currently fulfilling this role.



Pro-inflammatory Factors following Pars Plana Vitrectomy. Source: KV Marra, K Kovacs, S Wagley, et al. Angiogenic and Inflammatory Biomarkers Associated with Neovascular Glaucoma. ARVO 2014 (poster).

Yonekawa Y, Hacker HD, Lehman RE, Beal CJ, Veldman PB, Vyas NM, Shah AS, Wu D, Elliott D, Gardiner MF, Kuperwaser MC, Rosa RH Jr, Ramsey JE, Miller JW, Mazzoli RA, Lawrence MG, Arroyo JG. Ocular blast injuries in mass-casualty incidents: The Marathon bombing in Boston, Massachusetts and the fertilizer plant explosion in West, Texas. *Ophthalmology* 2014 Sep;121(9):1670-6.e1.

Yiu G, Marra KV, Wagley S, Krishnan S, Sandhu H, Kovacs K, Kuperwaser M, Arroyo JG. Surgical outcomes after epiretinal membrane peeling combined with cataract surgery. *Br J Ophthal* 2013 Sep;97(9):1197-201.

Thanos A, Hernandez-Siman J, Marra KV, Arroyo JG. Reversible vision loss and outer retinal abnormalities after intravitreal ocriplasmin injection. *Retin Cases Brief Rep* 2014;8(4):330-2.

A complete list of publications begins on page 15.



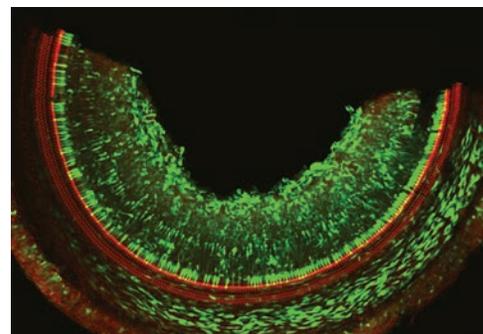
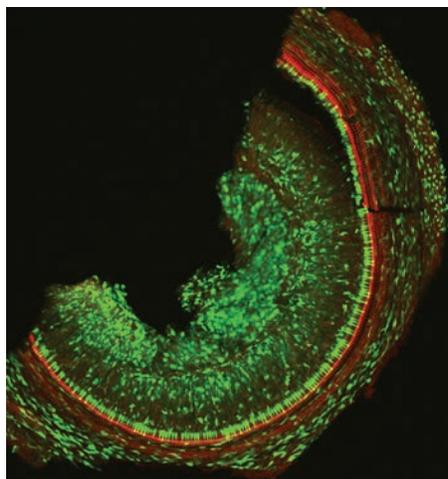
Selena E. Heman-Ackah, MD, MBA

Instructor in Otolaryngology

RESEARCH FOCUS

My major research interests are centered on the treatment and prevention of hearing loss. This winter, I will be 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. In addition to this research, I have been working within the Holt/Géléoc Laboratory investigating possible gene therapy for the treatment of genetic forms of congenital sensorineural hearing loss. Currently in a mouse model of Usher's syndrome type 1C, we are investigating the potential for prevention of hair cell loss and associated sensorineural hearing loss with intracochlear delivery of viral vectors.

In addition to basic science research, I have significant interests in clinical studies. During the past year and extending into the following year in collaboration with otologists around the city, I have been participating in a clinical project evaluating the impact of noise exposure in the civilian population on long-term otologic health. Additionally, 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).



▲ FIGURES: Flat mount histology from cochlea of USH1C mice following transfection with a viral vector (transfected cells fluorescing in green). Effective transfection of hair cells within the cochlea was noted.

ACCOMPLISHMENTS 2013-2014

This year, I was fortunate to be awarded the two-year Harvard Medical School Office of Diversity Inclusion and Community Development Faculty Fellowship in the amount of \$100,000. I am very grateful for the support of Harvard Medical School, Beth Israel Deaconess Medical Center, and the Department of Surgery for having the opportunity to further pursue my basic science interest in preventive therapies for hearing loss.

This year, I was also honored to be selected for the Beth Israel Deaconess Medical Center Physician Leadership Development Program. This has been a phenomenal experience – learning from leaders within the community and in the field, as well as networking with dedicated leaders within the BIDMC environment.

TEACHING, TRAINING, AND EDUCATION

Teaching and mentoring are among my passions. I have the opportunity to work with residents within the operating theater to provide training and instruction in otologic operative technique. Last winter I had the opportunity to go to Uganda, East Africa for an educational mission trip. While at Mulago Hospital in Kampala, Uganda, I presented didactic lectures, taught in the hospital's temporal bone lab, and instructed resident surgeons in otologic procedures within the operating theater. Here at BIDMC, I have been given the honor of being the Clerkship Director for the otolaryngology rotation of Harvard Medical School and visiting students during their surgery rotation.

ABSTRACT, POSTERS, AND EXHIBITS

Remenschneider AK, Lookabaugh SA, Brodsky JR, Aliphas A, Heman-Ackah SE, Lee D, Quesnel AM. Otologic outcomes following blast injury – The Boston Marathon Experience. American Otological Society, Las Vegas, NV, 2014

Bose R, Heman-Ackah SE. Design orientation to engage new faculty and accelerate high performance. 2014 Silverman Institute for Health Care Quality and Safety Symposium, Boston, MA, 2014

Askew C, Heman-Ackah SE, Asail Y, Pan B, Lentz JJ, Géléoc GSG. Gene augmentation therapy to treat Usher syndrome Type 1C. International Symposium on Usher Syndrome, Boston, MA, 2014

Heman-Ackah SE. The impact of cochlear implantation on recipient quality of life. Coalition for Global Hearing Health – 2014, Oxford, United Kingdom, 2014

SELECTED PUBLICATIONS

Heman-Ackah SE, Lalwani AK. Introduction to otolaryngic genetics. In: Johnson JT, Rosen C, editors. *Bailey's Otolaryngology – Head and Neck Surgery*, 5th Edition. New York: Lippincott Williams & Wilkins; 2013.

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.

Kohan D, Heman-Ackah SE, Chandrashakar S. *What do I do now: Neurotologic Disorders*. New York: Oxford University Press, Inc.; 2014.

Rogers SD, Heman-Ackah SE, Roland T Jr, Golfinos G. Microsurgery for acoustic neuromas. In: Sheehan J, Gerszten P, editors. *Controversies in Stereotactic Radiosurgery*. New York: Theime Medical; 2014.

Froemke R, Heman-Ackah SE, Waltzman SB. Auditory neuroplasticity. In: Waltzman SB, Roland JT Jr, editors. *Cochlear Implants*, 3rd edition. New York: Theime; 2014.

Heman-Ackah SE. The impact of cochlear implantation on recipient health-related quality of life. In: Waltzman SB, Roland JT Jr, editors. *Cochlear Implants*, 3rd edition. New York: Theime; 2014.



RESEARCH GROUP

Danielle Chuang
Oren Ganor, MD
Olivia Ho, MD
Christina Vargas, MD

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, our clinical research group is 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. Most recently, we have been examining patient access, health literacy, and readability of online resources for plastic surgery.

Near infrared imaging systems

Our most recent studies have focused on using the FLARE system to examine thrombosis in microsurgery. Using a fluorophore such as indocyanine green, we can identify areas of occlusion and clotting within the vasculature. This enables us to resect and repair vessels and identify reestablished perfusion with the FLARE system. This allows assessment of real-time perfusion characteristics and image guidance during surgery.

In a separate face transplantation model, we are using SFDI to identify perfusion characteristics by targeting tissue constituents (such as hemoglobin). Through the use of this imaging system, we can examine oxygenation of our face transplantation models over a large field of view. In conjunction with surface profilometry, we can provide gradient maps of three-dimensionally complex reconstructive flaps with a single capture snapshot for guidance in the operating room and during surgery. We have successfully translated this technology for use in a clinical trial in patients undergoing microsurgical breast reconstruction.

Patient access and health literacy in plastic and reconstructive surgery

Our clinical outcomes research team has recently begun to examine the area of health literacy and patient access. The AMA and NIH guidelines are for patient-directed health literature to be written at a 6th grade level. Unfortunately, most patient resources are well above this level. Our group has examined online patient resources and their readability for patients. In addition, we have surveyed plastic surgeons to determine how they assess patient literacy and what methods are used to communicate health information. Finally, our group is also designing new patient materials at appropriate reading levels to evaluate their use in patient education.

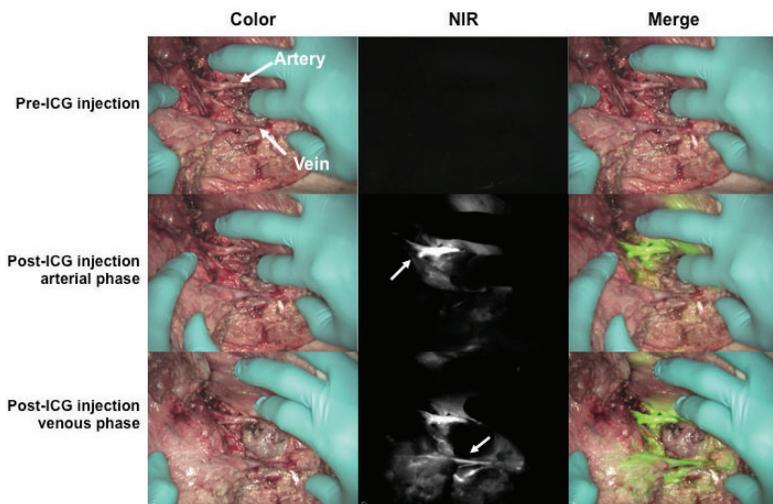


FIGURE 1: Imaging of the vascular pedicle of a hemifacial transplant flap model prior to injection (top row), during the arterial phase (middle row), and during the venous phase (bottom row). The imaging system provides surgical anatomy (left column), NIR fluorescence imaging (middle column), and a merged image of the two (right column).

ACCOMPLISHMENTS 2013-2014

I am currently the Chief of the Division of Plastic and Reconstructive Surgery at BIDMC. I am also Co-Director of the Peter Jay Sharp Program in Aesthetic and Reconstructive Breast Surgery. 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 (Program Committees). I am also the chair of the evidence-based guidelines work group on autologous breast reconstruction for the American Society of Plastic Surgeons.

I am currently the Editor-in-Chief of the *Journal of Reconstructive Microsurgery* and 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*; a new edition will be forthcoming later this year.

Invited Presentations

- Readability of online patient resources for the surgical treatment of breast cancer; Academic Surgical Congress
- Online patient resources for breast reconstruction – analysis of readability; Academic Surgical Congress
- Effects of statins on ischemia-reperfusion complications in autologous free flap breast reconstruction; Academic Surgical Congress
- Analyzing patient preference for nipple-areola complex reconstruction using utility outcome studies; American Association of Plastic Surgeons
- Utilization of spatial frequency domain imaging to monitor composite facial transplantation with microsurgical vascular anastomosis; World Society of Reconstructive Microsurgery
- Readability of online patient resources for breast reduction; Plastic Surgery Research Council
- Near-infrared imaging for evaluation of thrombosis in microsurgery; Northeastern Society 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 decade. 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)

SELECTED PUBLICATIONS

Vargas CR, Koolen PGL, Chuang DJ, Ganor O, Lee BT. Online patient resources for breast reconstruction: An analysis of readability. *Plast Reconstr Surg* 2014;134(3):406-13.

Vargas CR, Chuang DJ, Ganor O, Lee BT. Readability of online patient resources for the operative treatment of breast cancer. *Surgery* 2014;156(2):311-8.

Koolen PGL, Nguyen JT, Ibrahim AMS, Ganor O, Chuang DJ, Lin SJ, Lee BT. Effects of statins on ischemia/reperfusion complications in free flaps. *J Surg Res* 2014;156(2):311-8.

de Blacam C, Colakoglu S, Ogunleye AA, Nguyen JT, Ibrahim AMS, Lin SJ, Kim PS, Lee BT. Risk factors associated with complications in lower extremity reconstruction with the distally-based sural flap: A systematic review and pooled analysis. *J Plast Reconstr Aesthet Surg* 2014;67(5):607-16.

Ashraf AA, Colakoglu S, Nguyen JT, Anastasopoulos AJ, Ibrahim AMS, Yueh JH, Lin SJ, Tobias AM, Lee BT. Patient involvement in the decision making process improves satisfaction and quality of life in postmastectomy breast reconstruction. *J Surg Res* 2013;184(1):665-70.

Nguyen JT, Ashitate Y, Venugopal V, Neacsu F, Kettenring F, Frangioni JV, Gioux S, Lee BT. Near-infrared imaging of face transplants: Are both pedicles necessary? *J Surg Res* 2013;184(1):714-21.

A complete list of publications begins on page 15.



RESEARCH GROUP

Ahmed Ibrahim, MD
Kuylhee Kim, MD
Pieter Koolen, MD
Colette Martin
Marek Paul, MD
Jinesh Shah
Jie Sun

RESEARCH FOCUS

Over the last several years, my basic science and clinical research has focused on several primary areas. These are both collaborative projects utilizing the expertise and experiences of scientists, engineers, and clinicians. Our main collaborators include: Massachusetts Institute of Technology, Tufts University, Massachusetts General Hospital/Wellman Center, and Boston Children's Hospital, which gives us possibilities to explore new research areas in plastic and reconstructive surgery.

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) since 2008. 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.

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, see Figure 1). Our pilot data was published in *Nature Communications* in March 2014. These devices may be able to provide immediate surgical stabilization for orthopedic repair, promote active repair, and reduce infections by releasing therapeutics, and also be fully degrading, avoiding the need for future surgeries for removal.

3D printing in plastic surgery

We have been also focused on another applications of 3D printing, e.g. 3D printed surgical tools for use in plastic surgery either through customized implants or surgical planning.

In addition to our basic science projects, we 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.



▲ FIGURE 1: Screws made from biologic silk protein.

- 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 activities include writing plastic and reconstructive surgery books, atlases, and book chapters:

Books, Atlases:

Lin SJ, Mustoe TA, editors. *An Aesthetic Atlas of the Head and Neck*. New York: McGraw-Hill Publishing; 2013.

Lin SJ, Hijjawi J, editors. *Plastic and Reconstructive Surgery Board Review: Pearls of Wisdom*, 3rd Edition. New York: McGraw-Hill Publishing; in progress.

Book chapters:

Lin SJ. Nasal Deformities. In Yaremchuk M, Mrad A, Ed. *Harvard Atlas of Plastic Surgical Diagnoses*; in press.

- My editorial activities include serving as Academic Editor of Public Library of Science (*PLoS One*), Associate Editor of *Plastic and Reconstructive Surgery*, 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

- 2012-2014; Academic Scholar Award, American Association of Plastic Surgeons (AAPS)
- 2013; The National Endowment for Plastic Surgery, The Plastic Surgery Foundation Grant
- 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)
- 2014; BIDMC CAO Pilot Grant

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 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), 2011-2015; PI: Samuel J. Lin, MD

Developing a facial nerve paralysis neuroprosthetic device using ion selective membranes; AAPS/PSF Research Scholarship Grant, 2012-2015; PI: Samuel J. Lin, MD

Use of silk-based orthopedic devices to modulate healing; PSF National Endowment Research Grant, 2014-2015; PI: Samuel J. Lin, MD

Insulin receptor resistance in normal fat cells; BIDMC CAO Pilot Research Grant, 2014-2015; Co-PI: Samuel J. Lin, MD

Perrone GS, Leisk GG, Lo TJ, Moreau JE, Haas DS, Papenburg BJ, Golden EB, Partlow BP, Fox SE, Ibrahim AM, Lin SJ, Kaplan DL. The use of silk-based devices for fracture fixation. *Nat Commun* 2014;5:3385.

Ibrahim AM, Shuster M, Koolen PG, Kim K, Taghnia AH, Sinno HH, Lee BT, Lin SJ. Analysis of the National Surgical Quality Improvement Program database in 19,100 patients undergoing implant-based breast reconstruction: Complication rates with acellular dermal matrix. *Plast Reconstr Surg* 2013;132(5):1057-66.

Kim K, Ibrahim AM, Koolen PG, Lee BT, Lin SJ. Trends in facial fractures treatment using the ACS-NSQIP database. *Plast Reconstr Surg* 2014;133(3):627-38.

Kim PS, Malin E, Kirkham JC, Helliwell LA, Ibrahim AM, Tobias AM, Upton J, Lee BT, Lin SJ. The Boston marathon bombings: The early plastic surgery experience of one Boston hospital. *Plast Reconstr Surg* 2013;132(5):1351-63.

Sinno H, Izadpanah A, Tahiri Y, Christodoulou G, Thibaudeau S, Williams HB, Slavin SA, Lin SJ. The impact of living with severe lower extremity lymphedema: A utility outcomes score assessment. *Ann Plast Surg* 2014;73(2):210-4.

Ibrahim A MS, Koolen P GL, Ashraf AA, Mureau M AM, Lee BT, Lin SJ. Use of acellular dermal matrix in reconstructive breast surgery: A survey of current practice patterns. *Plast Reconstr Surgery-Global Open*, May 2014.

A complete list of publications begins on page 15.



RESEARCH FOCUS

With broad training in general surgery, orthopedic surgery, plastic surgery, and a fellowship in hand surgery, I was initially recruited to Boston 38 years ago to start microsurgery. My initial research was focused on congenital malformations of the upper limb plus tissue engineering. Research efforts during the last 15 years at the Beth Israel Deaconess Medical Center have been primarily clinically based, again dealing with complicated secondary hand reconstruction, all aspects of free tissue transfer and microsurgery, as well as the initial diagnosis and care of common hand problems.

I have also worked at the Shriners Burn Institute for several decades. There the primary focus of research has been clinical, dealing with reconstruction of severe contractures of both upper and lower extremities plus the treatment of congenital hand problems. I am a referral source for Shriners hospitals all over the country.

At Boston Children's Hospital, where I have been a staff member of the Department of Plastic Surgery for 38 years, I concentrate on the treatment of congenital hand anomalies. I am also an integral member of the Vascular Anomalies Center, a large, comprehensive program that treats patients from all over the world with vascular anomalies. I have been the primary provider for the upper limb.

Recently research efforts of Boston Children's Hospital have brought together many of the long-term follow-ups of the initial microsurgical procedures for head and neck reconstruction, facial reanimation, as well as congenital hand reconstructions, including toe to hand transfers. I mentor younger surgeons and continue to run the hand microvascular program at BIDMC.

Present clinical research projects are broad based and are dealing with skeletal distraction lengthening of the hand and forearm, difficult hand reconstructions, treatment of the Apert hand, and the molecular diagnosis and treatment of various overgrowth conditions (macroductyly).

For the past 40 years, I have served on the editorial boards of eight journals and contributed more than 300 articles and chapters in the field of plastic surgery and microsurgery. My unique molds of congenital hand malformations are still part of a permanent exhibit at the Boston Museum of Science. I was a founding member of and still remain on the Board of Directors of the Helping Hands Foundation.



▲ 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 2013-2014

- Director, Hand/Microsurgery Fellowship Program since its initiation in early 1980
- 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 the 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
- The Buncke Lecture, American Association for Reconstructive Microsurgery

TEACHING, TRAINING, AND EDUCATION

As a full-time member of the Division of Plastic and Reconstructive Surgery at BIDMC and the Department of Surgery at Boston Children's Hospital, I continue to teach medical students, general surgery residents, plastic surgery residents, and clinical fellows in the clinics and operating room. The fellowship is now in its 36th year, and I still remain as the Program Director.

SELECTED PUBLICATIONS

Upton J. Vascular malformations of the extremities. In: Mulliken JB, Burrows PE, Fishman SJ, editors. *Vascular Anomalies, Hemangiomas, and Malformations*, 2nd edition. Oxford University Press; 2013. p. 905-965.

Ibrahim AM, Rabie AN, Kim PS, Medina M, Upton J, Lee BT, Lin SJ. Static treatment modalities in facial paralysis: A 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;123(8):2035-42.

Kim PS, Malin E, Kirkham JC, Helliwell LA, Ibrahim AM, Tobias AM, Upton J, Lee BT, Lin SJ. The Boston marathon bombings: The early plastic surgery experience of one Boston hospital. *Plast Reconstr Surg* 2013;132(5):1351-63.

A complete list of publications begins on page 15.

Aristidis Veves, MD, DSc

Professor of Surgery



RESEARCH GROUP

Dimitrios Baltzis
Camille Borland
Thanh Dinh, DPM
Rhianna Hibbler
Yana Ostrovsky
Ana Tellechea, PharmD

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 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

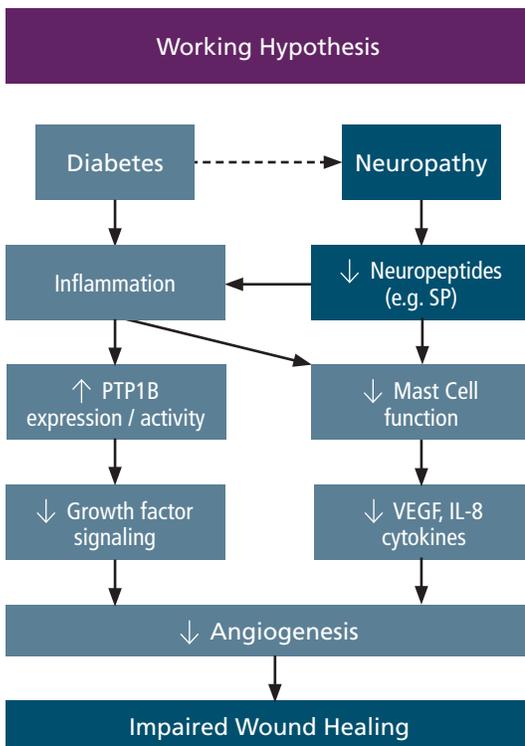
I conduct investigator-initiated research studies that examine the effects of various FDA-approved medications on cardiovascular function. These studies, although funded by the industry, have been conceived, designed, and executed by my unit and focus on possible new mechanisms through which these medications exert their beneficial effects. 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 Engineering School 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 supported by NIH funding allocated for small business. We have already completed numerous phase I studies and 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 with 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 2013-2014

In a prospective cohort study we showed that 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 the figure on the previous page.

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, and 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 of 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

SELECTED PUBLICATIONS

Dushay JR, Tecilizich 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. *J Renin Angiotensin Aldosterone Syst* 2013; in press.

Kaczmarek E, Bakker JP, Clarke DN, Csizmadia E, Kocher O, Veves A, Tecilizich F, O'Donnell CP, Ferran C, Malhotra A. Molecular biomarkers of vascular dysfunction in obstructive sleep apnea. *PLoS One* 2013;29;8(7):e70559.

Bakker JP, Balachandran JS, Tecilizich F, Deyoung PN, Smales E, Veves A, Malhotra A. A pilot study of the effects of bariatric surgery and CPAP treatment on vascular function in obese subjects with obstructive sleep apnea. *Intern Med J* 2013;43(9):993-8.

Carter SG, Zhu Z, Varadi G, Veves A, Riviere JE. Vasomodulation influences on the transdermal delivery of Ibuprofen. *J Pharm Sci* 2013;102(11):4072-8.

Tecilizich F, Dinh T, Pradhan-Nabzdyk L, Leal E, Tellechea A, Kafanas A, Gnardellis C, Magargee ML, Dejam A, Toxavidis V, Tigges JC, Carvalho E, Lyons TE, Veves A. Role of endothelial progenitor cells and inflammatory cytokines in healing of diabetic foot ulcers. *PLoS One* 8(12):e83314.

Shah RV, Abbasi SA, Heydari B, Farhad H, Dodson JA, Bakker JP, John RM, Veves A, Malhotra A, Blankstein R, Jerosch-Herold M, Kwong RY, Neilan TG. Obesity and sleep apnea are independently associated with adverse left ventricular remodeling and clinical outcome in patients with atrial fibrillation and preserved ventricular function. *Am Heart J* 2014;167(4):620-6.

A complete list of publications begins on page 15.



Per-Olof Hasselgren, MD, PhD

George H.A. Clowes Professor of Surgery

Vice Chair, Research

Director of Endocrine Surgery

RESEARCH FOCUS

During 2013-2014, my research has been focused on clinical studies related to endocrine surgery. Some of the studies have been concluded and have resulted in recent publications while other studies are ongoing. Several of the projects are based on a prospective database that was established in the Section of Endocrine Surgery approximately 10 years ago, which presently contains information for almost 4,000 patients undergoing surgery in the Section of Endocrine Surgery at Beth Israel Deaconess Medical Center.

Studies on the localization and characterization of brown fat in the human neck

Brown adipose tissue (BAT) was previously thought to have a functional role in rodents and human infants only. White adipose tissue stores excess calories whereas BAT consumes calories for thermogenesis using tissue-specific uncoupling protein 1 (UCP1). This is important because an imbalance between energy intake and expenditure plays an important role in obesity and diabetes. In the present project, examination of anatomically defined neck fat deposits in patients undergoing thyroidectomy or other types of neck surgery revealed that adult humans have significant amounts of BAT in the neck region. These results were published recently in *Nature Medicine* (2013;19: 635-639) and are important because they are the foundation of new ongoing studies in which the regulation of BAT by thyroid hormone is examined. Those studies are performed in patients undergoing thyroidectomy for cancer and who go through periods of hypothyroidism (when thyroid hormone medication is discontinued in preparation for radioiodine treatment) and periods with high thyroid hormone levels (during treatment with high doses of thyroid medication to prevent recurrence of thyroid cancer). The outcomes of these studies are important because they will have implications for the treatment of obesity and diabetes.

Studies on the hormonal regulation of muscle metabolism in cultured human muscle cells

During the last year, we have collaborated with Christos Mantzoros, MD, in Endocrinology, obtaining biopsies from the sternohyoid muscle in patients undergoing thyroidectomy. Muscle cells from these biopsies are isolated and then cultured for *ex vivo* studies, determining signaling pathways activated by leptin. These studies are important because they provide novel information about leptin signaling in human tissues and the results have implications for the treatment of insulin-resistance syndromes such as type 2 diabetes mellitus, inflammation, and obesity. Some of the results in this project are presently being published (*Diabetes* 2014; in press).

Studies on the follicular variant of papillary thyroid cancer (FVPTC)

The follicular variant of papillary thyroid cancer (FVPTC) is the most common subtype of PTC. In FVPTC, the pathology is characterized by a predominantly follicular histological architecture and cellular changes commonly seen in conventional PTC, such as nuclear inclusions, nuclear grooves, powdery chromatin, elongated overlapping nuclei, and nuclear irregularity. In contrast, the otherwise typical papillary structures are missing. The diagnosis of FVPTC therefore rests mainly on the cytological features (Figure 1).

Recent reports suggest that the incidence of FVPTC is on the rise and that one of the reasons for this may be diagnostic difficulties and a lowered threshold for the diagnosis of FVPTC. It has been suggested that some tumors that may have been reported as benign in the past are now instead being reported as FVPTC. If indeed that is the case, we may be seeing an overdiagnosis of FVPTC, potentially resulting in overtreatment of these patients (unnecessary additional surgery and radioiodine treatment).

In the current project, we are analyzing cases of FVPTC undergoing surgery in the Section of Endocrine Surgery during the last 10-year period. The study is conducted in collaboration with pathologists and cytologists at our institution. After reviewing our experience with approximately 1,000 patients undergoing thyroidectomy, preliminary results suggest that there has been a steady increase of cases signed out as FVPTC and a concomitant, almost parallel, decrease of certain benign conditions that may mimic FVPTC during the same period of time. These preliminary observations are important because they suggest that lesions that were previously reported as benign may now be signed out as cancer. This may have significant clinical implications with regard to the extent of surgery and additional treatment needed for these patients.

Studies on the levels of thyroid stimulating hormone (TSH) in patients with thyroid cancer

Thyroid cancer is the most common type of endocrine malignancy. Indeed, thyroid cancer is one of the fastest growing cancers in our population. Understanding mechanisms and risk factors in thyroid cancer, therefore, is of great clinical importance. Recent reports suggest that high TSH levels, even within normal range, may be associated with increased risk for thyroid cancer, but the potential role of elevated TSH levels for the development of thyroid malignancy is controversial. We are presently reviewing TSH levels in patients undergoing thyroidectomy in the Section of Endocrine Surgery for benign or malignant lesions by utilizing data in our prospective database. Our preliminary observations suggest that there is no correlation between preoperative TSH level and thyroid cancer, arguing against the notion that elevated TSH levels may be a risk factor for thyroid cancer.

Studies on the incidence of hypothyroidism after hemithyroidectomy

Hemithyroidectomy is commonly performed in patients with a solitary thyroid nodule having no or only low-grade evidence of malignancy. An important question is how many patients develop hypothyroidism after removal of one half of the thyroid gland. Although some reports in the literature suggest that approximately 20% of patients become hypothyroid after hemithyroidectomy, higher figures have also been reported. We are presently reviewing our experience in patients undergoing hemithyroidectomy in the Section of Endocrine Surgery by utilizing data in our prospective database. Our initial observations suggest that the development of hypothyroidism is substantially more common than previously reported. In addition, we have identified certain risk factors for hypothyroidism after hemithyroidectomy, including chronic thyroiditis and the amount of tissue removed at the time of hemithyroidectomy. The observations are important because they underscore the importance of following these patients closely with regard to thyroid hormone levels after hemithyroidectomy.

Studies on the intraoperative imaging and identification of parathyroid glands by the use of novel parathyroid targeting molecules

In a recent study (Hyun H, Park MH, Owens EA, Wada H, Henary M, Handgraaf HJM, Vahrmeijer AL, Frangioni JV, Choi HS. Structure-inherent targeting of NIR fluorophores for parathyroid and thyroid gland imaging. *Nature Medicine* 2014; in press), the development of parathyroid-specific targeting molecules allowing for the *in vivo* identification of parathyroid glands using a dual-channel near-infrared imaging system was reported. Those experiments were performed in a pig model. The molecules have not yet been tested in human patients. Hak Soo Choi, PhD, at the Center for Molecular Imaging at the Beth Israel Deaconess Medical Center, is the lead scientist behind the development of these targeting molecules. We have recently established collaboration with Dr. Choi in a project performed to test the molecules in patients undergoing thyroidectomy or parathyroidectomy in the Section of Endocrine Surgery. Those studies will be important because, if successful, they may facilitate the identification of normal parathyroid glands in patients undergoing thyroidectomy and help reduce the incidence of hypoparathyroidism and hypocalcemia after thyroidectomy. In addition, improved ability to identify enlarged parathyroid gland(s) in patients undergoing parathyroidectomy for hyperparathyroidism may have significant clinical benefits since this may help identify diseased parathyroid glands even when located in unusual places in the neck.

Cypess A, White AP, Vernochet C, Schulz TJ, Xue R, Sass CA, Roberts-Toler C, Weiner LS, Sze C, Chako AT, Deschamps LN, Herder L, Truchan N, Glasgow A, Holman AR, Gavrilu A, Hasselgren PO, Mori MA, Molla M, Tseng YH. Anatomical localization and bioenergetic potential of human brown adipose tissue. *Nat Med* 2013;19:635-639.

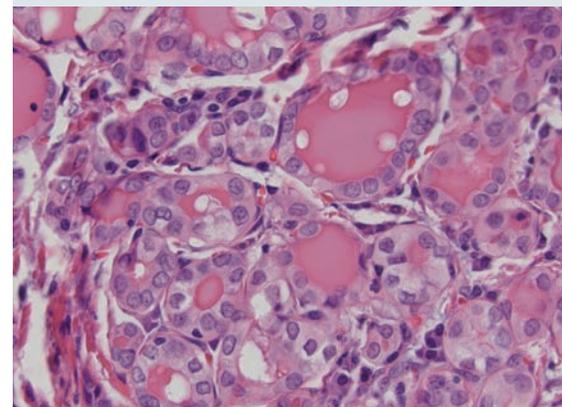
Aversa Z, Alamdari N, Castellero E, Muscaritoli M, Rossi Fanelli F, Hasselgren PO. CaMKII activity is reduced in skeletal muscle during sepsis. *J Cell Biochem* 2013;114:1294-1305.

Castillero E, Alamdari N, Lecker SH, Hasselgren PO. Suppression of atrogen-1 and MuRF1 prevents dexamethasone-induced atrophy of cultured myotubes. *Metabolism* 2013;62(10):1495-502.

Hasselgren PO. β -hydroxy- β -methylbutyrate (HMB) and prevention of muscle wasting. Editorial. *Metabolism* 2014;63(1):5-8.

Moon HS, Huh JY, Dincer F, Schneider BE, Hasselgren PO, Mantzoros CS. Identification, and saturable nature, of signaling pathways induced by metreleptin in humans: Comparative evaluation of *in vivo*, *ex vivo* and *in vitro* administration. *Diabetes* 2014; in press.

Mele A, Hasselgren PO. Adrenalectomy. In: Jones DB, Andrews R, Critchlow J, Schneider B, editors. *Minimally Invasive Surgery: Laparoscopy, Therapeutic Endoscopy and NOTES*. London: JP Medical Publishers 2014; in press.



▲ FIGURE 1: FVPTC. Note the presence of follicular histological architecture and the absence of papillary structures. The cytological changes include nuclear irregularities, nuclear overlapping and nuclear grooves.

A complete list of publications begins on page 15.



A. James Moser, MD

Associate Professor of Surgery
Co-Director, BIDMC Pancreas and Liver Institute

RESEARCH FOCUS

The five-year plan for the Institute for Hepatobiliary and Pancreatic Surgery at the Beth Israel Deaconess Medical Center is to evaluate the role of minimally invasive surgery for pancreatic cancer in a prospective study of comparative effectiveness to traditional open surgery. Our objective reflects a multicenter, collaborative effort including the University of Pittsburgh Medical Center, the University of Pisa (Italy), and Maastricht University (Netherlands).

Currently, more than 70% of patients with potentially resectable pancreatic cancer do not undergo potentially curative surgery. Although possible causes for this phenomenon are numerous, fear of traditional open surgery, perceived prolonged impairment of quality of life and nutrition afterward, as well as minimal proven survival benefits are all factors that can be studied in properly designed clinical trials.

Our published data to date demonstrates no apparent inferiority of cancer outcomes after minimally invasive resection, and mounting evidence suggests improved short-term postoperative outcomes and possibly better completion rates of adjuvant chemotherapy after minimal access surgery. Whether short-term benefits will translate into improved long-term outcomes and better nutrition are the subject of maturing multicenter studies. Methods to accelerate the training and adoption of new technologies are underway through evaluation of the learning curve for advanced minimally invasive surgery.

RESEARCH GROUP*

Courtney Barrows, MD
Manuel Castillo-Angeles, MD
Martin Dib, MD
William E. Gooding, MS
Sjors Klompmaker
Alessandra Storino, MD
Stijn Thoolen
Wald Van der Vliet
Ammara A. Watkins, MD



▲ Dr. Moser accepts a generous gift to support pancreatic cancer research from representatives of the Alliance of Families Fighting Pancreatic Cancer.



▲ Members of Dr. Moser's research group

* Courtney Barrows, MD, General Surgery Resident, BIDMC
Manuel Castillo-Angeles, MD, HPB Surgery Research Fellow, Dept. of Surgery, BIDMC
Martin Dib, MD, General Surgery Resident, BIDMC (graduated June 2014)
William E. Gooding, MS, Senior Biostatistician, University of Pittsburgh Cancer Institute
Sjors Klompmaker, HPB Surgery Research Student, Dept. of Surgery, BIDMC
Alessandra Storino, MD, HPB Surgery Research Fellow, Dept. of Surgery, BIDMC
Stijn Thoolen, HPB Surgery Research Student, Dept. of Surgery, BIDMC
Wald Van der Vliet, HPB Surgery Research Student, Dept. of Surgery, BIDMC
Ammara A. Watkins, MD, AFFPC Clinical Research Fellow in HPB Surgery, Categorical General Surgery Resident, Dept. of Surgery, BIDMC

ACCOMPLISHMENTS 2013-2014

- We received funding for an investigator-initiated Dana-Farber/Harvard Cancer Center clinical trial entitled "Phase II study of pancreatic enzyme replacement on completion rates of adjuvant therapy among subjects with resected pancreatic ductal adenocarcinoma." This study is funded by Actavis, PLC. The target accrual is 103 patients; the principal investigator is A. James Moser, MD. We expect to begin enrollment in Winter 2014.
- Ammara A. Watkins, MD, was accepted as a delegate in the Resident and Associate Society-American College Surgeons (RAS-ACS) International Exchange Scholar Program. Dr. Watkins will be studying in Australia in 2015.
- Our poster, "Initial experience and outcomes of a robotic-assisted hepatopancreatic and biliary (HPB)-surgery program," was awarded the Best Poster Presentation at the BIDMC Department of Surgery's fourth annual IDEAS Symposium on Surgical Robotics in 2014.

ABSTRACTS, POSTERS, AND EXHIBITS

Abbasi AA, Ruby Lo, Tseng JF, Moser AJ, Vollmer Jr CM, Callery MP, Kent TS. Role of surgical palliation in patients with pancreatic ductal adenocarcinoma. Americas Hepatico-Pancreatico-Biliary Association Annual Meeting, Miami, FL, 2014

van der Vliet WJ, Thoolen SJJ, Anez-Bustillos L, Abbasi AA, Kent TS, Callery MP, Tseng JF, Moser AJ. Initial experience and outcomes of a robotic-assisted hepatopancreatic and biliary (HPB)-surgery program. BIDMC IDEAS Symposium, Boston, MA, 2014. Awarded Best Poster Presentation for 2014 Session

van der Vliet WJ, Thoolen SJJ, Watkins AA, Boone BA, Zenati M, Zeh HJ, Callery MP, Kent TS, Moser AJ. Outcomes of procedure-specific credentialing and training for robot-assisted hepatobiliary and pancreatic surgery. New England Surgical Society Annual Resident Meeting, Worcester, MA, 2014

SELECTED RESEARCH SUPPORT

Phase II study of pancreatic enzyme replacement on completion rates of adjuvant therapy among subjects with resected pancreatic ductal adenocarcinoma; Actavis, PLC, 2015-2018; PI: A. James Moser, MD

The Institute for Hepatobiliary and Pancreatic Surgery is also funded through the dedication and generosity of non-profit family foundations hoping for a world without pancreatic cancer:

- The Griffith Family Foundation
- The John F. Fortney Charitable Pancreatic Cancer Research Group
- The Alliance of Families Fighting Pancreatic Cancer
 - The Wanda Bilec Foundation
 - The Woiner Foundation
 - J's Run
 - Mellie's Mission

SELECTED PUBLICATIONS

Jamal MH, Doi SA, Moser AJ, Dumitra S, Abou Khalil J, Simoneau E, Chaudhury P, Onitilo AA, Metrakos P, Barkun JS. McGill Brisbane Symptom Score for patients with resectable pancreatic head adenocarcinoma. *World J Gastroenterol* 2014;20(34):12226-32.

Boone BA, Sabbaghian S, Zenati M, Marsh JW, Moser AJ, Zureikat AH, Singhi AD, Zeh HJ 3rd, Krasinskas AM. Loss of SMAD4 staining in pre-operative cell blocks is associated with distant metastases following pancreaticoduodenectomy with venous resection for pancreatic cancer. *J Surg Oncol* 2014;110(2):171-5.

Rajagopalan MS, Heron DE, Wegner RE, Zeh HJ, Bahary N, Krasinskas AM, Lembersky B, Brand R, Moser AJ, Quinn AE, Burton SA. Pathologic response with neoadjuvant chemotherapy and stereotactic body radiotherapy for borderline resectable and locally-advanced pancreatic cancer. *Radiat Oncol* 2013;8:254.

Kim CH, Ling DC, Wegner RE, Flickinger JC, Heron DE, Zeh H, Moser AJ, Burton SA. Stereotactic body radiotherapy in the treatment of pancreatic adenocarcinoma in elderly patients. *Radiat Oncol* 2013;8:240.

Nath BD, Freedman SD, Moser AJ. The Frey procedure is a treatment for chronic pancreatitis, not pancreas divisum. *JAMA Surg* 2013;148(11):1062.

Zureikat AH*, Moser AJ*, Boone BA, Bartlett DL, Zenati M, Zeh HJ 3rd. 250 robotic pancreatic resections: Safety and feasibility. *Ann Surg* 2013;258(4):554-9;discussion 559-62. *equal credit in authorship

A complete list of publications begins on page 15.

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 developed a protocol and database 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 are examining a cohort of patients who are 80-89 years old versus a cohort who are 50-59 years old and are comparing 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 have developed a protocol and database 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.

Impact of the Oncotype DX DCIS Score on treatment decision-making in patients with ductal carcinoma *in situ*

BIDMC is participating in a multi-institutional prospective study to assess the impact of the Oncotype DX DCIS Score on physician decision-making in recommendations for adjuvant radiation therapy in patients with ductal carcinoma *in situ* (DCIS) who have been treated with surgical excision.

My translational research interests include:

Intraoperative real-time breast cancer margin assessment with nonlinear microscopy

We have developed a protocol using Acridine Orange dye with nonlinear microscopy for intra-operative evaluation of surgical margins in oncologic resection specimens. This study is currently in the pre-clinical phase.

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 vaccine. It is being tested 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+) who are not eligible for Herceptin, following completion of standard of care oncologic therapy.

ACCOMPLISHMENTS 2013-2014

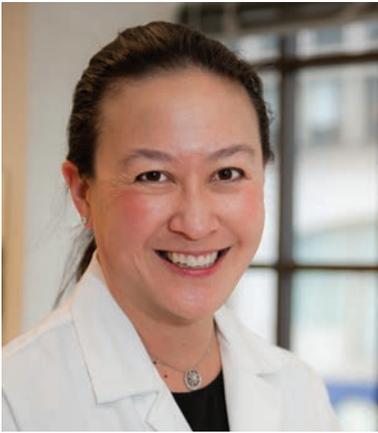
- Breast cancer Section Editor, Dynamed web-based education resource
- Question author, Breast Education and Self-Assessment Program (BESAP); American Society of Breast Surgeons
- BIDMC General Surgery Residency applicant interviewer
- Member, BIDMC Cancer Committee
- Medical Chart Reviewer for Quality Assurance, BIDMC Cancer Committee Tumor Registry
- Member: Society of Surgical Oncology, American Society of Breast Surgeons, American Society of Clinical Oncology, American College of Surgeons, Boston Surgical Society
- BIDMC Academy of Medical Educators, Academy Member

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
- Research Mentor, Pursuing Inquiry in Medicine course, Harvard Medical School first-year curriculum; Julie Gonzalez, HMS first-year student
- Best-in-Practice BIDMC MRI Lecture Series Fall Symposium: The use of MRI in a surgical practice
- Screening, diagnosis and treatment of breast cancer, Harvard Business School Breast Cancer Awareness Event

Jennifer F. Tseng, MD, MPH

Associate Professor of Surgery
Chief, Surgical Oncology

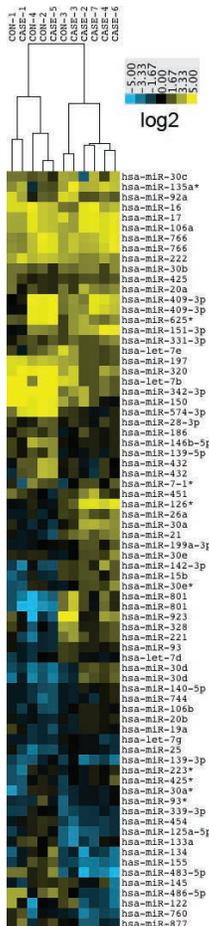


RESEARCH GROUP

- Lindsay Bliss, MD
- Zeling Chau, MD*
- Susanna DeGeus, BS
- Mariam Eskandar, MD
- Sing-Chau Ng, MS
- Emily Schapira, BS
- Catherine Yang, MD**

*completed June 2013

**completed June 2014



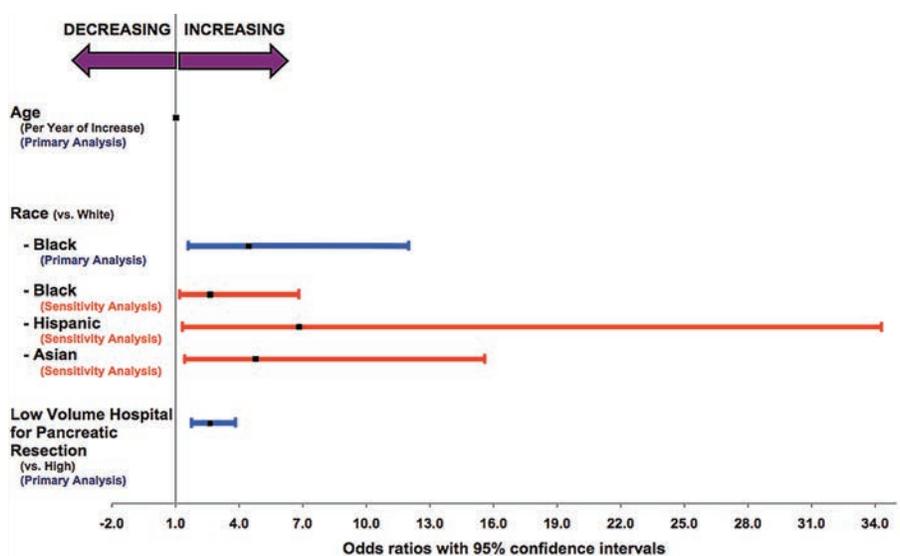
RESEARCH FOCUS

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 2013-2014

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 2014, 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. Dr. Mariam Eskandar, BIDMC categorical surgical resident, has joined us full-time for a two-year block (2014-2016) and is focusing on BIDMC and Massachusetts state data to determine predictors of outcomes for solid cancers, including pancreatic cancer. 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 for work on insurance and pancreatic adenocarcinoma outcomes.

TEACHING, TRAINING, AND RESEARCH

- 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 CMEs offered for pancreaticobiliary education
- Ongoing mentoring of two (primary) categorical PGY-1 surgical residents in the BIDMC Department of Surgery Clinical Scholarship Program
- Ongoing mentoring of two HMS students (Emily Schapira, HMS-2, and George Baison, HMS-4)
- 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

2014

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

Mariam Eskandar, MD; Research resident (BIDMC); ongoing; MPH student at HSPH

Susanna DeGeus, BS; Medical student research fellow from University of Leiden, the Netherlands

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

SELECTED PUBLICATIONS

Ragulin-Coyne E, Carroll JE, Smith JK, Witkowski ER, Ng SC, Shah SA, Zhou Z, Tseng JF. Perioperative mortality after pancreatotomy: 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;185(1):15-20.

Yang CJ, Bliss LA, Schapira EF, Freedman SD, Ng SC, Windsor JA, Tseng JF. Systematic review of early surgery for chronic pancreatitis: Impact on pain, pancreatic function, and re-intervention. *J Gastrointest Surg* 2014;18(10):1863-9.

Bliss LA, Yang CJ, Chau Z, Ng SC, McFadden DW, Kent TS, Moser AJ, Callery MP, Tseng JF. Patient selection and the volume effect in pancreatic surgery: Unequal benefits? *HPB (Oxford)* 2014;16(10):899-906.

Bliss LA, Yang CJ, Kent TS, Ng SC, Critchlow JF, Tseng JF. Appendicitis in the modern era: Universal problem and variable treatment. *Surg Endosc* 2014; in press.

A complete list of publications begins on page 15.



Erik Folch, MD, MSc

Instructor in Medicine

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 (interventional pulmonology) community around the world rallied behind a minimally invasive technique to biopsy the lymph nodes in the chest with ultrasound guidance. Six 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 help 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.

Research Group

Aishatu Aloma, MD, MPH
George Cheng, MD, PhD
Jey Chung, MD
Bryan Husta, MD
Adnan Majid, MD
Sebastian Ochoa, MD
Scott Oh, MD

ACCOMPLISHMENTS 2013-2014

At this time, I am involved in the development of new bronchoscopic technologies, including a clinician-initiated prospective study to evaluate the use of several complementary 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, which decided to support it through an unrestricted equipment grant.

One of my mentees, George Cheng, MD, PhD, was recently awarded the American Association of Bronchology and Interventional Pulmonology (AABIP) Research Award for the fiscal year 2014-2015. His research, titled "Use of combined vs. sequential deoxyribonuclease and tissue plasminogen activator in pleural effusions," was selected as the best among several outstanding projects.

Clinical Innovations

- Linear Endobronchial Ultrasound (EBUS)
- Radial Endobronchial Ultrasound (EBUS)
- Electromagnetic Navigation Bronchoscopy (EMNB)
- Bronchial Thermoplasty: An FDA approved, catheter-based therapy, which uses radiofrequency energy to ablate the smooth muscle within the airway wall of patients with severe persistent asthma. Several randomized clinical trials have shown that treated patients will have improvement of asthma-related symptoms.
- 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 in patients with limited treatment options.

Invited Presentations

- Endobronchial stents; LXXVII National Conference of Pulmonary and Thoracic Surgery, Mérida, México, 2013
- Management of malignant pleural effusions; LXXVII National Conference of Pulmonary and Thoracic Surgery, Mérida, México, 2013
- Diagnosis and management of malignant pleural effusions; Pulmonary and Critical Care Medicine Grand Rounds, Jefferson University Hospital, Philadelphia, PA, 2013
- Approach to the patient with hemoptysis; Medical Grand Rounds, Lawrence Memorial Hospital, Medford, MA, 2013
- Thoracic ultrasound; Harvard Medical School Continuing Medical Education, Beth Israel Deaconess Medical Center, Boston, MA, 2013
- Ultrasound guidance of vascular procedures; Harvard Medical School Continuing Medical Education, Beth Israel Deaconess Medical Center, Boston, MA, 2013

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 up to 60 highly motivated physicians from New England and around the country.

ABSTRACTS, POSTERS, AND EXHIBITS

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

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

SELECTED PUBLICATIONS

Folch E, Yamaguchi N, Vanderlaan PA, Kocher ON, Boucher DH, Goldstein MA, Huberman MS, Kent MS, Gangadharan SP, Costa DB, Majid A. Adequacy of lymph node transbronchial needle aspirates using convex probe endobronchial ultrasound for multiple tumor genotyping techniques in non-small-cell lung cancer. *J Thorac Oncol* 2013;8(11):1438-44.

Vanderlaan PA, Yamaguchi N, Folch E, Boucher DH, Kent MS, Gangadharan SP, Majid A, Goldstein MA, Huberman MS, Kocher ON, Costa DB. Success and failure rates of tumor genotyping techniques in routine pathological samples with non-small-cell lung cancer. *J Lung Can* 2014;84(1):39-44.

Vanderlaan P, Wang H, Majid A, Folch E. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): An overview and update for the cytopathologist. *Cancer Cytopathol* 2014;122(8):561-76.

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.

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.

A complete list of publications begins on page 15.



Sidharta P. Gangadharan, MD

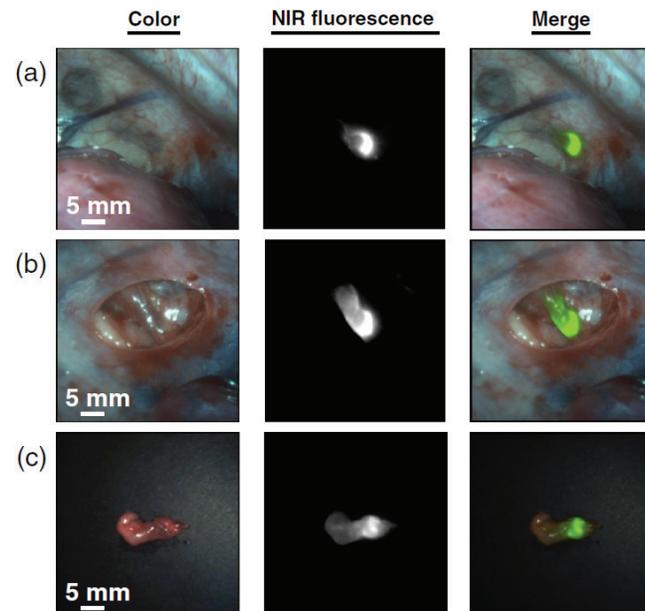
Associate Professor of Surgery

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. We are currently starting a project to evaluate the long-term outcomes of surgical and endoscopic interventions for tracheobronchomalacia. I am a co-investigator and mentor for a postgraduate research fellow on a Center for Integration of Medicine and Innovative Technology (CIMIT) Young Clinician Research Award (“Exploring 3D Printing in Designing Novel Airway Stents”). The aim of this study is to develop a platform to design, modify, and manufacture personalized airway stents based on a patient’s airway anatomy. Three-dimensional printer technology will be used to create custom stents, which will be tested in a large animal model.

In addition, I have 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. We have completed our preclinical testing in a porcine model and are currently working toward a pilot human study in patients with lung cancer. This study aims to improve identification of metastatic foci within mediastinal lymph nodes in lung cancer.



- ▲ *In vivo* evaluation of the endoscopic imaging system.
Snapshots:
(a) Lymph node detected 5 min after injection of ICG
(b) Exposed lymph node prior to resection
(c) Excised lymph node imaged *ex vivo*

ACCOMPLISHMENTS 2013-2014

- Treatment of complex airway disease, Grand Rounds, Beth Israel Deaconess Medical Center
- Novel techniques in esophageal and tracheal surgery, Course Co-Director and Table Instructor, Society of Thoracic Surgeons annual meeting, STS University Course, Orlando FL, 2014
- Surgery for early lung cancer, actual role for mediastinoscopy, lymph node dissection versus sampling, surgery for advanced lung cancer (4 presentations); Invited speaker for Lung Cancer Course – Multidisciplinary Approach, Clinica Alemana, Santiago, Chile

TEACHING, TRAINING, AND EDUCATION

I have been involved in education administration for the Department of Surgery as the Program Director for Cardiothoracic Surgery and as an Assistant Program Director for the General Surgery Residency Program. 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

Exploring 3D printing in designing novel airway stents; Center for Integration of Medicine and Innovative Technology (CIMIT) Young Clinician Research Award, 2014-2016; Co-Investigator: Sidharta P. Gangadharan, MD, mentoring George Cheng, MD, PhD

SELECTED PUBLICATIONS

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;58(9):1521-6.

Kent M, Wang T, Flores R, Whyte R, Gangadharan S. Open, video-assisted thoracic surgery and robotic lobectomy: Review of a national database. *Ann Thorac Surg* 2014;97(1):236-42.

Kent M, Wang T, Gangadharan S, Whyte R. What is the prevalence of a "non-therapeutic" thymectomy? *Ann Thorac Surg* 2014;97(1):276-82.

Venugopal V, Park M, Ashitate Y, Neacsu F, Kettenring F, Frangioni JV, Gangadharan SP, Gioux S. Design and characterization of an optimized simultaneous color and near-infrared fluorescence rigid endoscopic imaging system. *J Biomed Opt* 2013;18(12):126018.

Majid A, Cheng GZ, Kent MS, Gangadharan SP, Whyte R, Folch E. Evaluation of rigid bronchoscopy-guided percutaneous dilational tracheostomy: A pilot study. *Ann Am Thorac Soc* 2014;11(5):789-94.

Majid A, Gaurav K, Sanchez JM, Berger RL, Folch E, Fernandez-Bussy S, Ernst A, Gangadharan SP. Evaluation of tracheobronchomalacia by dynamic flexible bronchoscopy: A pilot study. *Ann Am Thorac Soc* 2014;11(6):951-5.



Adnan Majid, MD

Assistant Professor of Medicine
Director, Chest Disease Center

RESEARCH GROUP

Aishatu Aloma, MD, MPH
Marianne Barry, MD
George Cheng, MD, PhD
Jey Chung, MD
Erik Folch, MD, MSc
Brian Husta, MD
Sebastian Ochoa, MD
Scott Oh, 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 into three FDA-approved, multicenter, phase 3 clinical trials. We are the only center in New England participating in all three emphysema clinical trials:

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). We currently have seven patients enrolled in the study and have successfully implanted the ELVRC in two patients, with more patients to be treated before the end of the year. Benefits of the ELVRC to patients include: reduction in lung volume, improvement in lung function, reduction in number and severity of symptoms related to emphysema, and improved quality of life and exercise tolerance

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. We have successfully implanted the IBV® valve in one patient with dramatic improvement in the patient's lung function and quality of life. Benefits of the IBV to patients include: reduction in lung volume, improvement in pulmonary function and quality of life.

Lung Function Improvement after Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves (EBV) Used in Treatment of Emphysema (LIBERATE). This is a phase 3, multi-center, prospective, randomized, controlled study with EBV treatment statistically evaluated using Intent-to-Treat (ITT) analyses. We are assessing the safety and effectiveness of bronchoscopic lung volume reduction (BLVR) using the Pulmonx Endobronchial Valve (EBV) in treated study participants compared to control participants. Benefits to patients include: improvement in lung function and increased exercise tolerance.

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. We have completed enrollment for this study. All patients are currently in long-term follow-up. Benefits that our patients have experienced 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
- 3D printing in designing novel airway stents. Dr. George Cheng was awarded the CIMIT Young Clinician Award. His proposal, "Exploring 3D Printing in Designing Novel Airway Stents," is aimed at developing a platform for the design, modification, and manufacture of personalized airway stents based on patients' airway anatomies.

- We are the only center in New England involved in three multicenter clinical trials for patients with severe emphysema, namely: the RENEW, EMPROVE, and LIBERATE studies. We have been collaborating with pulmonary physicians, interventional pulmonologists, and interventional radiologists, as well as physicians from other pulmonary specialties to increase patient referrals and enrollment into these studies. The monthly COPD conference has also resulted in numerous referrals for these trials.
- Dr. George Cheng was recently awarded the 2014-2015 American Association of Bronchology and Interventional Pulmonology (AABIP) Research Award. I am one of the mentors on this project, entitled "Use of combined vs. sequential deoxyribonuclease and tissue plasminogen activator in pleural effusions." This proposal was selected as the best among several high-quality proposals sent to the AABIP award committee.

Invited Presentations

- Bronchoscopic management of tracheal stenosis; American College of Chest Physicians meeting (CHEST), Chicago, IL, 2013
- Endobronchial ultrasound: The interventional pulmonologist perspective; Puerto Rican Society of Pulmonology 16th Annual Convention, San Juan, PR, 2013
- Endobronchial Ultrasound: Clinical cases; Puerto Rican Society of Pulmonology 16th Annual Convention, San Juan, PR, 2013
- Radiofrequency ablation; Congreso Nacional Asociación Española Endoscopia Respiratoria, Cartagena, Espana, 2014
- Malignant mesothelioma—histologic diagnosis; Congreso Nacional Asociación Española Endoscopia Respiratoria, Cartagena, Spain, 2014
- Tracheostomy: Complications; Clinica Alemana-Universidad Del Desarrollo, Santiago de Chile, 2014
- Unclear exudate: Role for medical thoracoscopy; Clinica Alemana-Universidad Del Desarrollo, Santiago de Chile, 2014

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 13 years, 20 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

Ibrahim O, Folch E, Mahajan A, Shostak E, Inaty H, Majid A. Endobronchial electrosurgery for airway obstruction: A retrospective outcome and safety analysis. ATS Conference, San Diego, CA 2014

Mahajan A, Folch E, Ibrahim O, Shostak E, Majid A. Flexible bronchoscope-guided percutaneous endoscopic gastrostomy tube placement: A feasibility study. ATS Conference, San Diego, CA 2014

Jawad A, Vanderlaan P, Gangadharan S, Folch E, Majid A. Histopathological analysis of dynamic airway collapse. ATS Conference, San Diego, CA 2014

Fashjian M, Folch E, Roca E, Aloma A, Majid A. Use of tunneled pleural catheters in patients with congestive heart failure: A single institution experience. CHEST Conference, Austin, TX, 2014

Roca E, Folch E, Aloma A, Majid A. Safety and efficacy of medical thoracoscopy: A 10-year single-institution experience. CHEST Conference, Austin, TX, 2014

Wang R, Folch E, Paul M, Maskey A, Allard F, Majid A. The use of CP-EBUS-TBNA in the diagnosis of chondrosarcoma in a patient with Maffucci syndrome. *J Bronchology Interv Pulmonol* 2014;21(2):177-80.

Vanderlaan P, Wang H, Majid A, Folch E. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): An overview and update for the cytopathologist. *Cancer Cytopathol* 2014;122(8):561-76.

Majid A, Cheng G, Kent M, Gangadharan S, Whyte R, Folch E. Evaluation of rigid bronchoscopy-guided percutaneous dilational tracheostomy: A pilot study. *Ann Am Thorac Soc* 2014;11(5):789-94.

Jawad, A, Majid A, Maskey A, Vanderlaan P, Ibrahim O, Foch E. Pill aspiration presenting as an endobronchial tumor. *J Bronchology Interv Pulmonol* 2014;21(2):162-5.

Barros Casas D, Fernández-Bussy S, Folch E, Flandes Aldeyturriaga J, Majid A. Non-malignant central airway obstruction. *Arch Bronconeumol* 2014;50(8):345-54.

Majid A, Gaurav K, Sanchez J, Berger R, Folch E, Fernandez-Bussy S, Ernst A, Gangadharan S. Evaluation of tracheomalacia by dynamic flexible bronchoscopy: A pilot study. *Ann Am Thorac Soc* 2014;11(6):951-5.



Leo E. Otterbein, PhD

Associate Professor of Surgery

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 these genes 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 the gene. We are well integrated with the laboratory of Barbara Wegiel, PhD, who studies the role of HO-1 and BVR in models of cancer.

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 Affinity Research Collaborative (ARC) grant from the Department of Surgery, the research involves interactive studies with Carl Hauser, MD (BIDMC), Jim Lederer, PhD (Brigham and Women's Hospital), Wolfgang Junger, PhD (BIDMC), and Michael Yaffe, MD, PhD (BIDMC and MIT). Our data in sepsis models, generated with Barbara Wegiel, PhD, shows that HO-1 derived CO acts directly 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 Carl Hauser, MD, in which we have demonstrated that liver trauma predisposes to bacterial pneumonia, which is observed in patients and animals. We find that innate defense mechanisms and immune surveillance at barrier sites are weakened coinciding with lack of HO-1 activity. This effect can be rescued with inhaled CO where CO enhances bacterial killing by macrophages and modulating neutrophil NETosis.

HO-1 and neuroinflammation

We maintain an active collaboration 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. Inhaled CO enhances recovery, reduces inflammation and cell death, and improves cognitive function. The mechanism involves the ability of CO to boost phagocytosis of erythrocytes. Recently we have begun to dissect the role of HO-1/CO on circadian rhythm.

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 as it relates to liver regeneration and the role of intestinal flora.

RESEARCH GROUP

Eva Csizmadia, MS
David Gallo, BS
Ingred Goretti, PhD
Marcela Latancia
Nils Schallner, MD
Jing Zhang, PhD



▲ The Otterbein research group was selected to provide the cover image for the December 2013 issue of *Cancer Research* (Carbon monoxide expedites metabolic exhaustion to inhibit tumor growth. *Cancer Res* 2013;73:7009-21.)

We continue to be one of the leaders in the area of heme metabolism and the stress response, providing mechanistic insight into the bioactive products carbon monoxide and the bile pigments. Our publications continue to provide important contributions toward therapeutic use of these molecules in the clinic, which has guided the ongoing clinical trials with inhaled CO. The publication in *Cancer Research* drew media attention with national news coverage in newspapers and radio as well as the ABC affiliate, Channel 5, news report (www.wcvb.com/health/deadly-gas-being-tested-as-powerful-cancer-fighter). We consider ourselves a team with excellent technical skills combined with creative and innovative approaches to research design, always with translation to human disease in our sites.

Invited Presentations

- 8th International Conference on Heme Oxygenases, Bioiron and Oxidative Stress; Sydney, Australia
- Visiting Professor; University of Paris
- Hemoglobin-based oxygen carriers in medicine; San Diego, CA
- Macrophage Symposium; Paris, France
- 17th Biennial Meeting of Society for Free Radical Research International; Kyoto, Japan
- Visiting Professor; University of Birmingham, UK

Other Accomplishments

- Elected Chair of the BIDMC Institutional Animal Care and Use Committee
- Center for Integration of Medicine and Innovative Technology (CIMIT), Site Miner for BIDMC
- Boston Biomedical Innovations Center (B-BIC), member of the Technology Assessment and Development Group
- Continued in my 11th year as a regular NIH study section member for K01, K08, K02, and K99 grant applications
- Served as grant reviewer for the 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, grant proposals, and career guidance. As the BIDMC CIMIT site miner and more recently as a member of the B-BIC Technology Assessment and Development Group, I mentor and provide specialized expertise in entrepreneurial start-up ventures for innovative technologies. In addition to the science, I also advise on grant submissions, potential commercialization of ideas, interactions with the Technology Ventures Offices, and various accelerator and venture opportunities.

SELECTED RESEARCH SUPPORT

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

Heme degradation pathway and immunomodulation in prostate cancer; NIH, 2013-2015; Co-PI: Leo E. Otterbein, PhD

Effects of RES12 in the treatment of liver fibrosis; Lasso Inc., 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)

Wegiel B, Gallo D, Csizmadia E, Harris C, Belcher J, Vercellotti GM, Penacho, N, Seth P, Sukhatme V, Ahmed A, Pandolfi PP, Helczynski L, Bjartell A, Persson JL, Otterbein LE. Carbon monoxide expedites metabolic exhaustion to inhibit tumor growth. *Cancer Res* 2013;73:7009-21 (Cover).

Wegiel B, Hedblom A, Li M, Gallo D, Csizmadia E, Harris C, Nemeth Z, Zuckerbraun BS, Soares M, Persson JL, Otterbein LE. Heme oxygenase-1 derived carbon monoxide permits maturation of myeloid cells. *Cell Death Dis* 2014;5:e1139.

Li M, Gallo D, Csizmadia E, Otterbein LE, Wegiel B. Carbon monoxide induces chromatin remodelling to facilitate endothelial cell migration. *Thromb Haemost* 2014;111(5):951-9.

Wegiel B, Nemeth Z, Correa-Costa M, Bulmer AC, Otterbein LE. Heme oxygenase-1: A metabolic Nike. *Antioxid Redox Signal* 2014;20(11):1709-22.

A complete list of publications begins on page 15.



James R. Rodrigue, PhD

Professor

Vice Chair, Clinical Research

Director, Center for Transplant Outcomes and Quality Improvement

Director, Behavioral Health Services and Research, The Transplant Institute

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 more than 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.

RESEARCH GROUP

Jodi-Ann Dattadeen

Aaron Fleishman

Alexa Hiley

Maeve Moore

Sucheta Ravindran

Denny Tsai

Tanya Vishnevsky, PhD



Surgical Outcomes Analysis & Research

ACCOMPLISHMENTS 2013-2014

We received NIH funding to evaluate strategies to reduce racial and income disparities in live donor kidney transplantation, as well as another Health Resources and Services Administration (HRSA) grant to evaluate a novel organ-donation education program in drivers education classes. 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 examining outcomes in living kidney donors (*Transplantation*, 2014), risk factors for relapse to alcohol use after liver transplantation (*Liver Transplantation*, 2013), and disparity-reducing benefits of the novel House Calls intervention (*Transplantation*, 2014). I accepted invitations to present our work at the World Transplant Congress in San Francisco, CA and the International Conference on Living Donor Abdominal Organ Transplantation in Padova, Italy. I also served on the Steering Committee of the Invitational Meeting on Pediatric Organ Donation and Transplantation in Geneva, Switzerland.

Other recent accomplishments include:

- Nomination to serve on the Board of the American Society of Transplantation
- Continued service on NIH Study Section (Behavioral Medicine)
- Co-Chair of the Consensus Conference on Best Practices in Living Kidney Donation (sponsored by 11 organizations)

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, Jennifer Tseng, MD, MPH, 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

SELECTED RESEARCH SUPPORT

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; HRSA, 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

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

Increasing donor designation rates in teenagers: Effectiveness of a driver's education intervention; HRSA, 2014-2017; PI: James Rodrigue, PhD

SELECTED PUBLICATIONS

Rodrigue JR, Schold JD, Mandelbrot DA. The decline in living kidney donation in the United States: Random variation or cause for concern? *Transplantation* 2013;96(9):767-73.

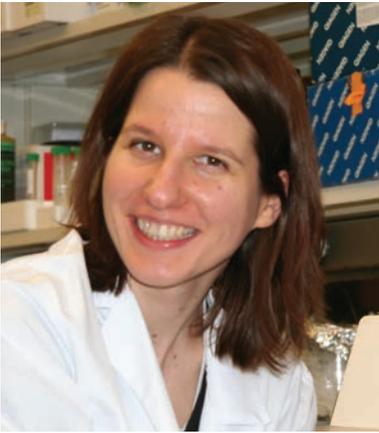
Rodrigue JR, Hanto DW, Curry MP. Substance abuse treatment and its association with relapse to alcohol use following liver transplantation. *Liver Transpl* 2013;19(12):1387-95.

Rodrigue JR, Paek M, Whiting J, Vella J, Garrison K, Pavlakis M, Mandelbrot DA. Trajectories of perceived benefits in living kidney donors: Association with donor characteristics and recipient outcomes. *Transplantation* 2014;97(7):762-8.

Rodrigue JR, Fleishman A, Vishnevsky T, Whiting J, Vella J, Garrison K, Moore D, Kayler L, Baliga P, Chavin K, Karp S, Mandelbrot DA. Development and validation of a questionnaire to assess fear of kidney failure following living donation. *Transpl Int* 2014;27(6):570-5.

Rodrigue JR, Fleishman A, Fitzpatrick S, Boger M. Organ donation knowledge, willingness, and beliefs of motor vehicle clerks. *Transplantation*; in press.

A complete list of publications begins on page 15.



Barbara Wegiel, PhD, MSc

Assistant Professor of Surgery

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 as well as a key regulator of tumorigenesis, 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).

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.

RESEARCH GROUP

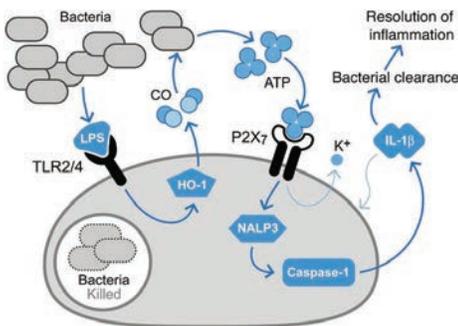
Kavita Bisht, MSc

Mailin Li

Aidan Low

Zsuzsanna Nemeth, PhD

Lisa Vikstrom



▲ FIGURE 1: Schematic depicting a proposed mechanism of action for HO-1 and CO in bacteria recognition and activation of innate immune defense machinery.

ACCOMPLISHMENTS 2013-2014

- 2013-2015 Eleanor and Miles Shore 50th Anniversary Fellow
- Cover of December 2013 issue of *Cancer Research*. Carbon monoxide expedites metabolic exhaustion to inhibit tumor growth. *Cancer Res* 2013;73(23):7009-21.
- Ad hoc reviewer for the following journals: *Cancer Research*, *PLoS One*, *European Urology*, *Molecular and Cellular Biochemistry*, *Respiratory Care*, *Current Chemical Biology*, *Radiation Oncology*, *Neurological Research*, *Antioxidant Redox Signaling*
- Reviewer of Polish National Academy grants, 2013
- Member of American Heart Association, American Association for Cancer Research, and DF/HCC
- Visiting Scientist, Lund University, Sweden
- Honorary Lecturer in Molecular Oncology, Aston University, UK
- External co-supervisor: PhD thesis–Kavita Bisht, Australia; Master thesis–Lisa Vikstrom, Lund University, Sweden; BS thesis–Mailin Li, Tufts University

Invited Presentation

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, one master's 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, 2013-2015; PI: Barbara Wegiel, PhD, MSc

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

The role of heme oxygenase-1 derived carbon monoxide in vascular injury and repair; NCRP Scientist Development Grant, American Heart Association, 2009-2014; PI: Barbara Wegiel, PhD, MSc

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

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

SELECTED PUBLICATIONS

Wegiel B, Gallo D, Csizmadia E, Harris C, Belcher J, Vercellotti GM, Penacho N, Seth P, Sukhatme V, Ahmed A, Pandolfi PP, Helczynski L, Bjartell A, Persson JL, Otterbein LE. Carbon monoxide expedites metabolic exhaustion to inhibit tumor growth. *Cancer Res* 2013;73:7009-21 (Cover).

Li M, Gallo D, Csizmadia E, Otterbein LE, Wegiel B. Carbon monoxide induces chromatin remodelling to facilitate endothelial cell migration. *Thromb Haemost* 2014;111(5):951-9.

Wegiel B, Hedblom A, Li M, Gallo D, Csizmadia E, Harris C, Nemeth Z, Zuckerbraun BS, Soares M, Persson JL, Otterbein LE. Heme oxygenase-1 derived carbon monoxide permits maturation of myeloid cells. *Cell Death Dis* 2014;5:e1139.

Wegiel B, Larsen R, Gallo D, Chin BY, Harris C, Mannam P, Kaczmarek E, Lee P, Zuckerbraun BS, Flavell R, Soares MP and Otterbein LE. Bacterial sensing by macrophages through carbon monoxide-dependent inflammasome activation. *J Clin Invest* 2014; in press.

Wegiel B, Nemeth Z, Correa-Costa M, Bulmer AC, Otterbein LE. Heme oxygenase-1: A metabolic Nike. *Antioxid Redox Signal* 2014;20(11):1709-22.

A complete list of publications begins on page 15.



RESEARCH GROUP

Daniel McManus
Chris Seungtae On

RESEARCH FOCUS

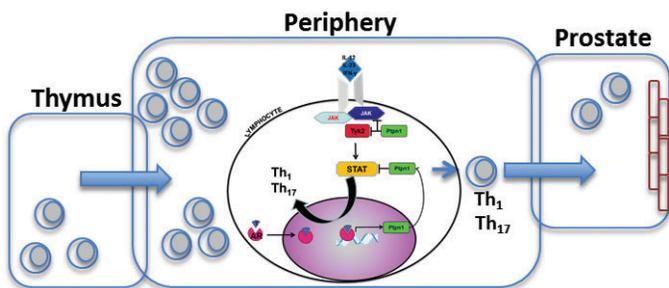
The field of cancer immunology and immunotherapy has gained momentum in recent years. It is expected that cancer immunotherapy will rival other modalities of cancer therapy in the near future. My research revolves around immunology and immunotherapy of prostate cancer, with a special emphasis on exploring mechanisms driving immune tolerance to tumor antigens, and preclinically 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. I have developed a set of related projects that reflect the vision I have for my future scientific career. Four representative projects are described below.

Personalized vaccine design for cancer immunotherapy

This project explores the use of immunogenic epitopes that arise from patients' tumor-specific coding mutations for personalized cancer vaccine design. Peptide-based immunogens are identified *in silico*, then tested *in vitro* and *in vivo* using an array of bioinformatics tools, binding assays with humanized mice, and human peripheral blood.

Listeria-based vaccine delivery platforms for cancer treatment

This research consists of two innovative collaborations with Aduro Biotech and Johns Hopkins with the goal of implementing phase I clinical trials as soon as preclinical testing is completed. The live-attenuated Listeria platform provides high immunogenicity with this pathogen, based on the capacity to insert a full or partial antigen sequence, or even a single immunogenic epitope. Both platforms have entered pre- and clinical trials and have demonstrated efficacy and safety.



▲ FIGURE 1: Androgens act on the immune system in the thymus, as well as in the periphery, including the prostate.

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

This project aims to uncover how androgens modulate the immune system and how androgens' effects on T cells impact hormone therapy. It has three specific aims that test: 1) the importance of androgen receptor expression in the thymus and periphery in androgen-induced suppression of immunity to cognate and prostate tumor antigens, 2) the role of androgen deprivation on T cell differentiation and the implication of EGR2 and PTPN1 in the process, and 3) validation of findings from the murine experiments in PBMC from prostate cancer patients before and after hormone therapy.

Investigating the inflammation-cancer link

Increasing evidence indicates a link between inflammation and carcinogenesis. We are using select transgenic mouse models and cell lines to dissect the cause of antigen-independent and antigen-specific, non-bacterial inflammation, and to determine the molecular immune and non-immune components that impact the onset and progression of tumorigenesis in the prostate. A special emphasis is put on non-lymphocytic players such as myeloid cells, but also stromal cells within the tumor. The goal is to identify druggable targets that could help manipulate the tumor environment to achieve anti-tumor effect.

My research team has accomplished a number of milestones in the past year. We have completed preclinical testing of the live attenuated *Listeria* vaccine platform, thus validating the concept of minigene delivery to elicit epitope-specific immunity in the context of prostate cancer immunotherapy.

Our personalized cancer vaccine platform was initiated in a syngeneic mouse model of prostate cancer. Exome sequencing of the TRAMP-C2 cell line allowed identification of a number of coding mutations that generate immunogenic epitopes. Vaccine peptide cocktails based on these epitopes are being tested *in vivo* for their anti-tumor effect. Using androgen deprivation therapy as a model for immunopotentialization of anti-tumor immunity coupled with gene expression profiling, we have been able to identify an array of molecular players that regulates androgen effects on lymphocytes. Specifically, we identified the phosphatase PTPN1 as a potential driver of testosterone-induced immunosuppression. Pharmacological inhibition of PTPN1 allowed reduced immune dysfunction in CD4 T lymphocytes, suggesting this approach could be applied in conjunction with cancer immunotherapy for better outcomes.

In addition, we characterized the role of the receptor MARCO, a scavenger receptor known to diminish anti-tumor immune responses, in regulating toll-like receptor-induced dendritic cell activation. Our findings might impact the way TLR agonists are used as adjuvants in cancer immunotherapy, and provide new avenues for MARCO targeting to enhance anti-tumor immunity.

Finally, my team has contributed to the success of several collaborative projects that resulted in publications in prestigious journals. These include: the α -GalCer-based vaccine for prostate cancer (a collaboration with Dr. Steven Balk at BIDMC and Dr. Mark Exley at Brigham and Women's Hospital and the University of Manchester (UK)), CD21-driven EBV infection of B lymphocytes (a collaboration with Dr. Joyce Fingerth at UMass Medical School), and reversing autoimmune disease in mice through metabolic manipulation of T lymphocyte differentiation (a collaboration with Dr. Abdala El Khal at Brigham and Women's Hospital).

Administrative

- Reviewer, Department of Defense CDMRP PRPC Review Panel
- Reviewer, Prostate Cancer Foundation Challenge Grants
- Reviewer, Qatar National Research Funds
- Ad-hoc reviewer, *Neoplasia*
- Joined the BIDMC "Metabolism and Cancer" Affinity Research Collaborative (ARC) Faculty
- Assessor, PhD thesis, candidate: Mette Thomsen, MD; Copenhagen University School of Medicine, Denmark

TEACHING, TRAINING, AND EDUCATION

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 research in my laboratory.

Kissick HT, Dunn LK, Ghosh S, Nechama M, Kobzik L, Arredouani MS. The scavenger receptor MARCO modulates TLR-induced responses in dendritic cells. *PLoS One* 2014;9(8):e104148.

Kissick HT, Sanda MG, Dunn LK, Pellegrini KL, On ST, Noel JK, Arredouani MS. Androgens alter T cell immunity by inhibiting T helper 1 differentiation. *Proc Natl Acad Sci USA* 2014;111(27):9887-92.

Kissick HT, Sanda MG, Dunn LK, Arredouani MS. Immunization with a peptide containing MHC class I and II epitopes derived from the tumor antigen SIM2 induces an effective CD4 and CD8 T-cell response. *PLoS One* 2014;9(4):e93231.

Arredouani MS, Bhasin MK, Sage D, Dunn LK, Gill MB, Agnani D, Libermann TA, Fingerth J. Analysis of host gene expression changes reveals distinct roles for the cytoplasmic domain of the Epstein-Barr virus receptor/CD21 in B-cell maturation, activation and initiation of virus infection. *J Virol* 2014;88(10):5559-77.

Kissick HT, Sanda MG, Dunn LK, Arredouani MS. Development of a peptide-based vaccine targeting TMPRSS2:ERG fusion-positive prostate cancer. *Cancer Immunol Immunother* 2013;62(12):1831-40.

Tullius SG, Rodriguez H, Biefer C, Li S, Trachtenberg AJ, Edtinger K, Quante M, Krenzien F, Uehara H, Yang X, Kissick HT, Kuo WP, Ghiran I, de la Fuente MA, Arredouani MS, Camacho V, Tigges JC, Toxavidis V, Rachid EF, Smith BD, Vasudevan A, ElKhal A. NAD⁺ protects against EAE by regulating CD4⁺ T cell differentiation and promoting remyelination and neuroregeneration. *Nat Comm* 2014; in press.

Invited Presentations

- Androgen regulation of adaptive immunity: Implications for prostate cancer immunotherapy; Rigshospitalet, Copenhagen University, Denmark, 2013
- The transcription factor ERG confers a nerve-like phenotype to prostate cancer cells and enhances responsiveness to neurotransmitters; ARC Seminar Series, BIDMC, 2014
- Hormonal immune regulation; BIDMC Cancer Center, 2014

SELECTED RESEARCH SUPPORT

Nanoparticle-targeted peptide vaccines for prostate cancer; Prostate Cancer Foundation Challenge Grant, 2011-2014; 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, 2014-2015; PI: Mohamed Arredouani, PhD



Peter Chang, MD, MPH

Instructor in Surgery

Director, BIDMC Prostate Cancer Care Center

Martin and Diane Trust Career Development Chair in Surgery

RESEARCH FOCUS

My research focus is in urologic cancer, and is highly collaborative in nature, most importantly within BIDMC, but also with outside institutions. I work very closely with Andrew Wagner, MD, and together we co-lead the Urology research team and share research personnel. Our team's research in kidney and bladder cancer is described in Dr. Wagner's report. As Director of the BIDMC Prostate Cancer Care Center, I will describe my research efforts to optimize quality-of-life in prostate cancer patients.

RESEARCH GROUP

Catrina M. Crociani, MPH

Kyle McAnally

Kimberly Taylor

Andrew Wagner, MD

Prostate cancer

Quality-of-life assessment in prostate cancer patients

At BIDMC, we are committed to giving every patient with prostate cancer a chance to have the best quality of life possible. Unfortunately, prostate cancer treatment can cause significant side effects, and doctors tend to underestimate how bad these are, potentially leaving patients with long-lasting quality of life problems. My research focuses on accurate and objective measurement of prostate cancer quality of life using patient-reported outcome questionnaires. I developed a new questionnaire called "EPIC for Clinical Practice (EPIC-CP)," designed to be used by clinicians rather than researchers (Chang P et al, J Urol Sep 2011). I recently showed that EPIC-CP can allow a doctor to estimate the chances of a patient recovering sexual function after prostate cancer surgery (Chipman et al, J Urol Mar 2014). Due to its development here at BIDMC, our institution is at the forefront in using EPIC-CP as part of prostate cancer care. Dr. Wagner and I recently presented our results on the "real-world" use of EPIC-CP in post-surgery patients at the New England Section of the American Urological Association. As a next step, I hope to show how using EPIC-CP can improve the practitioner work-flow, and improve patient outcomes.

Quality-of-life outcomes after prostate cancer treatment

I am also interested in finding out what problems patients have after different treatments (surgery, external radiation, radioactive seed implants), and determining whether we can use this information to better guide patients toward optimal treatments. I have recently been named Co-overall Principal Investigator of the PROST-QA study; this is a prospective, multicenter, longitudinal study that has the most complete and rigorous collection of prostate cancer quality-of-life data in the world. Working with Martin Sanda, MD, at Emory University, I recently applied some analytic methods acquired at the Harvard School of Public Health to identify predictors of favorable urinary outcomes after prostate cancer treatment; these results are pending submission for publication.

Helping prostate cancer patients make treatment decisions

Unlike other cancers, in which options may be limited after initial diagnosis, prostate cancer patients face a seemingly impossible task of choosing among several treatment options. Working with Donna Berry, PhD, RN (Dana-Farber Cancer Institute), I serve as BIDMC site-responsible Principal Investigator for an NIH R01-funded randomized trial called Personal Patient Profile – Prostate (P3P). This unique study investigates the effectiveness of a web-based interactive program that gathers patient characteristics, quality-of-life (using EPIC-CP), personal preferences, and priorities, and uses this information to customize videos that counsel patients on how to discuss these issues with their doctor.

Patient Testa		Patient Report Date	
HEM: H3453	DOB: 01/01/1960	03/03/2013	
Baseline Treatment Preference			
Do you think you know which prostate care option you want? Yes			
External beam radiation therapy			
Decisional Control Preference			
"I prefer that my doctor and I share responsibility for deciding which care option is best."			
Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)			
Overall Prostate Cancer QOL Score		25 out of 60	
Higher scores indicate worse QOL. Two most serious problems indicated with this icon.			
Overall Urinary Bother		Moderate Problem	
Urinary Incontinence Symptom Score			
2 out of 12			
Dribbling		Occasional Dribbling	
Pad Use		None	
Leaking		Very Small Problem	
Influential Personal Factors			
A lot of influence		Spouse or Partner Family Member Sexual Function Recreational Activities	
Some influence		Friend Co-worker Bowel Function Bladder Work Activities	
Bowel Symptom Score			
1 out of 12			
Pain/Urgency		No Problem	
Frequency		No Problem	
Bowel Control		Very Small Problem	
Sexual Symptom Score			
10 out of 12			
Orgasm Ability		Very Poor to None	
Erections		Not Firm Enough for Sexual Activity	
Overall Function		Big Problem	

▲ Clinician report from the Personal Patient Profile – Prostate (P3P) study, describing patients' preferences and quality-of-life.

ACCOMPLISHMENTS 2013-2014

I am honored and fortunate to be the first incumbent of the Martin and Diane Trust Career Development Chair in Surgery. This position, made possible by the generosity of the Trust Family, will enable my growth as a research investigator while building my clinical practice during these formative early years of my career.

In June of 2014, I completed my tenure as a Urology Care Foundation Research Scholar, a two-year competitive grant sponsored by the research arm of the American Urological Association (AUA). The support from this grant allowed me to continue my research investigations and obtain a Masters of Public Health degree from the Harvard School of Public Health while also acting as a clinical fellow in here at BIDMC.

Through a nomination by Aria Olumi, MD, Associate Professor of Urology at Massachusetts General Hospital and New England section representative to the AUA Research Council, I was named one of the nation's top 10 Urology researchers within the first 10 years of training. As such, I presented at the Early Investigators Showcase of the AUA Research Forum at the 2014 AUA Annual Meeting in Orlando, FL.

My research interest in patient-reported outcome (PRO) use in Urology has led me to serve on several national committees and panels in the last year, the two most significant of which were the PRO panel for the AUA Quality Registry (AQUA), and the True Nth Prostate Cancer Decision Support group, sponsored by the Movember Foundation.

In an effort to bolster academic collaborations within the GU Oncology multidisciplinary group here at BIDMC, I recently started organizing and hosting a monthly GU Oncology research conference that features sharing of research ideas among Urology, Radiation Oncology, Medical Oncology, Radiology, and Pathology.

Lastly, I made my third annual one-week trip to the Cape Verde islands as part of the Mission to Bridge the Healthcare Gap, a joint effort among Urology, Urogynecology, Vascular Surgery, and Interpreter Services that focuses on providing surgical care and training to the Cape Verdean population.

TEACHING, TRAINING, AND EDUCATION

As a proud graduate of the Harvard Longwood Program in Urology and the BIDMC Minimally Invasive Urologic Oncology fellowship, I now have the privilege of training the next generation of residents and this year's fellow, Ostap Dovirak, MD.

I led a session on retroperitoneal surgical anatomy in the PGY-3 resident course titled "Anatomical Basis of General Surgery," and reprised my yearly role in teaching the GU physical exam to HMS II students. I was elected to the BIDMC Academy of Medical Educators, and continue broadening my role in surgical education.

I was a faculty member for the third consecutive year in the New England Urology Training Course in Robotic Surgery, a two-day course that attracted residents and attendings from across the nation.

SELECTED PUBLICATIONS

Gay H, Michalski J, Hamstra D, Wei JT, Dun RL, Klein E, Sandler HM, Saigal C, Litwin M, Kuban D, Hembroff L, Chang P, Sanda MG, PROSTQA Consortium. Neoadjuvant androgen deprivation therapy (NADT) leads to immediate impairment of vitality/hormonal and sexual quality of life: Results of a multi-center, prospective study. *Urology* 2013;82(6):1363-8.

Chipman JJ, Sanda MG, Dunn RL, Wei JT, Litwin MS, Crociani C, Regan MM, Chang P. Measuring and predicting prostate cancer quality of life changes using the EPIC for Clinical Practice (EPIC-CP). *J Urol* 2014;191(3):638-45.

Chen RC, Chang P, Vetter RJ, Lukka H, Stokes WA, Sanda MG, Watkins-Bruner D, Reeve BB, Sandler HM. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. *J Natl Cancer Inst* 2014;(8) 106(7).

Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, Wei JT, and the PROST-QA Consortium. Minimally important difference for the expanded prostate cancer index composite short form. *Urology* 2014; in press.

Carneiro A, Sasse AD, Wagner AA, Peixoto G, Katagiri A, Neto AS, Bianco BA, Chang P, Pompeo AC, Tobias-Machado M. Cardiovascular events associated with androgen deprivation therapy in patients with prostate cancer: A systematic review and meta-analysis. *World J Urol* 2014; in press.

Castaneda CV, Danzig MR, Finkelstein JB, RoyChowdhury A, Wagner AA, Chang P, Pierorazio PM, Allaf ME, McKiernan JM. The natural history of renal functional decline in patients undergoing surveillance in the DISSRM registry. *Urol Oncol*; accepted.

SELECTED RESEARCH SUPPORT

Assessment of circulating tumor DNA to detect metastatic disease in primary prostate cancer; Department of Defense, 2015-2016; Collaborator: Peter Chang, MD, MPH (PI: Adam Sowalsky, PhD)

Measuring prostate cancer patient-reported outcomes at the point of care; Urology Care Foundation, 2012-2014; PI: Peter Chang, MD, MPH (Mentors: Martin Sanda, MD, Donna Berry, PhD, RN, Andrew Wagner, MD)

Personal patient profile-prostate (p3p) II: An effectiveness-implementation trial in diverse health care networks; NIH, 2012-2016; Co-investigator/Site PI: Peter Chang, MD, MPH (PI: Donna Berry, PhD, RN)

Prostate active surveillance study; Canary Foundation, 2013-2014; Co-investigator: Peter Chang, MD, MPH (PI: Daniel Lin, MD)



William C. DeWolf, MD

Professor of Surgery
Chief, Urology

RESEARCH FOCUS

Clinical research

Clinical research, which deals with active surveillance in the management of prostate cancer, is quite active. Currently we have more than 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 who 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.

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 year our Minimally Invasive Urologic Surgery Fellowship Program moved ahead with its second fellow, Ostap Dovirak, MD, from the University at Buffalo, New York. The first fellow, Peter Chang, MD, MPH, has joined the staff as our sixth full-time urologic surgeon. Dr. Chang is the Director of the Prostate Cancer Care Center as well as coordinator of the Minimally Invasive Bladder Cancer Program. In addition, he is the recipient of the Martin and Diane Trust Career Development Chair in Surgery. The GU service continues to be staffed by three residents from Brigham and Woman’s Hospital and our physician assistant. We are looking to add a second physician assistant, as well as actively campaigning for additional space to accommodate our expanding research and clinical needs.

TEACHING, TRAINING, AND EDUCATION

The division sponsors a biennial CME course on “Men’s Health for Primary Care and Innovation.” This year it was held at the Fairmont Copley Plaza Hotel in Boston on April 11-12, 2014. In addition, Andrew Wagner, MD, and staff also sponsor an instructional course sponsored by Intuitive, Inc. for basic training in minimally invasive surgery for residents. Finally, Michael Kearney, MD, and I are preceptors for a general Harvard Medical School course in urologic science for HMS students that includes a rotation on the Urology service and clinical and didactic experience. Our training also focuses on the education of our residents, which include PGY-2,3, and 5 trainees, as well as a physician assistant and a fellow.

I have also presented numerous lectures and served in various leadership capacities in national organizations, including: AUA Program Co-Chair for Basic Research in Prostate Cancer, Medical Advisory Board for the Boston Prostate Cancer Walk, invited speaker for the Boston Coalition for Prostate Cancer, Visiting Professor at the University of Minnesota resident graduation, and the editorial boards of *Urology*, *Harvard Men’s Health Watch* and *Harvard Perspectives in Prostate Disease*.

Delto JC, Kacker R, Bublely G, DeWolf WC. Intravesical mitomycin therapy for stage T1 and Tis high-grade squamous cell carcinoma of the bladder. *Clin Genitourin Cancer* 2014;12(1):e35-6.

Costa DN, Bloch BN, Yao DF, Sanda MG, Ngo I, Genega EM, Pedroza I, DeWolf WC, Rofsky NM. Diagnosis of relevant prostate cancer using supplementary cores from MRI imaging prompted areas following multiple failed biopsies. *Magn Reson Imaging* 2013;31:947-52.

San Francisco IF, Rojas PA, DeWolf WC, Morgentaler A. Low free testosterone levels predict disease reclassification in men with prostate cancer undergoing active surveillance. *BJU Int* 2014;114(2):229-35.

DeWolf WC. (Editorial) Anterior fascial fixation does not reduce the parastomal hernia rate after radical cystectomy and ileal conduit. *J Urol* 2014;1427-1432.



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, as well as the benefits and adverse events associated with testosterone therapy.

Testosterone deficiency has been a focus of my clinical and academic activities for more than 20 years. This past year it gained enormous national and global publicity due to the publication of two articles suggesting increased cardiovascular risk, with such a strong public response that the FDA announced it would investigate the issue. Much of my non-clinical work this past year has been investigating the cardiovascular risks of testosterone, lecturing on this topic, publishing analyses of the new reports, as well as reviewing the broader literature. Together with several colleagues, we have successfully been able to provide perspective on this issue for medical and lay audiences, restoring some common sense and perspective to an issue that had become associated with non-scientific hysteria.

Work with testosterone deficiency and its treatment fits nicely into my practice, Men's Health Boston, which is affiliated with BIDMC and its Department of Surgery. In 1999, Men's Health Boston became the first center established in the U.S. to provide comprehensive evaluation and management of male-specific health issues. These include 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 to a revolution in concept regarding the long-held belief that higher serum testosterone causes more rapid prostate cancer. Current data from our own center and others indicates that this concept is incorrect. Our current work now addresses the newer concern regarding testosterone therapy; namely, cardiovascular risks.

ACCOMPLISHMENTS 2013-2014

- Three regional societies of the AUA this year invited me to give my testosterone course at their regional meetings. Each of these societies is allowed to select one course from approximately 100 at the national meeting, paid by the national AUA.
- I made an oral presentation to the FDA on behalf of the Androgen Study Group at the advisory committee meeting regarding the use of testosterone therapies.
- I chair the newly formed Androgen Study Group, a multidisciplinary group of testosterone investigators, which aims to provide accurate information to the public and the medical community regarding testosterone research.
- I was an invited lecturer in three foreign countries.
- I gave the state-of-the-art lecture at the annual meeting of the Sexual Medicine Society of North America.
- I have authored or co-authored 16 articles in medical journals over the last year.
- I am a member of two international groups developing testosterone guidelines: The International Society for the Study of the Aging Male (ISSAM) and the International Society for Sexual Medicine (ISSM).

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. I co-direct the Andrology Fellowship at BIDMC and Men's Health Boston, together with Dr. William DeWolf. I participated as faculty at approximately 10 CME events over the past year. For the last 12 years I have co-chaired the Endocrine Forum at the annual meeting of the American Urological Association, one of the most popular sessions at that meeting.

ABSTRACTS, POSTERS, AND EXHIBITS

Testosterone therapy in men with prostate cancer. American Urologic Association, Orlando, FL; May 2014 (poster)

Increased body fat is associated with higher LH levels in testosterone-deficient men. Sexual Medicine Society of North America, New Orleans, LA; Nov. 2013 (poster)

Safety of testosterone therapy in men with prostate cancer. Sexual Medicine Society of North America, New Orleans, LA; Nov. 2013 (poster)

Salvage pharmacotherapy for orgasmic dysfunction after treatment for testosterone deficiency. Sexual Medicine Society of North America, New Orleans, LA; Nov. 2013 (poster)

Free testosterone by directed and calculated measurement versus equilibrium dialysis in a clinical population. Sexual Medicine Society of North America, New Orleans, LA; Nov. 2013 (poster)

Bone mineral density and response to treatment in testosterone-deficient men younger than 50 years old. Sexual Medicine Society of North America, New Orleans, LA; Nov. 2013 (poster)

SELECTED PUBLICATIONS

Morgentaler A. Testosterone, cardiovascular risk, and hormonophobia. *J Sex Med* 2014;11(6):1362-6.

San Francisco IF, Rojas PA, DeWolf WC, Morgentaler A. Low free testosterone levels predict disease reclassification in men with prostate cancer undergoing active surveillance. *BJU Int* 2014;114(2):229-35.

Morgentaler A, Benesh JA, Denes BS, Kan-Dobrosky N, Harb D, Miller MG. Factors influencing prostate-specific antigen response among men treated with testosterone therapy for 6 months. *J Sex Med* 2014;11(11):2818-25.

Morgentaler A, Kacker R. Andrology: Testosterone and cardiovascular risk – deciphering the statistics. *Nature Rev Urol* 2014;11(3):131-2.

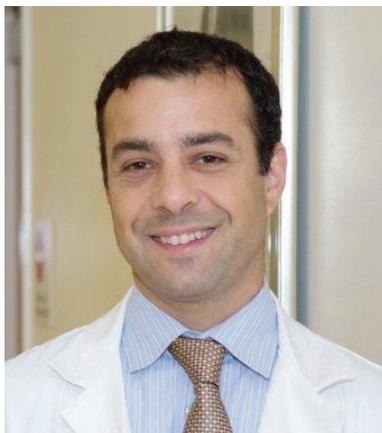
Zarotsky V, Huang MY, Carman W, Morgentaler A, Singhal PK, Coffin D, Jones TH. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology* 2014;2(6):819-34.

Balbontin FG, Moreno SA, Bley E, Chacon R, Silva A, Morgentaler A. Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. *BJU Int* 2014;114(1):125-30.

Andrew A. Wagner, MD

Assistant Professor of Surgery

Director, Minimally Invasive Urologic Surgery



RESEARCH GROUP

Peter Chang, MD, MPH

Catrina Crociani, MPH

Ostap Dovirak, MD

Kyle McAnally

Peter Renehan

Kimberly Taylor

RESEARCH FOCUS

Kidney cancer

Although we are the busiest robotic kidney surgery team in Boston, there remains much to learn about the ideal method of performing kidney surgery. We are interested in evaluating recovery trends (as measured by prospectively collecting patient reported quality of life data) and costs after both open and minimally invasive (including laparoscopic and robotic) kidney surgery. Our pilot data was published in *Urology* in 2012 and we presented our work comparing recovery after laparoscopic radical and robotic partial nephrectomy at the New England Meeting of the American Association of Urology in October 2014. Our ultimate goal is to develop a New England-wide consortium to evaluate recovery trends in kidney cancer surgery. 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. 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 are also interested in non-operative approaches to small renal masses. Together with researchers from Johns Hopkins, we have developed the DISSRM trial (Delayed Intervention and Surveillance for Small Renal Masses). This is a multicenter, prospective study evaluating the role of surveillance of small kidney tumors over time. We have developed a scoring system to help clinicians during the decision-making process regarding surgery versus surveillance for these masses. Our work was presented at the American Association of Urology Meeting in Orlando, FL in 2014.

Prostate cancer

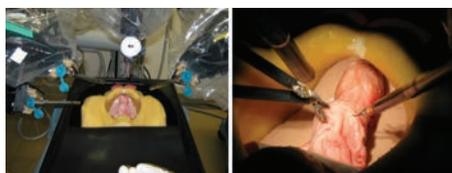
BIDMC has been a strong supporter of active surveillance for low-risk prostate cancer for a decade. We are the only Northeast center to be a member of the Prostate Cancer Active Surveillance Study (PASS). This is the largest multi-center study of active surveillance for prostate cancer, with more than 1,200 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.

Our team is also helping to validate a novel technique for educating newly diagnosed prostate cancer patients. The Personal Patient Profile-Prostate study (P3P), led at BIDMC by Dr. Peter Chang, is evaluating a web-based system designed to assist men with newly diagnosed prostate cancer become more educated about their disease, and to help clinicians learn more about their patients’ treatment priorities.

Robotic training and simulation remains a priority for our group. Our work on a new robotic prostatectomy simulator using porcine tissue was published this year in the *Journal of Endourology* (Figure 1). Our simulator allows trainees to practice robotic surgery in a safe environment prior to operating on patients. Our group was also selected to help validate the Fundamentals of Robotic Surgery, a novel basic training program for robotic surgery.

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. This work was also presented at the 2014 AUA meeting in Orlando, FL.



▲ FIGURE 1: Robotic prostatectomy simulator using porcine tissue.

- Our kidney surgery clinical database now includes over 750 patients. Over 450 of these patients have been consented for our quality of life and cost-effectiveness studies. Data from these patients has been used in several projects this year, including a comparison of quality of life outcomes between radical and partial nephrectomy, and a societal cost evaluation – work that will be presented in May 2015 at the American Urologic Association (AUA) annual meeting in New Orleans, LA.
- Maine Medical Center was added as an official collaborator for our prospective kidney surgery quality of life and cost projects.
- We developed a robust clinical and quality of life database for robotic prostatectomy patients. Over 500 patients are entered into this database. Among other projects, this database was used to evaluate the EPIC-CP point-of-care quality-of-life instrument in robotic prostatectomy patients – work that will be presented at the AUA in May 2015.
- Enrollment for the multi-center PASS prostate cancer active surveillance cohort exceeded 1200 patients, with BIDMC contributing 120 patients.
- We evaluated patient-reported quality of life outcomes following laparoscopic adrenalectomy, a first of its kind analysis, which was accepted as a podium presentation at the AUA in New Orleans, 2015.

TEACHING, TRAINING, AND EDUCATION

In addition to training our urology residents from the Harvard Combined Urology program, in July 2010 we launched a Minimally Invasive Urologic Surgery Fellowship Program. Following urology residency training, fellows spend one to two years at BIDMC pursuing minimally invasive surgical (in particular, robotic surgery) techniques and urologic research. Fellows also have the option of training in clinical effectiveness through the Harvard School of Public Health. This fellowship is a unique training opportunity in New England, allowing fellows exposure to several hundred laparoscopic and robotic surgery cases per year. Our current fellow is Ostap Dovirak, MD, who trained in urology at SUNY at the University at Buffalo, New York.

As regional leaders in robotic urologic surgery, we are committed to training area surgeons in robotics. Therefore, in May 2012 we hosted the first-ever New England Urologic Resident Robotic Training Course. This two-day course attracted residents, fellows, and attending surgeons from New England and beyond. The third annual course was held at BIDMC in November 2014.

ABSTRACTS, POSTERS, AND EXHIBITS

Kaplan IK, Wagner AA, Mahadevan A, Dagoglu RN. Stereotactic body radiosurgery for primary small renal tumors: A retrospective analysis. GU ASCO, San Francisco, CA, 2014

Pierorazio P, Kaye D, Danzig M, Ghandour R, Chang P, Hartman R, Wagner AA, McKiernan J, Allaf M. The DSSRM score: Objective scoring system identifies patients with small renal masses most suitable for active surveillance. AUA Annual Meeting, Orlando, FL, 2014

Pierorazio P, Ball M, Danzig M, Ghandour R, Chang P, Hartman R, Wagner AA, McKiernan J, Allaf M. Active surveillance for small renal masses non-inferior to primary intervention: 5-year analysis of the multi-institutional, prospective DISSRM (Delayed Intervention and Surveillance for Small Renal Masses) registry. AUA Annual Meeting, Orlando, FL, 2014

Raza, Wagner AA et al. Long-term survival outcomes of robot-assisted radical cystectomy: Results from the international robotic cystectomy consortium. AUA Annual Meeting, Orlando, FL, 2014

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;27:1096.

Alemezaffar M, Percy AA, Narayan R, Minnillo BB, Steinberg P, Haleblan G, Gautam S, Matthes K, Wagner AA. Validation of a novel, tissue-based simulator for robot assisted radical prostatectomy. *J Endourol* 2014;28(8):995-1000.

Alemezaffar 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.

Carneiro A, Sasse AD, Wagner AA, Peixoto G, Katagiri A, Neto AS, Bianco BA, Chang P, Pompeo AC, Tobias-Machado M. Cardiovascular events associated with androgen deprivation therapy in patients with prostate cancer: A systematic review and meta-analysis. *World J Urol* 2014; in press.

Castaneda CV, Danzig MR, Finkelstein JB, RoyChowdhury A, Wagner AA, Chang P, Pierorazio PM, Allaf ME, McKiernan JM. The natural history of renal functional decline in patients undergoing surveillance in the DISSRM registry. *Urol Oncol*; accepted.

Garg N, Wagner AA, Steinman TI. Systematic employment of laparoscopic decortication for maximal pain control in polycystic kidney disease. *J Nephrol and Urol*; in press.



Elliot L. Chaikof, MD, PhD

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Surgeon-in-Chief

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Jessie Jeon, PhD
Wookhyun Kim, PhD
Venkata R. Krishnamurthy, PhD
Liyong Liu, MD
David Miranda Nieves
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 vessel substitutes for cardiac or vascular 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.



▲ Members of Dr. Chaikof's laboratory

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 that 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.

ACCOMPLISHMENTS 2013-2014

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.

- U.S. Patent 8,846,624. Chaikof EL, Conticello VP. Modified protein polymers. September 30, 2014
- Elected to the Institute of Medicine of the National Academies

TEACHING, TRAINING, AND EDUCATION

Harvard-MIT HST PhD candidate David Miranda Nieves received a National Defense Science and Engineering Graduate Fellowship to support his PhD studies

Post-doctoral fellow Jennifer Gagner, PhD, received fellowship support from the AHA

Post-doctoral fellow Donny Hanjaya-Putra, PhD, received fellowship support from JDRF

Post-doctoral fellow, Jessie Jeon, PhD, received fellowship support from the NIH

Post-doctoral fellow, Vickie Dydek, PhD, joined the scientific staff of Lincoln Labs

Post-doctoral fellow, Stephanie Grainger, PhD, joined the scientific staff of Infraredx, Inc.

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; Wyss Institute for Biologically Inspired Engineering, 2014-2015; PI: Elliot L. Chaikof, MD, PhD

SELECTED PUBLICATIONS

Kumar VA, Caves JM, Haller CA, Dai E, Li L, Grainger S, Chaikof EL. Acellular vascular grafts generated from collagen and elastin analogues. *Acta Biomaterialia* 2013;8:8067-8074.

Dorr BM, Ham O, An C, Chaikof EL, Liu DR. Reprogramming the specificity of sortase enzymes by directed evolution. *Proc Natl Acad Sci USA* 2014;111:13343-13348.

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 Healthcare Mater* 2014;3(1):30-5.

Angsana J, Chen J, Smith S, Xiao J, Wen J, Liu L, Haller CA, Chaikof EL. Syndecan-1 modulates the motility and resolution responses of macrophages. *Arteriosclerosis Thromb Vasc Biol* 2014; in press.

Kim W, Haller CA, Dai E, Wang X, Hagemeyer CE, Liu DR, Peter K, Chaikof EL. Targeted anti-thrombotic protein micelles. *Angew Chemie* 2014; in press.

Krishnamurthy VR, Sardar MYR, Yu Y, Song X, Haller CA, Dai E, Wang X, Hanjaya-Putra D, Sun L, Morikis V, Simon SI, Woods R, Cummings RD, Chaikof EL. Glycopeptide analogues of PSGL-1 inhibit P-selectin *in vitro* and *in vivo*. *Nat Commun* 2015; in press.

Fellow Mohammed Sardar, PhD



A complete list of publications begins on page 15.



Mauricio A. Contreras, MD

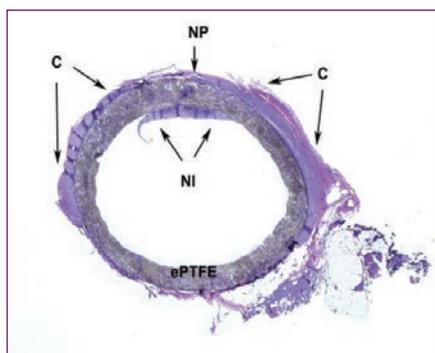
Instructor in Surgery

RESEARCH FOCUS

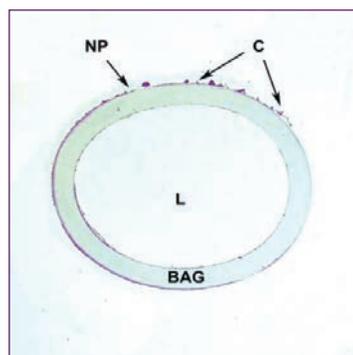
Our research has focused on three main areas of vascular biology: 1) Evaluating mechanisms responsible for prosthetic graft failure, 2) preventing intimal hyperplasia (IH) in vein grafts, and 3) developing novel biomaterials as well as surface modification.

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 completed one of our projects, our 4mm ID Dacron prosthetic vascular graft, where the luminal surface was modified with Activated Protein C (APC), a natural anticoagulant and implanted in our common carotid artery (CCA) model. Even though our final histology, immunohistochemistry, and morphometric studies show differences in healing between control and APC treated grafts (APC-TG), the effect of increased patency on the APC-TG was mainly attributed to the clopidogrel (Plavix) effect. Thus, longer implantation time points (6-12 months) are required to help determine if complete graft healing could occur, which would eliminate the need for the use of Plavix beyond this point. We are currently seeking NIH funding to continue our studies. Our results were presented at the annual American Society for Investigative Pathology (ASIP) meeting at the Federation of the American Society for Experimental Biology (FASEB), in San Diego, CA in April 2014. Our manuscript is in progress and will be submitted to the *American Society for Artificial Internal Organs Journal*.



▲ FIGURE 1: Cross section ePTFE graft-Midd-portion-AVF. C=Capsule, NP=Needle Puncture, NI=Neointima. H&E, 1X



▲ FIGURE 2: Cross section BAG-Midd-portion-AVF. C=Capsule, NP=Needle Puncture, NI=Neointima. H&E, 1X

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 (BAG), which was designed with anti-thrombin, anti-proliferative, and anti-microbial properties by incorporating recombinant Hirudin (rHir), paclitaxel (Pac), and moxifloxacin (Moxi) dissolved in an organic solvent prior to electrospinning. Our preliminary results show striking differences in healing between our BAG and ePTFE AV-fistula graft. At the arterial and venous anastomosis, there is no capsule (C) or neointima (NI) formation up to 60 days on our BAG grafts, unlike the control ePTFE grafts.

However, perhaps more striking is the effect through the needle puncture (NP) sites created to mimic dialysis (Figures 1 and 2). There, fibroblasts and smooth muscle cells from the capsule penetrate and migrate through the ePTFE graft's wall into the lumen, but do not in our BAG, where its self-sealing bioengineered properties (Dacron/Polyurethane) and Pac prevent such migration/proliferation. Our immunohistochemistry and morphometric studies are ongoing. Our preliminary results were presented at the annual American Society for Artificial Internal Organs (ASAIO) meeting in Washington, DC, in June 2014.

Our first-generation nanofibrous bioactive graft design demonstrated that a combinatorial approach using rHir and VEGF 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.

We also have been working on 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, which are currently under review.

At present, we are working closely with the FDA and have submitted an IDA application for approval of our bioengineered vascular graft that we hope we will be able to test in a small clinical trial within the next year.

In the past year, the results of our work were presented at national conferences:

- Linderman S, Araya J, Pathan S, Nelson D, LoGerfo F, Phaneuf M, Contreras MA. Small-diameter bioactive prosthetic vascular graft with Activated Protein C (APC). Proceedings, Federation of the American Society for Experimental Biology (FASEB) Conference, April 2014 (poster)
- Contreras MA, Patan Saif, Nelson D, Phaneuf T, Phaneuf MD. A nanofibrous bioactive hemodialysis access graft. Proceedings, American Society for Artificial Internal Organs (ASAIO) Conference, June 2014 (oral presentation)

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, including 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.

In addition, I am a member of the Boston University pre-med mentoring program, which provides the opportunity to work with students and gives them the opportunity to be involved and participate in our research studies.

SELECTED RESEARCH SUPPORT

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)

A bioactive nanofibrous sewing cuff for treatment of cardiac valvular disease; NIH, 2014; Co-PI: Mauricio A. Contreras, MD (PI: Matthew D. Phaneuf)

Vissapragada R, Contreras MA, da Silva CG, Kumar VA, Ochoa A, Vasudevan A, Selim MH, Ferran C, Thomas AJ. Bidirectional crosstalk between periventricular endothelial cells and neural progenitor cells promotes the formation of a neurovascular unit. *Brain Res* 2014;27;1565:8-17.



RESEARCH GROUP

Maria Beatriz Arvelo, MD
 Eva Cszmadia, MS
 Cleide Gonçalves Da Silva, PhD
 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
- 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

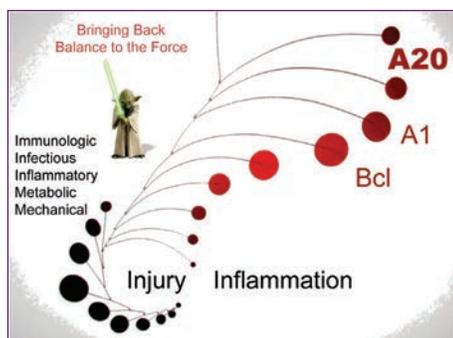
We have also extensively established a potent “hepatoprotective” role for A20 in the liver, stemming from combined anti-inflammatory, anti-apoptotic, and pro-proliferative functions of A20 in hepatocytes. Accordingly, A20-based therapies protect mice from lethality in models of acute chemically-induced 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.

Additionally, 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.

Recently, we also discovered that A20 regulates lipid metabolism. This translated in improved fatty liver disease in a mouse model of human non-alcoholic fatty liver disease.

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. This work was just published in the *Journal of Biological Chemistry*.
- **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 novel means to cure diabetes.

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 (PI: Wolfgang Junger, PhD)
- Training in Transplantation Biology; NIH, 1998-2019; Faculty: Christiane Ferran, MD, PhD (Director: David Sachs, MD)

Awards and honors

- Jesus Revuelta-Cervantes, PhD: Best abstract and selected oral presentation at the annual Center for Vascular Biology Research (CVBR) retreat for his work on fatty liver diseases
- Herwig Moll, PhD: Selected for oral presentation at the Harvard Surgery Research Day 2014 for his work on A20 and interferon- γ signaling in the vasculature

Departmental contributions

I was Chair and a member of the organizing committee for the Harvard Surgery Research days, 2012-2014; Chair of the Affinity Research Collaborative (ARC) initiative, BIDMC Surgery; member of Harvard Search Committees for several division chiefs at BIDMC, Massachusetts General Hospital, and Boston Children's Hospital, and member of the Promotions, Appointments, and Reappointments Committee, HMS.

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. In addition, I 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, 2003-2015; PI: Christiane J. Ferran, MD, PhD

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

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

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

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

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

Da Silva CG, Minussi DC, Ferran C, Bredel M. A20 expressing tumors and anticancer drug resistance. *Adv Exp Med Biol* 2014;809:65-81.

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Ferran C. *The Multiple Therapeutic Targets of A20*, 1st edition. New York: Landes Bioscience and Springer Science+Business Media, LLC; 2014.

Vissapragada R, Contreras MA, da Silva CG, Kumar VA, Ochoa A, Vasudevan A, Selim MH, Ferran C, Thomas AJ. Bidirectional crosstalk between periventricular endothelial cells and neural progenitor cells promotes the formation of a neurovascular unit. *Brain Res* 2014 27;1565:8-17.

Guedes RP, Csizmadia E, Moll HP, Ma A, Ferran C, da Silva CG. A20 deficiency causes spontaneous neuroinflammation in mice. *J Neuroinflammation* 2014;11(1):122.

Moll HP, Lee A, Minussi DC, da Silva CG, Csizmadia E, Bhasin M, Ferran C. A20 regulates atherogenic interferon (IFN)- γ signaling in vascular cells by modulating basal IFN β levels. *J Biol Chem* 2014;289:1-13.

A complete list of publications begins on page 15.



Raul J. Guzman, MD

Associate Professor of Surgery

RESEARCH GROUP

Tonghui Lin, PhD
Susan Wang

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 2013-2014

My lab moved to Boston from our previous home in Nashville, Tenn. in early 2013. Over the past year and a-half, we 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 have entered 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 data set 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 also enjoy teaching in the laboratory and, in particular, enjoy 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 J. Guzman, MD

Methods to reduce vein harvest injury; NIH, 2013-2016; Co-investigator: Raul J. 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.

Frank W. LoGerfo, MD

William V. McDermott Professor of Surgery

Leena Pradhan-Nabzdyk, PhD

Assistant Professor of Surgery



RESEARCH GROUP

Thomas Bodewes, MD
Mauricio Contreras, MD
Aniket Gurav, MS
Joel Johnson
Nurazhani Raof, PhD
Chace Stewart

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 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, Division of Podiatry, using 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 investigating their role in diabetic heart failure as well. In collaboration with Vitaliy Poylin, MD, Division of Colon and Rectal Surgery, Dr. Pradhan-Nabzdyk is also investigating the role of neuropeptides in colorectal diseases including Crohn's disease and ulcerative colitis.

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) and interleukin (IL) -18, 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., the LoGerfo group is developing electrospun (e) prosthetic grafts made of polyethylene terephthalate (PET) polymer to which siRNA could be adsorbed. Their preliminary experiments suggest successful siRNA delivery to a rat carotid artery from the ePET graft. Similarly they have been successful with the direct intraluminal delivery of TSP-2 siRNA in presence of transfection reagent Polyethylimine (PEI).

The diabetic rabbit model developed by Dr. Pradhan-Nabzdyk 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. In another collaboration with David Mooney, PhD, of the Wyss Institute, Dr. Pradhan-Nabzdyk is conducting studies in a diabetic rabbit hindlimb ischemia model to test the therapeutic effect of growth factors encapsulated in alginate gel.

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:

Jack Aguilar (6/2014-8/2014)
Sarah Dougherty (2013-2014)
Joel Johnson (2012-present)
Nurazhani Raof, PhD (2012-present)
David Allen Weiss (2013-2014)

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

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 P, Chun M, Auster M, Nabzdyk C, Deso S, Andersen N, LoGerfo FW, Veves A. Expression of neuropeptides and cytokines in a novel rabbit model of diabetic neuroischemic wound healing. *J Vasc Surg* 2013;58(3):766-75.

Tecilazich F, Dinh T, Pradhan-Nabzdyk L, Leal E, Tellechea A, Kafanas A, Gnardellis C, Magargee ML, Dejam A, Toxavidis V, Tigges JC, Carvalho E, Lyons TE, Veves A. Role of endothelial progenitor cells and inflammatory cytokines in healing of diabetic foot ulcers. *PLoS One* 2013;8(12):e83314.

Nabzdyk CS, Chun MC, Oliver-Allen HS, Pathan SG, Phaneuf MD, You JO, Pradhan-Nabzdyk LK*, LoGerfo FW. Gene silencing in human aortic smooth muscle cells induced by PEI-siRNA complexes released from dip-coated electrospun poly(ethylene terephthalate) grafts. *Biomaterials* 2014;35(9):3071-9.

**Co-Senior Author*

Pradhan-Nabzdyk L, Huang C, LoGerfo FW, Nabzdyk CS. Current siRNA targets in atherosclerosis and aortic aneurysm. *Discov Med* 2014;17(95):233-46.



RESEARCH FOCUS

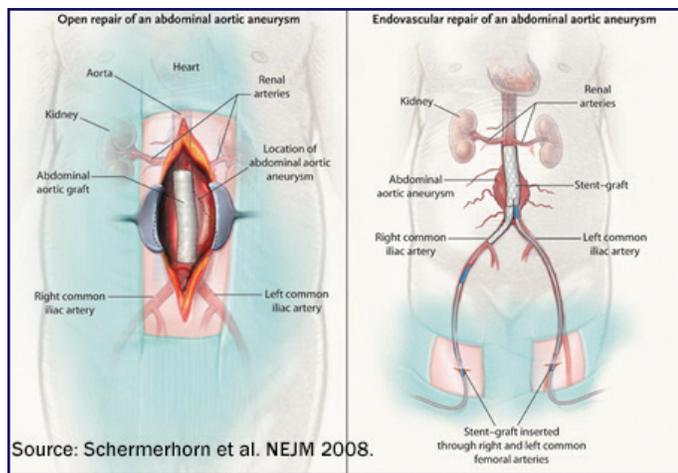
My clinical research group has an active interest in outcomes research in vascular surgery on a local and national level. As the surgical armamentarium evolves to include emerging technologies in a variety of clinical settings, comparative effectiveness research has been instrumental in the identification 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 use 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 regional differences in patient selection, treatment, and outcomes of abdominal aortic aneurysms (AAA), carotid artery stenosis, and peripheral arterial disease (PAD) 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, which has enabled us to study and publish a study on rates and indications for readmission after lower extremity bypass.

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 long-term outcomes and temporal survival trends. We have also demonstrated that late rupture after endovascular repair is a subsisting concern that merits further research. 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.

RESEARCH GROUP

- Dominique Buck, MD
- Thomas Curran, MD
- Jeremy Darling
- James Fitzgerald
- John Hon
- Vanessa Lee
- Nicholas Leonard
- Ruby Lo, MD
- Rishi Mamtani
- John McCallum, MD
- YiFang Meng
- Alexandra Nee
- Peter Soden, MD
- Sara Zettervall, MD



▲ Open repair and endovascular repair of an infrarenal abdominal aortic aneurysm.

ACCOMPLISHMENTS 2013-2014

With 25 peer-reviewed publications and 25 presentations* at national and regional 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 2013 and six presentations in 2014), and the Society for Clinical Vascular Surgery Annual Symposium (seven presentations in 2013 and five presentations in 2014).*

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 fourth year of existence. In addition, we have developed research collaborations with Rotterdam, Amsterdam, and Milan. 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

Zhang JQ, Curran T, McCallum JC, Wang L, Wyers MC, Hamdan AD, Guzman RJ, Schermerhorn ML. Risk factors for readmission after lower extremity bypass in the American College of Surgeons National Surgery Quality Improvement Program. *J Vasc Surg* 2014;59(5):1331-9.

Lo RC, Lu B, Fokkema MT, Conrad M, Patel VI, Fillinger M, Matyal R, Schermerhorn ML; Vascular Study Group of New England. Relative importance of aneurysm diameter and body size for predicting abdominal aortic aneurysm rupture in men and women. *J Vasc Surg* 2014;59(5):1209-16.

Fokkema M, de Borst GJ, Nolan BW, Indes J, Buck DB, Lo RC, Moll FL, Schermerhorn ML; Vascular Study Group of New England. Clinical relevance of cranial nerve injury following carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2014;47(1):2-7.

Lo RC, Bensley RP, Dahlberg SE, Matyal R, Hamdan AD, Wyers M, Chaikof EL, Schermerhorn ML. Presentation, treatment, and outcome differences between men and women undergoing revascularization or amputation for lower extremity peripheral arterial disease. *J Vasc Surg* 2014;59(2):409-18.

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Liang P, Hurks R, Bensley RP, Hamdan A, Wyers M, Chaikof E, Schermerhorn ML. The rise and fall of renal artery angioplasty and stenting in the United States, 1988-2009. *J Vasc Surg* 2013;58(5):1331-8.

A complete list of publications begins on page 15.

Investigators

Arle, Jeffrey	64
Arredouani, Mohamed	98
Arroyo, Jorge	66
Blackburn, George	52
Callery, Mark	54
Chaikof, Elliot	108
Chang, Peter	100
Contreras, Mauricio	110
DeWolf, William	102
Ferran, Christiane	112
Folch, Erik	86
Gangadharan, Sidharta	88
Guzman, Raul	114
Hagen, Susan	56
Hasselgren, Per-Olof	78
Hauser, Carl	34
Heman-Ackah, Selena	68
Jones, Daniel	58
Junger, Wolfgang	36
Kent, Tara	60
Khabbaz, Kamal	42
Lee, Bernard	70
Levitsky, Sidney	44
Lin, Samuel	72
LoGerfo, Frank	116
Majid, Adnan	90
McCully, James	44
Morgentaler, Abraham	104
Moser, A. James	80
Nagle, Deborah	48
Otterbein, Leo	92
Poylin, Vitaliy	50
Pradhan-Nabzdyk, Leena	116
Rodrigue, James	94
Sanchez, Teresa	38
Schermerhorn, Marc	118
Sharma, Ranjna	82
Sun, Lijun	46
Tseng, Jennifer	84
Upton, Joseph	74
Veves, Aristidis	76
Wagner, Andrew	106
Wegiel, Barbara	96
Yaffe, Michael	40
Zhou, Jin-Rong	62



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