Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Roberta and Stephen R. Weiner Department of Surgery

Surgery Research Report

COVER: Getty Images/Westend61

Contents

From the Chair

Innovation and discovery occur at the interface of disciplines—where diverse viewpoints interact, problems are examined from different perspectives, and ideas germinate into new solutions to intractable clinical problems.

The Department of Surgery at Beth Israel Deaconess Medical Center (BIDMC) is committed to fostering innovation and discovery by providing a research environment that nurtures intellectual diversity, embraces individual freedom, encourages flexibility, and promotes spontaneity and originality. By embracing these values, we are able to further our mission to develop more effective approaches to promoting health, preventing illness, and treating or curing disease.

The 2019 issue of our Surgery Research Report highlights research that spans from bench to bedside. Our robust research platform has more than $22 million in funding from the NIH and other federal sources, major philanthropic organizations, and private industry. We conduct laboratory-based investigations that define the molecular basis of disease; develop novel surgical approaches, tools, and devices; and evaluate the effectiveness of clinical interventions on large populations of patients. We also carry out studies that shed light on disparities in the delivery of surgical care or access to treatment for our most vulnerable citizens.

This research has international impact. Our faculty and residents have published hundreds of papers in peer-reviewed scientific journals. Many of our faculty also serve as editors and reviewers for high-impact journals such as *JAMA, The New England Journal of Medicine,* and *Nature,* among others. In addition, they participate in leading medical and scientific organizations.

We are also committed to training and mentoring the next generation of surgeon-investigators—master-surgeons who will change the practice of medicine. We offer both exceptional clinical training in surgery and novel educational opportunities that promote innovative problem finding and problem solving.

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

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

Overview of Surgical Research October 1, 2018–September 30, 2019

Introduction

In addition to delivering outstanding patient care and preparing future leaders in surgery, translational and clinical research constitutes one of the cornerstones of the Department of Surgery at Beth Israel Deaconess Medical Center (BIDMC). Our research programs are focused on six thematic areas:

- Cancer biology
- Glycobiology
- Health services research
- Innate and adaptive immunity
- Nutrition and metabolism
- Regenerative medicine

Important cross-cutting platforms in the Department of Surgery include the Center for Drug Discovery, the Harvard Surgical Program in Innovation (SPIN), Surgical Informatics, and the FIRST (Facilitating Innovative Research and Surgical Trials) Program, which supports clinical research and surgical trials.

All divisions and nearly all faculty members participate in translational or clinical research programs. In FY19, 36 faculty members had funded research programs with dedicated research space, postdoctoral fellows, graduate students, and surgical residents. Many of these programs also include undergraduate and medical students pursuing research electives and fellowships. Additionally, numerous research nurses and clinical coordinators support these research efforts.

Our research initiatives include clinical trials focused on the development and assessment of new drugs and surgical technologies, health services research focused on the development of effective clinical-decision tools, addressing challenges in health inequities and global health, and novel applications of machine learning and recent innovations in the field of data science. Our faculty members are principal investigators of more than 320 open clinical research protocols.

All of the research projects share in common the drive to advance scientific discovery and foster the translation of research into clinical practice to improve the health and well-being of patients. In the process, the Department of Surgery has expanded its clinical research mentorship program for faculty, research fellows, and surgical residents. Our goal to prepare future leaders in American surgery who excel as master clinicians, "own" an important question, and embrace lifelong scholarship remains a core mission of the Department of Surgery.

Leadership

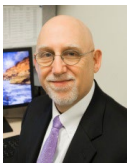
In FY19, research programs in the Department of Surgery were led by Richard D. Cummings, PhD, Vice Chair of Basic and Translational Research; James R. Rodrigue, PhD, Vice Chair of Clinical Research; and Raul Guzman, MD, Vice Chair of Resident Research. In July 2019, Dr. Guzman assumed the position of Chief of Vascular Surgery at Yale New Haven Hospital, and in early 2020 Benjamin C. James, MD, MS, was named Director of Resident Research.

Richard D. Cummings, PhD

Dr. Cummings is the S. Daniel Abraham Professor of Surgery at Harvard Medical School in the field of Nutrition Medicine, Director of the NIH-funded National Center for Functional Glycomics, and Director of the Harvard Medical School Center for Glycoscience, all based in the Department of Surgery. In his roles as the Vice-Chair of Basic and Translational Research, Chair of the Research Council, and Associate Director for Drug Discovery and Translational Research, Dr. Cummings works with faculty to initiate research projects, identify laboratory space and collaborative research resources to assist faculty in their research, and mentor faculty and their fellows in research and advancement at Harvard Medical School.

As Chair of the Surgery Research Council, Dr. Cummings helps lead faculty in promoting research initiatives and identifying ways in which the department and BIDMC can facilitate basic and translational science. Dr. Cummings works closely with Surgery Chair

Elliot Chaikof, MD, PhD, in regularly meeting with faculty, discussing their career and research directions, and helping identify ways to promote faculty development. Dr. Cummings also leads the Feihe Nutrition Laboratory at BIDMC and is Director of the Cancer Glycomics Program within the Cancer Research Institute at BIDMC.



James R. Rodrigue, PhD

Dr. Rodrigue, Professor at Harvard Medical School, oversees the FIRST (Facilitating Innovative Research and Surgical Trials) Program, the Faculty Clinician-Investigator Mentorship Program, and the Clinical Scholarship Program. He also serves as Chair of the Academic Promotions Committee in the Department of Surgery.

Benjamin C. James, MD, MS

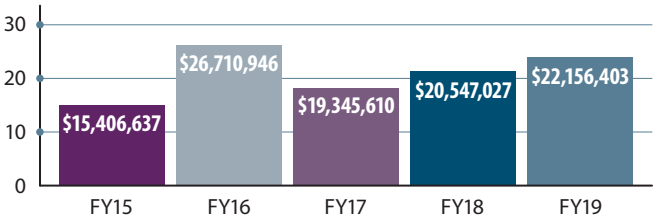
Dr. James is an Assistant Professor of Surgery at Harvard Medical School, Section Chief of Endocrine Surgery in the Division of Surgical Oncology at BIDMC, and Associate Surgery Clerkship Director in the Department of Surgery. In his role as Director of Resident Research, Dr. James oversees resident pre-research advising, resident research mentorship and career development, and the resident and fellow research community.

Research Infrastructure

In FY19, research in the Department of Surgery occupied 26,500 square feet of space, including wet labs, special purpose rooms (cold rooms, tissue culture rooms, microscope rooms, shared equipment rooms), clinical research space, and office space. Research labs and offices are located throughout the BIDMC campus, with wet labs on the eighth floor of the Dana/Research West building on the East Campus, the Center for Life Sciences, Research North, and Stoneman building. Renovated space for clinical research is located in the Deaconess building. The overall dollar density for research space in FY19 was $237 per square foot.

Research Funding

Investigators in the Department of Surgery hold numerous federal awards from the National Institutes of Health (14 R01 grants, 10 R01 subcontracts, and numerous R03, R21, R39, R43/R44, RF1, U01, DP3, P30, P41, UG3, and U39 grants) and from the Department of Defense (U.S. Army grant). Surgery investigators also hold numerous grants from non-profit agencies and industry.



Total research funding in FY19 was more than $22 million (Figure 1), which represents a 7.8% increase from funding levels in FY18. Grant awards showed a broad distribution among divisions within the Department of Surgery (Table 1).

◀ FIGURE 1: Total (federal, non-profit, and industry) research dollars awarded per year during fiscal years (FY) 2015–2019.

▼ TABLE 1. Number of T32, T35, and K training or investigator-initiated research awards and total amount of research funding in FY19, by division.

DIVISION	T32, T35, AND K TRAINING AWARDS	INVESTIGATOR-INITIATED RESEARCH AWARDS	TOTAL AMOUNT OF FUNDING
Acute Care Surgery, Trauma, and Surgical Critical Care	1	6	$2,437,981
Cardiac Surgery		1	$229,485
General Surgery	1	14	$1,456,496
Interdisciplinary Surgery		18	$6,561,702
Neurosurgery		10	$236,331
Plastic and Reconstructive Surgery		4	$181,108
Podiatry		7	$846,753
Surgical Oncology		4	$640,184
Thoracic Surgery and Interventional Pulmonology		17	$351,096
Transplant Surgery		15	$2,019,655
Urologic Surgery		3	$319,647
Vascular and Endovascular Surgery	4	45	$6,870,558

Research Training and Mentored Clinical Scientist Grants

The Department of Surgery continued its longstanding NIH T32 training grant in Vascular Surgery Research (PI: Frank W. LoGerfo, MD) and an NIH T35-funded program directed at providing summer research opportunities for medical students (PI: Frank W. LoGerfo, MD). The NIH-funded T32 training grant in Inflammation and Trauma (PI: Wolfgang G. Junger, PhD) also continued to host research fellows. Investigators in Surgery also 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, Massachusetts General Hospital).

In addition to T32/T35 training grants, the Department of Surgery offers up to five research training grants for residents via the Sandra and Richard Cummings Resident Research Fellowship in Surgery. This fellowship provides a minimum of $25,000 of annual funding to residents in support of an approved research project. In FY19, recipients of these training awards were Gabrielle Cervoni, MD, and Daniel Wong, MD.

Recipients of the Sandra and Richard Cummings Resident Research Fellowship in Surgery in FY19 were (foreground) Gabrielle Cervoni, MD, and Daniel Wong, MD, here with Sandra Cummings and Richard D. Cummings, PhD.

The Department of Surgery was also awarded two Mentored Clinical Scientist awards (NIH-K12) to assist clinical fellows with their transition to becoming independent research investigators. These highly competitive grants were awarded to Jiaxuan Chen, PhD (PI: Elliot L. Chaikof, MD, PhD) and Kathryn Stackhouse, MD (PI: Richard D. Cummings, PhD).

Surgical Residents, Postdoctoral Fellows, and Research

Clinical Scholarship Program

Our Clinical Scholarship Program, directed by James Rodrigue, PhD, pairs all first-year categorical general surgery residents with a faculty research mentor who guides the residents throughout the year as they acquire the skills to develop and implement a clinical research project. Residents are given one month of protected time during the second half of the first year in which to complete their project.

The objectives of the Clinical Scholarship Program are to provide residents with a robust foundation for scholarship early in their training, promote additional clinical mentorship opportunities, and enhance the opportunity to engage in efforts that will ultimately change the way we care for surgical patients. By providing this experience early in the training program, our goal is to facilitate residents' interests in scholarship, research, and an academic career.

Within the structure of the Clinical Scholarship Program, residents meet regularly with research mentor(s), participate in research laboratory 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 Department of Surgery's annual George H. A. Clowes, MD, Surgery Research Symposium and the annual Harvard Medical School Surgery Research Day. In addition, residents are expected to submit abstracts for presentations at conferences, and manuscripts for publication in peer-reviewed scientific journals.

Residents' Research Rotation

Nearly all of our residents pursue a two- or three-year research fellowship in translational or clinical research as part of their surgical training, typically after their second or third clinical years. The residents perform research in basic science laboratories or conduct clinical outcomes research. It is also possible for residents to seek advanced degrees in public health, business administration, or education. We recognize the importance of developing the next generation of surgeon-scientists and are supportive of residents who wish to pursue a PhD during residency training.

An important aspect of a resident's research training is obtaining funding. To assist residents in this effort, the Office for Surgical Research provides a booklet entitled "Funding Sources for Surgical Residents," which describes various funding sources, deadlines, available financial support, and application forms.

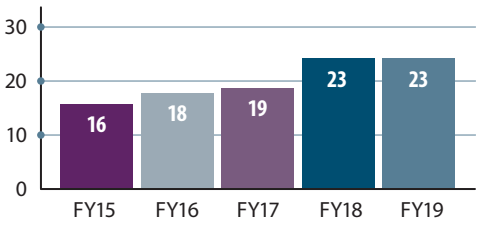


FIGURE 3: Number of surgical residents per fiscal year (FY) spending two to three years in a research elective.

FIRST Program

Clinical research serves as the catalyst for patient care that is innovative, cutting edge, and empirically supported. A robust clinical research infrastructure is necessary to support the myriad tasks associated with clinical research efforts within a complex regulatory environment, including study design and implementation, data collection, and biostatistics and data analysis.

The FIRST (Facilitating Innovative Research and Surgical Trials) Program was established to provide a robust clinical research platform upon which clinical research can be cultivated, nourished, and expanded. Moreover, this program provides the framework necessary for supporting and mentoring the next generation of surgeon-investigators focused on patient-centered research.

Led by James R. Rodrigue, PhD, Vice Chair for Clinical Research, and biostatistician Aaron Fleishman, MPH, Associate Director, the FIRST Program is a comprehensive initiative to:

- Advance scientific discovery and foster the translation of research into clinical practice to improve the lives of patients
- Provide Department of Surgery faculty, fellows, and residents with robust and comprehensive clinical research support
- Employ dedicated clinical research staff with extensive experience in all facets of clinical research conducted in the department
- Consolidate clinical research resources and expertise in the department
- Provide mentorship and guidance to clinical investigators and research staff
- Position the Department of Surgery to compete successfully for industry, federal, and private foundation funding
- Serve as a formal liaison between the department's clinical research programs and regulatory agencies, including the Institutional Review Board, Office of Human Research Protections, Clinical Trials Office, and others

The FIRST Program is staffed by clinical trials specialists, clinical research assistants and coordinators, a research nurse, and a biostatistician. The program offers services that are an essential part of most clinical research programs. These include, but are not limited to, research mentorship, protocol guidance and development, regulatory support, industry engagement, biostatistics support, study coordination, data collection and analysis, and grant application preparation and review.

Recently in the *Journal of Surgical Research*, the FIRST leadership described the development and outcomes of this program, which include high utilization of its services across all divisions, a substantial increase in new clinical research protocols, increased applications submitted to funding agencies, and a high level of user satisfaction.

Research-focused Events and Seminars

George H. A. Clowes, MD, Visiting Professor Research Symposium

The George H. A. Clowes, MD, Visiting Professor of Surgical Research in FY19 was Ronald Weigel, MD, PhD, MBA, EA Crowell Jr. Professor and Chair of the Department of Surgery at the University of Iowa. Events during Dr. Weigel's visit included a Research Symposium, with abstracts submitted by research trainees in the Department of Surgery, including postdoctoral research fellows; clinical residents; residents on a research rotation; and medical, graduate, and undergraduate students working in research labs in the Department of Surgery. Peer-review grading by Dr. Weigel and faculty of the Department of Surgery identified five basic science and four clinical abstracts selected for oral presentation, listed below:

Basic Science

Giacomo Canesin, PhD
"Hemopexin is a Suppressor of Heme-Driven Cancer"
Mentor: Barbara Wegiel, PhD, MSc

Chun Li, MD
"Differential Post-Translational Glycosylation of Proteins in Papillary Thyroid Cancer"
Mentor: Benjamin C. James, MD, MS

Kathryn Stackhouse, MD
"Tumor-Associated Glycans are Diagnostic Predictors of High-Grade Dysplasia and Malignancy in Intraductal Papillary Mucinous Neoplasms of the Pancreas"
Mentor: Richard D. Cummings, PhD

Georgios Theocharidis, PhD
"Epidermal Stem Cell Derived Exosomes Improve Impaired Diabetic Wound Healing through Modulation of Macrophage Polarization"
Mentor: Aristidis Veves, MD, DSc

Quanzhi Zhang, MS
"Inhibition of Mitochondrial Formyl Peptide Interactions with Formyl Peptide Receptor-1 by Cyclosporin H Can Prevent Nosocomial Pneumonia after Trauma"
Mentors: Carl J. Hauser, MD, and Kiyoshi Itagaki, PhD

Clinical Research

Daniel Buitrago, MD
"Tracheobronchoplasty Provides Long-Term Anatomic, Functional, and Subjective Benefit for Patients with Severe, Diffuse Tracheobronchomalacia"
Mentor: Sidharta P. Gangadharan, MD, MHCM

Carlos A. Cordova-Cassia, MD
"Role of Antiplatelet and Statin Therapy in Patients with Cerebral Cavernous Malformations"
Mentors: Ajith J. Thomas, MD, and Christopher S. Ogilvy, MD

Nicholas G. Cuccolo, BS
"Reconstruction of the External Ear for Congenital Microtia and Anotia: An Analysis of Practitioner Epidemiology and Postoperative Outcomes"
Mentor: Samuel J. Lin, MD

Santiago Gomez-Paz, MD
"Combined Antiplatelet and Statin Therapy among Patients with a Cerebral Cavernous Malformation: Symptomatic Hemorrhage Assessment"
Mentors: Ajith J. Thomas, MD, and Christopher S. Ogilvy, MD

Surgical Horizons Seminar Series

Held monthly throughout the academic year, Surgical Horizons is the major seminar series for basic research in the Department of Surgery. The seminars host emerging and senior leaders from both surgical and non-surgical disciplines—including those who work in the engineering, physical, and social sciences—whose endeavors promise to dramatically alter the landscape of care for surgical patients.

October 19, 2018	**Mehmet Toner, PhD** Helen Andrus Benedict Professor of Surgery, Harvard Medical School Co-Director, Institute for Bioengineering and Biotechnology, Massachusetts General Hospital "Bioengineering and Clinical Applications of Circulating Tumor Cells"
November 30, 2018	**Samir Mitragotri, PhD** Hiller Professor of Bioengineering, and Hansjorg Wyss Professor of Biologically-Inspired Engineering, Harvard University "Overcoming Biological Barriers for Drug Delivery"
December 14, 2018	**Lynn Bry, MD, PhD** Associate Professor of Pathology, Harvard Medical School Director, Massachusetts Host Microbiome Center "Clinical Applications of the Microbiome"
January 18, 2019	**Sekar Kathiresan, MD** Associate Professor of Medicine, Harvard Medical School Director of the Center for Genomic Medicine at Massachusetts General Hospital Institute Member, Broad Institute of MIT and Harvard "Genetics of Myocardial Infarction"

February 22, 2019

Ali Tavakkoli, MD
Associate Professor of Surgery, Harvard Medical School
Co-Director of the Center for Weight Management and Metabolic Surgery, Brigham and Women's Hospital
"Bariatric Surgical Research: Understanding the Science to Make Surgery Even Better"

March 22, 2019

James R. Rodrigue, PhD
Professor, Harvard Medical School
Vice Chair of Clinical Research, Department of Surgery, Beth Israel Deaconess Medical Center
"From Identifying to Mitigating Disparities in Surgical Access and Outcomes: A Call to Action"

April 26, 2019

Gad A. Getz, PhD
Professor of Pathology, Harvard Medical School
Director, Cancer Genome Computational Analysis, Broad Institute of MIT and Harvard
Director, Bioinformatics Program, Massachusetts General Hospital Cancer Center
"Studying Resistance in Cancer"

May 17, 2019

Clary B. Clish, PhD
Senior Director, Metabolite Profiling, Institute Scientist, Broad Institute of MIT and Harvard
"Application of Metabolomics to Find Early Indicators of Disease and Explore Associations with the Microbiome"

June 21, 2019

Arlene H. Sharpe, MD, PhD
George Fabyan Professor of Comparative Pathology, Microbiology, and Immunobiology, Harvard Medical School
Co-Chair, Microbiology and Immunology, Co-Director, Evergrande Center for Immunologic Diseases, Harvard Medical School
"Biology of PD-1 Checkpoint Blockade"

FIRST Program Seminars

The FIRST Program (see page 8) also hosts seminars throughout the academic year.

October 9, 2018

Rens Varkevisser
Research Intern, Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center
"Fenestrated EVAR is Associated with Lower Perioperative Morbidity and Mortality Compared to Open Repair for Complex Abdominal Aortic Aneurysms"

James R. Rodrigue, PhD
Vice Chair of Clinical Research, Department of Surgery, Beth Israel Deaconess Medical Center
Professor, Harvard Medical School
"Genetic Testing for Non-diabetic Nephropathy (apolipoprotein L1 gene): Attitudes of African-American Transplant Patients, Living Donors, and Non-patients/Non-donors"

October 23, 2018

Gabriel Brat, MD, MPH, MSc
Division of Acute Care Surgery, Trauma, and Surgical Critical Care, Beth Israel Deaconess Medical Center
Assistant Professor of Surgery, Harvard Medical School
"Surgery and Opioids: Lessons from 6200 Patients"

November 11, 2018

Benjamin C. James, MD, MS
Chief of Endocrine Surgery, Division of Surgical Oncology, Beth Israel Deaconess Medical Center
Assistant Professor of Surgery, Harvard Medical School
"Discussion of the Research Program in Endocrine Surgery"

November 27, 2018

Marc L. Schermerhorn, MD
Chief of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center
George H. A. Clowes, Jr. Professor of Surgery, Harvard Medical School
"Discussion of the Research Program in Vascular Surgery"

December 11, 2018

Dhruv Singhal, MD
Director, BIDMC Lymphatic Center, Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center
Associate Professor of Surgery, Harvard Medical School

Anna Rose Johnson, MPH
Research Student Intern, Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center
"Reflections on the Development of a Lymphedema Research Program"

February 12, 2019

Elliot L. Chaikof, MD, PhD
Chair, Department of Surgery, Beth Israel Deaconess Medical Center
Johnson and Johnson Professor of Surgery, Harvard Medical School
"Anatomy of an Academic Career: Research Q & A with the Chair"

April 9, 2019

Aaron Fleishman, MPH
Associate Director and biostatistician, FIRST Program, Department of Surgery, Beth Israel Deaconess Medical Center
"Common Statistical Issues in Surgical Clinical Research"

National and International Impact

Faculty members in the Department of Surgery have a national and international impact through their research published in many high-impact journals, such as *New England Journal of Medicine, Nature Medicine, Gastroenterology, Nature Communications, JAMA Surgery, Cancer Research, FASEB Journal,* and the *American Journal of Clinical Nutrition* (see Bibliography, page 15). In addition, our faculty members have published books and textbooks that influence surgical practice (see page 13). Members of our faculty also hold leadership positions in influential medical societies and serve as editors or on editorial boards of national and international journals (see page 14).

Leadership Positions

Jeffrey Arle, MD, PhD
Appointed Co-Chair, Research and Scientific Policy Committee, International Neuromodulation Society
Appointed Board member, International Society of Intraoperative Neurophysiology

Gabriel Brat, MD, MPH, MSc
Member, Technology and Communications Committee, Association for Academic Surgery

Mark P. Callery, MD
President, Society for Surgery of the Alimentary Tract (SSAT)
Incoming Chair, SSAT Board of Trustees
President, Americas Hepato-Pancreato-Biliary Association (AHPBA) Foundation

Elliot L. Chaikof, MD, PhD
Chair, Section 1, National Academy of Medicine (one of 12 standing NAM committees)
Co-Chair, Health and Technology Interest Group (IG18), National Academy of Medicine
Member, Committee on Emerging Science, Technology, and Innovation in Health and Medicine, National Academy of Medicine
Recipient, American Surgical Association 2019 Flance-Karl Award

Alex Chee, MD
Appointed Chair, Fundraising Committee, World Association of Bronchology and Interventional Pulmonology

Richard D. Cummings, PhD
Received NIH grant (with Elliot Chaikof, MD, PhD) to support the Harvard Program in Translational Glycobiology Career Development (ProTG), serving as Co-Director with Dr. Chaikof
Received 2019 IGO Award from International Glycoconjugate Organization (IGO)
Appointed as S. Daniel Abraham Professor of Surgery at Harvard Medical School

Thanh Dinh, DPM
Elected Secretary-Treasurer, American College of Foot and Ankle Surgeons

Amy Evenson, MD, MPH
Inducted as Associate Member, American College of Surgeons Academy of Master Surgeon Educators

Christiane Ferran, MD, PhD
Elected as Member, Harvard Medical School Faculty Council

Sidharta P. Gangadharan, MD, MHCM
Appointed to Board of Advisors, Geisel School of Medicine at Dartmouth

Boris Gershman, MD
Appointed as reviewer for American Urological Association (AUA) Guidelines on the Diagnosis and Treatment of Early Stage Testicular Cancer
Appointed as Member, Program Committee, New England section of the American Urological Association

Ernest (Ted) Gomez, MD, MTR
Elected to Administrative Board, American Association of Medical Colleges Organization of Resident Representatives

Benjamin C. James, MD, MS
Elected to Research Committee, American Association of Endocrine Surgeons
Named Director of Resident Research, BIDMC Surgery

Ted A. James, MD, MHCM
Selected to participate in Emerging Leaders in Health and Medicine Forum, National Academy of Medicine

Daniel B. Jones, MD, MS
Trustee-at-Large, Society for Surgery of the Alimentary Tract (SSAT)
Elected as Honorary Member, Peruvian Society of Laparoscopic Surgery
Nominated for 2019 Excellence in Mentoring Award, Harvard Medical School
Honorary Member, Korean Society of Endoscopic and Laparoscopic Surgeons

Tara S. Kent, MD, MS
Inducted as Associate Member, American College of Surgeons Academy of Master Surgeon Educators

Ruslan Korets, MD
Elected to the Judicial and Ethics Committee, New England section of the American Urological Association

Bernard T. Lee, MD, MBA, MPH
Elected as Director, American Board of Plastic Surgery
Elected as Member, Harvard Medical School Faculty Council
Treasurer, American Society for Reconstructive Microsurgery
Appointed, Harvard Alumni Association Board of Directors

Frank W. LoGerfo, MD
Recipient of the Society for Vascular Surgery award for exemplary achievements and mentoring

Adnan Majid, MD
Recipient of the Interventional Pulmonology Educator Award from the Association of Interventional Pulmonology Educators
Elected to Board of Directors, American Association for Bronchology and Interventional Pulmonology

Aria F. Olumi, MD
Obtained ACGME approval for independent urology residency training program: Beth Israel Deaconess/Harvard Medical School Urology Program
State-of-the-Art Speaker, New England section of the American Urological Association annual meeting

James R. Rodrigue, PhD
Elected to Board of Directors, American Society of Transplantation
Appointed to Living Donor Committee, American Society of Transplantation

Barry Rosenblum, DPM
Received 2019 Distinguished Service Award from American College of Foot and Ankle Surgeons

Marc L. Schermerhorn, MD
President, New England Society for Vascular Surgery
Executive and Research Advisory Committee, Vascular Study Group of New England
Executive and Research Advisory Committee, Vascular Quality Initiative
Appointed as George H. A. Clowes Jr. Professor of Surgery at Harvard Medical School

Dhruv Singhal, MD
Named Director, BIDMC Lymphatic Center

Martina Stippler, MD
Named BIDMC Site Principal Investigator for BOOST-3 multicenter clinical trial funded by the NIH (only Boston hospital)
Inducted as a Fellow of the American College of Surgeons (FACS)
Selected for a 2019-2020 Rabkin Fellowship in Medical Education
Elected to Board of Directors, ThinkFirst, and established BIDMC ThinkFirst chapter

Ajith J. Thomas, MD
Awarded 2018 Brain Aneurysm Foundation Physician Champion Award
Selected to participate in Emerging Leaders in Health and Medicine Forum, National Academy of Medicine

Nurhan Torun, MD
Guest of Honor, 52nd National Congress, Turkish Ophthalmological Association

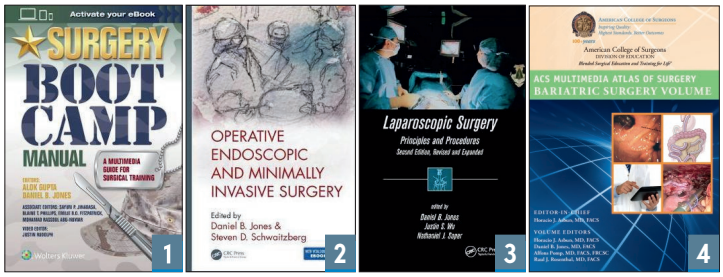
Richard Whyte, MD, MBA
President, Western Thoracic Surgical Association

Jennifer L. Wilson, MD
Inducted as a Fellow of the American College of Surgeons (FACS)

Michael B. Yaffe, MD, PhD
Recipient of Massachusetts Institute of Technology Teaching with Digital Technology Award
One of eight investigators nationally to win the Revolutionizing Innovative Visionary Environmental Health Research (RIVER) award from the National Institutes of Health
Appointed Director, Massachusetts Institute of Technology Center for Precision Cancer Medicine

Books

1. Alok Gupta, Daniel B. Jones, Editors; Blaine T. Phillips, Emilie Fitzpatrick, Rassoul A. Abu-Nuwar, Associate Editors. *Surgery Boot Camp Manual: A Multimedia Guide for Surgical Training*. Wolters Kluwer, 2019.
2. Daniel B. Jones, Steven D. Schwaitzberg, Editors. *Operative Endoscopy and Minimally Invasive Surgery*. CRC Press, 2019.
3. Daniel B. Jones, Justin S. Wu, Nathaniel J. Soper, Editors. *Laparoscopic Surgery: Principles and Procedures*, Second Edition. CRC Press, 2019.
4. Horacio J. Asbun, Daniel B. Jones, Alfons Pomp, Raul J. Rosenthal, Volume Editors; Horacio J. Asbun, Editor-in-Chief. American College of Surgeons (ACS) *Multimedia Atlas of Surgery: Bariatric Surgery Volume.* Ciné-Med, 2019.
5. O. Yusef Kudsi, Alfredo M. Carbonell, Anusak Yiengpruksawan, Daniel B. Jones, Editors. *Atlas of Robotic Surgery.* Ciné-Med, 2019.
6. Daniel B. Jones, Editor. *Pocket Surgery*, Second Edition. Wolters Kluwer, 2018.
7. Aristidis Veves, John Giurini, Raul Guzman, Editors. *The Diabetic Foot: Medical and Surgical Management*, 4th edition. Humana Press, 2018.



Editors

- *Frontiers in Biosciences*: Jin-Rong Zhou, PhD, Editor
- *HPB*: Tara S. Kent, MD, MS, Associate Editor
- *Integrative Oncology and Rehabilitation*: Jin-Rong Zhou, PhD, Associate Editor
- *Journal of Health Sciences*: Jin-Rong Zhou, PhD, Editor-in-Chief
- *Journal of Reconstructive Microsurgery*: Bernard T. Lee, MD, MBA, MPH, Editor-in-Chief; Samuel J. Lin, MD, Associate Editor
- *Neuromodulation*: Jeffrey Arle, MD, PhD, Associate Editor
- *Neurosurgery*: Jeffrey Arle, MD, PhD, Associate Editor
- *Nutrition and Metabolic Insights*: Jin-Rong Zhou, PhD, Editor-in-Chief
- *Plastic and Reconstructive Surgery*: Samuel J. Lin, MD, Associate Editor and Outcomes Section Editor
- *Plastic and Reconstructive Surgery-Global Open*: Samuel J. Lin, MD, Associate Editor
- *Purinergic Signalling*: Wolfgang G. Junger, PhD, Associate Editor
- *Science Signaling*: Michael B. Yaffe, MD, PhD, Chief Scientific Advisor and Academic Editor

Editorial Board Members

- *Annals of Plastic Surgery*: Bernard T. Lee, MD, MBA, MPH
- *Archives of Plastic Surgery*: Bernard T. Lee, MD, MBA, MPH
- *Bariatric Times*: Daniel B. Jones, MD, MS
- *Biomolecules*: Richard D. Cummings, PhD
- *Cardiothoracic and Vascular Anesthesia*: Kamal Khabbaz, MD
- *Digital Chinese Medicine*: Jin-Rong Zhou, PhD
- *Diseases of the Colon and Rectum*: Evangelos Messaris, MD, PhD
- *e-Plasty*: Bernard T. Lee, MD, MBA, MPH
- *Glycobiology*: Richard D. Cummings, PhD
- *Glycoconjugate Journal*: Richard D. Cummings, PhD
- *Health*: Jin-Rong Zhou, PhD
- *Hepatobiliary Surgery and Nutrition*: Jin-Rong Zhou, PhD
- *International Journal of Carbohydrate Chemistry*: Richard D. Cummings, PhD
- *International Journal of Microsurgery*: Dhruv Singhal, MD
- *International Journal of Tropical Disease & Health*: Jin-Rong Zhou, PhD
- *Journal of Cardiothoracic and Vascular Anesthesia*: Kamal Khabbaz, MD
- *Journal of Disease and Global Health*: Jin-Rong Zhou, PhD
- *Journal of Foot and Ankle Surgery*: Barry Rosenblum, DPM
- *Journal of Gastrointestinal Surgery*: Tara S. Kent, MD, MS
- *Journal of Genetic, Molecular and Cellular Biology*: Jin-Rong Zhou, PhD
- *Journal of Plastic, Reconstructive, & Aesthetic Surgery*: Bernard T. Lee, MD, MBA, MPH
- *Journal of Surgical Education*: Tara S. Kent, MD, MS
- *Journal of Surgical Research*: Benjamin C. James, MD, MS
- *Journal of Thoracic Disease*: Sidharta P. Gangadharan, MD, MHCM; Alex CM. Chee, MD
- *Molecular and Cellular Proteomics*: Richard D. Cummings, PhD
- *Nature Scientific Reports*: Richard D. Cummings, PhD
- *Neurosurgery*: Christopher S. Ogilvy, MD
- *Scientific Report*: Richard D. Cummings, PhD
- *Shock*: Wolfgang G. Junger, PhD
- *Single Cell Biology*: Jin-Rong Zhou, PhD
- *Surgery for Obesity and Related Diseases*: Daniel B. Jones, MD, MS
- *Tissue Barriers*: Susan J. Hagen, PhD
- *UpToDate*: Daniel B. Jones, MD, MS
- *World Journal of Clinical Oncology*: Jin-Rong Zhou, PhD
- *World Journal of Otolaryngology-Head and Neck Surgery*: James G. Naples, MD

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Swerdlow NJ, Wu WW, Schermerhorn ML. Open and endovascular management of aortic aneurysms. Circ Res 2019;124(4):647-61.

Ultee KHJ, Büttner S, Huurman R, Bastos Gonçalves F, Hoeks SE, Bramer WM, **Schermerhorn ML**, Verhagen HJM. Editor's choice - Systematic review and meta-analysis of the outcome of treatment for type II endoleak following endovascular aneurysm repair. Eur J Vasc Endovasc Surg 2018;56(6):794-807.

Van Orden K, Farber A, **Schermerhorn ML**, Goodney PP, Kalish JA, Jones DW, Rybin D, Siracuse JJ; Vascular Quality Initiative. Local anesthesia for percutaneous endovascular abdominal aortic aneurysm repair is associated with fewer pulmonary complications. J Vasc Surg 2018;68(4):1023-9.

Varkevisser RRB, O'Donnell TFX, Swerdlow NJ, Liang P, Li C, Ultee KHJ, **Pothof AB, De Guerre LEVM**, Verhagen HJM, **Schermerhorn ML**. Fenestrated endovascular aneurysm repair is associated with lower perioperative morbidity and mortality compared with open repair for complex abdominal aortic aneurysms. J Vasc Surg 2019;69(6):1670-8.

Wu WW, Liang P, O'Donnell TFX, Swerdlow NJ, Li C, Wyers MC, Schermerhorn ML. Anatomic eligibility for transcarotid artery revascularization and transfemoral carotid artery stenting. J Vasc Surg 2019;69(5):1452-60.

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In press papers:

Columbo JA, Martinez-Camblor P, O'Malley AJ, Suckow BD, Hoel AW, Stone DH, Schanzer A, **Schermerhorn ML**, Sedrakyan A, Goodney PP; Society for Vascular Surgery's Vascular Quality Initiative. Long-term reintervention after endovascular abdominal aortic aneurysm repair. Ann Surg 2019; in press.

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Deery SE, Zettervall SL, O'Donnell TFX, Goodney PP, Weaver FA, Teixeira PG, Patel VI, **Schermerhorn ML**. Transabdominal open abdominal aortic aneurysm repair is associated with higher rates of late reintervention and readmission compared with the retroperitoneal approach. J Vasc Surg 2019; in press.

de Guerre LEVM, Varkevisser RRB, Swerdlow NJ, Liang P, Li C, Dansey K, van Herwaarden JA, **Schermerhorn ML**. Sex differences in perioperative outcomes after complex abdominal aortic aneurysm repair. J Vasc Surg 2019; in press.

Fairman AS, Beck AW, Malas MB, Goodney PP, Osborne NH, **Schermerhorn ML, Wang GJ**. Reinterventions in the modern era of thoracic endovascular aortic repair. J Vasc Surg 2019; in press.

Jones DW, Deery SE, Schneider DB, Rybin DV, Siracuse JJ, Farber A, **Schermerhorn ML**; Vascular Quality Initiative. Differences in patient selection and outcomes based on abdominal aortic aneurysm diameter thresholds in the Vascular Quality Initiative. J Vasc Surg 2019; in press.

Liang P, O'Donnell TFX, Swerdlow NJ, Li C, Lee A, Wyers MC, Hamdan AD, Schermerhorn ML. Preoperative risk score for access site failure in ultrasound-guided percutaneous aortic procedures. J Vasc Surg 2019; in press.

Locham S, Shaaban A, Wang L, Bandyk D, **Schermerhorn M**, Malas MD. Impact of gender on outcomes following abdominal aortic aneurysm repair. Vasc Endovascular Surg 2019; in press

Mohapatra A, Liang NL, Makaroun MS, **Schermerhorn ML**, Farber A, Eslami MH. Risk factors for mortality after endovascular repair for blunt thoracic aortic injury. J Vasc Surg 2019; in press.

O'Donnell TFX, Boitano LT, Deery SE, Lancaster RT, Siracuse JJ, **Schermerhorn ML**, Scali ST, Patel VI. Hospital volume matters: The volume-outcome relationship in open juxtarenal AAA repair. Ann Surg 2018; in press.

O'Donnell TFX, Boitano LT, Deery SE, **Schermerhorn ML**, Schanzer A, Beck AW, Green RM, Takayama H, Patel VI. Open versus fenestrated endovascular repair of complex abdominal aortic aneurysms. Ann Surg 2019; in press.

O'Donnell TFX, Verhagen HJ, Pratesi G, Pratesi C, Teijink JAW, Vermassen FEG, Mwipatayi P, Forbes TL, **Schermerhorn ML**. Female sex is associated with comparable 5-year outcomes after contemporary endovascular aneurysm repair despite more challenging anatomy. J Vasc Surg 2019; in press.

Rao V, Liang P, Swerdlow N, Li C, Solomon Y, Wyers M, Schermerhorn M. Contemporary outcomes after carotid endarterectomy in high-risk anatomic and physiologic patients. J Vasc Surg 2019; in press.

Schermerhorn ML, Liang P, Dakour-Aridi H, Kashyap VS, Wang GJ, Nolan BW, Cronenwett JL, Eldrup-Jorgensen J, Malas MB. In-hospital outcomes of transcarotid artery revascularization and carotid endarterectomy in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg 2019; in press.

Shalhub S, Byers PH, Hicks KL, Charlton-Ouw K, Zarkowsky D, Coleman DM, Davis FM, Regalado ES, De Caridi G, Weaver KN, Miller EM, **Schermerhorn ML, Shean K**, Oderich G, Ribeiro M, Nishikawa C, Behrendt CA, Debus ES, von Kodolitsch Y, Powell RJ, Pepin M, Milewicz DM, Lawrence PF, Woo K. A multi-institutional experience in the aortic and arterial pathology in individuals with genetically confirmed vascular Ehlers-Danlos syndrome. J Vasc Surg 2019; in press.

Swerdlow NJ, Lyden SP, Verhagen HJM, **Schermerhorn ML**. Five-year results of endovascular abdominal aortic aneurysm repair with the Ovation abdominal stent graft. J Vasc Surg 2019; in press.

Swerdlow NJ, Varkevisser RRB, Soden PA, Zettervall SL, McCallum JC, Li C, Wyers MC, Schermerhorn ML. Thirty-day outcomes after open revascularization for acute mesenteric ischemia from the American College of Surgeons National Surgical Quality Improvement Program. Ann Vasc Surg 2019; in press.

Varkevisser RRB, O'Donnell TFX, Swerdlow NJ, Liang P, Li C, Ultee KHJ, Patel VI, Scali ST, Verhagen HJM, **Schermerhorn ML**, Society for Vascular Surgery Vascular Quality Initiative. Factors associated with in-hospital complications and long-term implications of these complications in elderly patients undergoing endovascular aneurysm repair. J Vasc Surg 2019; in press.

Acute Care Surgery, Trauma, and Surgical Critical Care

RESEARCH GROUP

Michael Dombek, MD
Thomas Marandu, PhD

Charles Cook, MD

Associate Professor of Surgery
Chief, Acute Care Surgery, Trauma, and Surgical Critical Care

RESEARCH FOCUS

Most people are infected with multiple herpes family viruses. Unlike many viral infections, these viruses are not eradicated from the host, but become dormant in the host's tissues for their lifetime. During periods of immune compromise or stress, these viruses can reactivate. It is understood that herpes family viral reactivation is pathologic in immunocompromised people, such as transplant recipients or AIDS patients. My laboratory has been focused on defining the impact that these persistent viral infections have on immune-competent hosts.

During the past 20 years, we and others have confirmed that these viruses can reactivate during critical illness. Of the family, cytomegalovirus (CMV) reactivation has been associated with worsened outcomes. My laboratory spent our early years of funding defining mechanisms by which CMV reactivation might be triggered using murine models to test our hypotheses. This transitioned to understanding the consequences of such reactivations; specifically how CMV reactivation might harm an immune competent host.

We identified the lungs as a potential target for CMV reactivation, and showed that reactivation is associated with lung injury during bacterial sepsis, something that we named CMV-ALI (cytomegalovirus associated acute lung injury). Clinical outcomes support this hypothesis, with roughly doubled durations of mechanical ventilation required for patients with CMV reactivation. Perhaps most importantly, our work showed that such reactivation events (and their attendant lung injury) can be prevented by antiviral prophylaxis. These results have been foundational to several clinical trials (two completed, one ongoing) that are beginning to corroborate these experimental observations.

Our current focus is to try to understand the mechanism of CMV-ALI. CMV infection/latency makes a lasting imprint in the immunity of its host, leaving CMV-latent hosts with exaggerated immune potential in their lungs. This means that when they encounter bacterial infections (like pneumonia or sepsis) they are more prone to inflammation and lung injury. We are currently evaluating different immune cell populations to understand their individual contributions to CMV-ALI. Our most recent work, done in collaboration with Drs. Carl Hauser, Michael Yaffe, Leo Otterbein, and the HALO group at BIDMC, suggests that neutrophils may play a pivotal role in these exaggerated immune responses.

Because we have a robust understanding of CMV biology and have an animal model, we have been fortunate to develop numerous collaborations with colleagues in overlapping fields. We are currently supported for work with Dr. Antonio Chiocca's group at Brigham and Women's Hospital, studying the interactions between CMV and glioblastoma. Our current results have confirmed a contributory role of CMV to progression of this deadly brain tumor. More importantly, we are defining mechanistic pathways that should lead to novel therapies. We have also begun early collaborations with Dr. Richard Cummings at BIDMC to understand how CMV infection impacts cellular protein glycosylation.

ACCOMPLISHMENTS 2018-2019

Invited Lectures:

- Surgical Infections: We Need to Start Thinking Differently. Department of Surgery Grand Rounds, Mount Auburn Hospital, Cambridge, MA
- Surgical Infections: We Need to Think Differently, Department of Surgery Grand Rounds, Beth Israel Deaconess Medical Center, Boston, MA
- Cytomegalovirus as Vaccine Vector: Pre-Existing Immunity and Reinfections. Visiting Professor, Helmholtz Zentrum für Infektionsforschung, Braunschweig, Germany
- Impact of CMV on Host Response to Sepsis. 7th International Workshop on Cytomegalovirus and Immunosenescence, Mainz, Germany
- CMV Reactivation in Immunocompetent Hosts. Keynote Lecture, 17th International CMV Workshop, Birmingham, AL
- Cytomegalovirus during Critical Illness: Everything You Need to Know But Never Thought to Ask. Massachusetts General Hospital, Boston, MA
- Neutrophil Activation during Chronic CMV Infection, CMV/Cancer Meeting, Boston, MA
- Operative Fixation for Rib Fractures: Con. Harvard Trauma and Critical Care Symposium, Boston, MA

TEACHING, TRAINING, AND EDUCATION

Thomas Marandu, PhD, successfully completed his postdoctoral training in my laboratory in 2019 and returned to his academic position in Tanzania. Michael Dombek, MD, is pursuing postdoctoral training in 2018-2020.

SELECTED RESEARCH SUPPORT

Investigating the cytomegalovirus link to glioblastoma using a novel mouse model; NIH, 2015-2020; Co-Investigator: Charles Cook, MD

SELECTED PUBLICATIONS

Kaczmarek E, Hauser CJ, Kwon WY, Riça I, Chen L, Sandler N, Otterbein LE, Campbell Y, Cook CH, Yaffe MB, Marusich MF, Itagaki K. A subset of five human mitochondrial formyl peptides mimics bacterial peptides and functionally deactivates human neutrophils. J Trauma Acute Care Surgery 2018;85(5):936-43.

Mansfield SA, Dwivedi V, Elgharably H, Griessl M, Zimmerman PD, Limaye AP, Cook CH. Cytomegalovirus immunoglobulin G titers do not predict reactivation risk in immunocompetent hosts. J Med Virol 2019;91(5):836-44.

Krenzlin H, Behera P, Lorenz V, Passaro C, Zdioruk M, Nowicki MO, Grauwet K, Zhang H, Skubal M, Ito H, Zane R, Gutknecht M, Griessl MB, Ricklefs F, Ding L, Peled S, Rooj A, James CD, Cobbs CS, Cook CH, Chiocca EA, Lawler SE. Cytomegalovirus promotes murine glioblastoma growth via pericyte recruitment and angiogenesis. J Clin Invest 2019;130:1671-83.

A complete list of publications begins on page 15.

Acute Care Surgery, Trauma, and Surgical Critical Care

RESEARCH GROUP

Kiyoshi Itagaki, PhD
Barbora Konecna, PhD
Jimbong Park, MD

Carl J. Hauser, MD

Lecturer on Surgery
Trauma Medical Director

RESEARCH FOCUS

The major basic science research focus of our 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 2,000 times. Important known mitochondrial DAMPs include mitochondrial DNA, formyl peptides, mitochondrial lipids, ATP, and heme. Our recent work has shown that mitochondrial formyl peptides act as potent DAMPs. They circulate in plasma after injury where they activate innate immune cells while simultaneously causing heterologous suppression of cell-surface G-protein coupled receptors for critically important chemoattractants like chemokines and leukotrienes. Thus they are both innate immune chemoattractant-activators and immune modulators. Mitochondrial (mt)DNA is also a potent agonist that targets toll-like receptor 9 (TLR-9). We have shown mtDNA 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 (mtFPs) are 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 compete for the immune system's "attention" in systemically injured patients. In work presented at the 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 participated in the development of novel antagonists for the human and mouse formal peptide receptors (FPRs) we are doing studies that use this information to create tools for diagnosis and therapeutic intervention. Most recently, we have shown that immune suppression by formal peptides is specifically the result of FPR-1 receptor engagement. Current studies with knockout mice will be used to describe this effect more completely.

Our current work, therefore, centers on modulating inflammation in a way that balances the need for inflammation after injury as an initiator of tissue repair and the susceptibility to infection that systemic inflammation incurs. Molecular aspects of these problems that we study (and which participants can become expert in) include neutrophil signaling, chemokine biology (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 laboratories of Leo Otterbein, PhD, Wolfgang Junger, PhD, and Simon Robson MD, PhD.

For the last three years we have been funded by the Department of Defense to perform a "focused program award" that addresses the role of DAMPs in creating susceptibility of wounded war-fighters to infection. This multi-PI grant includes work with the laboratories of Leo Otterbein, PhD, Michael Yaffe, MD, PhD, Simon Robson, MD, PhD, James Lederer, PhD, and Daniel Talmor, MD. These labs have grouped together as the Harvard-Longwood ("HALO") consortium for translational biology. This collaborative program uses computational biology to address the interactive rolls of DAMPs like formyl peptides, mitochondrial DNA, heme, carbon

monoxide, purine metabolites (ATP and adenosine), reactive oxygen intermediates, complement, with the changing physical-chemical environment of the lung over time to result in altered innate immune cellular phenotypes. These are then permissive of health care-acquired pneumonia.

ACCOMPLISHMENTS 2018-2019

- Medical Director of Trauma Services, BIDMC
- Led the Harvard Longwood (HALO) consortium for translational inflammation biology
- Immediate Past President of the Western Trauma Association

Visiting Professorships and Invited Presentations

- Activation of Critical Inflammation by Mitochondrial DAMPs. Queen Mary Hospital Trauma Science Colloquium, London, England
- Visiting Professor, BioLab instructor, University of Aachen, Aachen, Germany
- Grunenthal Trial Board for "FLIX" bioglue. Brussels, Belgium
- Department of Defense PRMRP FY15 FPA Milestone Meeting, Falls Church, VA
- Mechanisms and Management of Inflammation in Trauma and Shock. Keynote address, 43rd International Congress on Military Medicine, Basel, Switzerland
- Sterile and Infective Danger Signaling in Surgery. Visiting Professor, Ryder Trauma Center, University of Miami, Miami, FL
- Danger Signals: The Origin of Immune Dysfunction after Injury. Nicole E. Herman Visiting Professor in Acute Care Surgery, University of Florida, Gainesville, FL
- Mononuclear Cells Create Danger-Signal Specific Neutrophil Chemoattraction by Releasing Chemokines, Leukotrienes and Mitochondria. Plenary Lecture, Military Health Sciences Research Symposium, Orlando, FL
- Ownership. Presidential Address, The Western Trauma Association, Snowbird, UT
- Danger signaling: An Important New Principle in Trauma and Surgical Injury, AAST webinar
- A Subset of Five Human Mitochondrial Formyl Peptides Mimic Bacterial Peptides and Functionally Deactivate Human Neutrophils (PMN). Plenary presentation, Western Trauma Association, Whistler, BC

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

DAMP-mediated innate immune failure and pneumonia after trauma; Department of Defense Focused Program Award, 2016-2021; PI: Carl J. Hauser, MD

Harvard Trauma Inflammation T32 Training Program in Trauma, Burn, and Peri-operative Injury; NIH, 2013-2018; Co-Director: Carl J. Hauser, MD (PI: Wolfgang Junger, PhD)

HBI-002 to treat traumatic injury; NIH, 2017-2019; Collaborator: Carl J. Hauser, MD (PI: Stephen Gomperts, MD, PhD, MGH; Academic Site PI: Leo Otterbein, PhD)

SELECTED PUBLICATIONS

Itagaki K, Riça I, Zhang J, Gallo D, DePrato M, Otterbein LE, Hauser CJ. Intratracheal instillation of neutrophils rescues bacterial overgrowth initiated by trauma damage-associated molecular patterns. J Trauma Acute Care Surg 2017;82(5):853-860.

Atefi G, Aisiku O, Shapiro N, Hauser CJ, Dalle Lucca J, Flaumenhaft R, Tsokos GC. Complement activation in trauma patients alters platelet function. Shock 2016;46 (3 Suppl 1):83-8

Sandler N, Kaczmarek E, Itagaki K, Zheng Y, Otterbein L, Khabbaz K, Liu D, Senthilnathan V, Gruen RL, Hauser CJ. Mitochondrial DAMPs are released during cardiopulmonary bypass surgery and are associated with postoperative atrial fibrillation. Heart Lung Circ 2018;27(1): 122-129.

Coimbra R, Kozar RA, Smith JW, Zarzaur BL, Hauser CJ, Moore FA, Bailey JA, Valadka A, Jurkovich GJ, Jenkins DH, Davis KA, Price MA, Maier RV. The Coalition for National Trauma Research (CNTR) supports the call for a national trauma research action plan. J Trauma Acute Care Surg 2017;82(3):637-645.

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 2016;80(2):229-36.

A complete list of publications begins on page 15.

Acute Care Surgery, Trauma, and Surgical Critical Care

Kiyoshi Itagaki, PhD

Assistant Professor of Surgery

RESEARCH GROUP

Carl J. Hauser, MD
Sarena Ho, BS
Barbora Vlkova, PhD
Quanzhi Zhang, MS

RESEARCH FOCUS

I am interested in the prevention and treatment of nosocomial pneumonia after serious injury. We have hypothesized/established a new paradigm that involves release of our own mitochondria after injury, causing dysfunction of neutrophils upon interaction of formyl peptides contained in mitochondria. This causes a limited number of neutrophils migrating toward bacteria-infected lungs to clear bacteria. Thus more seriously injured people are prone to develop nosocomial pneumonia.

We hypothesized/developed two methods that may prevent seriously injured people from developing nosocomial pneumonia: 1) Reduce the number of neutrophils that encounter mitochondrial formyl peptides so that many neutrophils will remain functional and respond to bacterial infection in the lungs; 2) If only a reduced number of neutrophils can reach bacteria-infected lungs, apply exogenous neutrophils directly to the bacteria-infected lungs.

Both methods are working very well in our mouse models. Especially with method number two, we were concerned this may cause immune rejection or lung damage to the recipients. So far, we have not encountered any issues even when we applied human neutrophils to wild-type animals. These are not antibiotics that may immediately lead to antibiotic-resistant bacteria. We plan to use different animal models, such as pigs, that are well known to react similarly to humans before we move on to primates and humans.

ACCOMPLISHMENTS 2018-2019

- We received a compound produced by Polyphor in Switzerland, which antagonizes FPR1: one of the most important receptors after injury. We have completed characterizations of this compound together with data showing the importance of this FPR1 after injury and nosocomial pneumonia using animal models and KO animals. Our manuscript including these data was accepted by *Critical Care Medicine* on Sept. 24, 2019.
- I accepted Quanzhi Zhang, MS, who had a master's degree in a very different field, as a joint PhD student. Although she was an associate professor in China, she had limited knowledge/experience in our research field. I taught her patiently and identified techniques that she would feel comfortable with to produce reliable data that can be published. In a year, she produced very reliable both *in vivo* and *in vitro* data that were included in our recent publication. Some other results will lead to additional publications and future grants. Sarena Ho was a summer intern who had just finished her junior year in college and had research experience. Under my mentorship, she produced very good data that we can use in our future study.

TEACHING, TRAINING, AND EDUCATION

My teaching involved theory and methodologies of day-to-day research experiments for an experienced scientist (Barbora Vlkova, PhD), a less experienced scientist (Quanzhi Zhang, MS) and a student (Sarena Ho, summer undergraduate intern). All worked very well, enjoyed working in our lab, and produced reliable data.

SELECTED RESEARCH SUPPORT

mtDAMPs and nosocomial pneumonia after injury; National Institute of Allergy and Infectious Diseases, 2018-2020; PI: Kiyoshi Itagaki, PhD

DAMP-mediated innate immune failure and pneumonia after trauma; Department of Defense, 2016-2021; Co-Investigator: Kiyoshi Itagaki, PhD (PI: Carl J. Hauser, MD)

SELECTED PUBLICATIONS

Sandler N, Kaczmarek E, Itagaki K, Zheng Y, Otterbein L, Khabbaz K, Liu D, Senthilnathan V, Gruen RL, Hauser CJ. Mitochondrial DAMPs are released during cardiopulmonary bypass surgery and are associated with postoperative atrial fibrillation. Heart Lung Circ 2018;27(1): 122-129.

Aswani A, Manson J, Itagaki K, Chiazza F, Collino M, Wupeng WL, Chan TK, Wong WSF, Hauser CJ, Thiemermann C, Brohi K. Scavenging circulating MTDNA as a potential therapeutic option for multiple organ dysfunction in trauma hemorrhage. Front Immunol 2018;9:891.

Kaczmarek E, Hauser CJ, Kwon WY, Riça I, Chen L, Sandler N, Otterbein LE, Campbell Y, Cook CH, Yaffe MB, Marusich M, Itagaki K. A subset of five human mitochondrial formyl peptides mimics bacterial peptides and functionally deactivates human neutrophils. J Trauma Acute Care Surg 2018;85(5):936-943.

Singel KL, Crzankowski KS, Khan ANMNH, Grimm MJ, D'Auria AC, Morrell K, Eng KH, Hylander B, Mayor PC, Emmons TR, Lenart N, Fekete R, Kornyei Z, Muthukrishnan U, Gilthorpe JD, Urban CF, Itagaki K, Hauser CJ, Leifer C, Moysich KB, Odunsi K, Denes A, and Segal BH. Mitochondrial DNA in the tumour microenvironment activates neutrophils and is associated with worse outcomes in patients with advanced epithelial ovarian cancer. Br J Cancer 2019;120(2):207-217.

Itagaki K, Kaczmarek E, Kwon WY, Chen L, Vlkova B, Zhang Q, Riça I, Yaffe MB, Gong WH, Wang JM, Gao JL, Jung F, Douglas G, Campbell Y, Marusich MF, Otterbein LE, Hauser CJ. FPR1 blockade prevents receptor regulation by mitochondrial DAMPs and preserves neutrophil function after trauma. Critical Care Med 2019; accepted.

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Acute Care Surgery, Trauma, and Surgical Critical Care

Wolfgang G. Junger, PhD

Professor of Surgery

RESEARCH GROUP

Dilan Aytan
Sophie Bromberger
Sara Denicoló
Thomas Dertig
Johannes Hubner
Yutaka Kondo, MD, PhD
Kirstin Konrad
Carola Ledderose, PhD
Yong Shen
Christian Slubowski, PhD
Koichiro Sueyoshi, MD, PhD

RESEARCH FOCUS

Immune cells release cellular ATP that fuels inside-out signaling mechanisms that regulate cell activation and functions. These autocrine signaling mechanisms are essential for proper immune cell functions. Under normal circumstances, the released ATP regulates chemotaxis, antigen recognition, cell proliferation, and other immune cell functions needed for host defense. These autocrine feedback mechanisms involve a large set of different ATP and adenosine receptors on the cell surface of immune cells. These purinergic receptors regulate calcium influx and downstream signaling pathways that initiate cell activation, organize cytoskeletal rearrangement, and processes involved in cell proliferation. Severe injuries, burns, and infections cause the release of ATP from inflamed tissues and damaged cells, which results in the accumulation of ATP in the systemic circulation of critically ill patients. Systemic ATP accumulation interferes with the autocrine purinergic signaling mechanisms that regulate immune cell responses. This results in immune dysfunction that contributes to lethal complications such as immunosuppression, sepsis, and multiple organ failure. The focus of this laboratory is to define the cellular and molecular mechanisms that lead to these complications.

Our work has revealed metabolic pathways that regulate ATP release and purinergic signaling mechanisms that control the functions of neutrophils, T lymphocytes, and monocytes. We found that mitochondria are responsible for the production of the ATP that fuels the purinergic signaling of immune cells, placing mitochondria at the core of the regulatory systems that define immune cell functions. We found that mitochondrial function is impaired in immune cells of critical ill patients. Thus, impaired mitochondrial function and systemic ATP accumulation are likely causes of immune dysfunction in critically ill patients. In our ongoing work, we study whether targeting these disruptive processes can improve immune functions in critically ill patients.

Selected Collaborations

- Irina Anselm, MD, Assistant Professor of Neurology, Boston Children's Hospital
- Monika Haack, PhD, Associate Professor of Neurology, Beth Israel Deaconess Medical Center
- Amel Karaa, MD, Assistant Professor of Pediatrics, Massachusetts General Hospital
- Adrienne Randolph, MD, Professor of Anaesthesia, Boston Children's Hospital
- Simon Robson, MD, PhD, Professor of Anaesthesia, Beth Israel Deaconess Medical Center
- Nathan Shapiro, MD, Professor of Emergency Medicine, Beth Israel Deaconess Medical Center
- Gary Visner, DO, Associate Professor of Pediatrics, Boston Children's Hospital

ACCOMPLISHMENTS 2018–2019

- Ad hoc reviewer for scientific journals including *Nature, Science, Nature Reviews, Nature Medicine, Nature Biotechnology, Nature Communications, Nature Medicine, Science Signaling, PLoS ONE, EMBO Journal, Shock, Critical Care Medicine, Purinergic Signalling, Journal of Clinical Investigations, Journal of Leukocyte Biology, FASEB Journal,* and many more
- Reviewer of grant proposals submitted to National Institutes of Health, the Swiss National Research Foundation, the French National Research Agency, Israeli National Research Foundation, Austrian National Research Foundation, Belgium National Research Foundation, Wellcome Trust, and others
- Invited plenary session speaker at Annual Shock Society Meeting in San Diego, California; invited Visiting Professor, Case Western Reserve University School of Medicine, Cleveland, OH
- Editorial board member of the journal *Shock: Injury, Inflammation, and Sepsis: Laboratory and Clinical Approaches;* Associate Editor of *Purinergic Signalling*

TEACHING, TRAINING, AND EDUCATION

- Advisor and career counseling mentor of Christian Slubowski, PhD, and Carola Ledderose, PhD
- Thesis advisor of medical students from the Paracelsus Medical University, Salzburg, Austria
- Program Director of Harvard Trauma Inflammation Training Program
- Thesis advisor of master students from the Fachhochschule Technikum, Vienna, Austria
- Faculty mentor of T32 fellows enrolled in the Harvard Trauma Inflammation Training Program

SELECTED RESEARCH SUPPORT

Role of purinergic signaling in pediatric multi-organ failure; NIH/NICHD, 2019–2024; PI: Wolfgang Junger, PhD

Harvard Trauma Inflammation Training Program; NIH/NIGMS, 2013–2018; PI: Wolfgang Junger, PhD

Autocrine regulation of neutrophil chemotaxis; NIH/NIGMS, 2009–2019; PI: Wolfgang Junger, PhD

Regulation of T cell signaling in trauma; NIH/NIGMS, 2013–2018; 2019–2024; PI: Wolfgang Junger, PhD

SELECTED PUBLICATIONS

Kondo Y, Sueyoshi K, Zhang J, Bao Y, Li X, Fakhari M, Slubowski CJ, Bahrami S, Ledderose C, Junger WG. Adenosine 5'-monophosphate protects from hypoxia by lowering mitochondrial metabolism and oxygen demand. Shock 2019; Aug 27 (Epub ahead of print).

Kondo Y, Ledderose C, Slubowski CJ, Fakhari M, Sumi Y, Sueyoshi K, Bezler AK, Aytan D, Arbab M, Junger WG. Frontline Science: *Escherichia coli* use LPS as decoy to impair neutrophil chemotaxis and defeat antimicrobial host defense. J Leukoc Biol 2019; Aug 8 (Epub ahead of print).

Mühleder S, Fuchs C, Basílio J, Szwarc D, Pill K, Labuda K, Slezak P, Siehs C, Pröll J, Priglinger E, Hoffmann C, Junger WG, Redl H, Holnthoner W. Purinergic P2Y(2) receptors modulate endothelial sprouting. Cell Mol Life Sci 2019; Jul 5 (Epub ahead of print).

Woehrle T, Ledderose C, Rink J, Slubowski C, Junger WG. Autocrine stimulation of P2Y1 receptors is part of the purinergic signaling mechanism that regulates T cell activation. Purinergic Signal 2019;15(2): 127–137.

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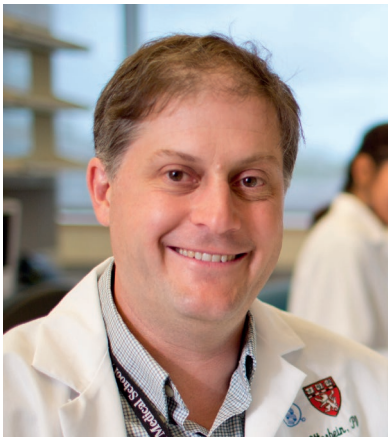
A complete list of publications begins on page 15.

Acute Care Surgery, Trauma, and Surgical Critical Care



Leo E. Otterbein, PhD

Professor of Surgery

RESEARCH GROUP

Eva Csizmadia, MS
Julius Ekert
David Gallo
James Harbison
Sree Kolli
Ghee Lee, MS
Alexa Schaufler
Shazhad Shaefi, MD
Sidharth Shankar
Rosalba Siracusa
Rodrigo Souza, PhD

RESEARCH FOCUS

Inhaled carbon monoxide (CO) is in numerous FDA phase trials, based in large part from the research that has arisen from my laboratory over the past two decades. 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 and function in large part by generating CO and bilirubin as endogenous bioactive products. We have expanded our research program to include collaborative projects on cancer, neurology, gastrointestinal disease, and exercise physiology. Each complements and advances our understanding of the acute stress response, tissue injury and repair, and the roles of HO-1/CO as they relate to immunologic and pathophysiologic responses. Ultimately, we are interested in translational research to provide solutions toward alleviating human suffering.

Role of Heme in Trauma and Infection

This year we reinforced collaborative efforts in models of trauma and the impact on susceptibility to pneumonia. As Co-Director of a six-project CDMRP Department of Defense focused research award ($10M) awarded in 2017, we continue our efforts toward identifying and characterizing deliverables to benefit the injured warfighter. As PI of one of the projects my team and I are defining how heme influences recovery from trauma and subsequent susceptibility to bacterial infection. The research involves interactive studies with Carl Hauser, MD (BIDMC, Surgery), Jim Lederer, PhD (BWH, Surgery), Daniel Talmor, MD (BIDMC, Anesthesiology), Simon Robson, MD, PhD (BIDMC, Medicine), and Michael Yaffe, MD, PhD (BIDMC Surgery/MIT). Our data in sepsis models shows that HO-1 and CO are critical determinants in fighting infection and tissue repair after trauma. We are also funded with an NIH SBIR (2018-2020, $250K) to evaluate a novel orally delivered CO solution that can be rapidly consumed for effective CO delivery. As part of a collaborative project, we are studying how noncoding RNA (lncRNA) influences macrophage signaling funded by a multi-PI R01 (2019-2024, $350K).

Neuroprotection with HO-1 and the Role of the Circadian Clock

We maintain an active collaboration with Patrick Fuller, PhD (BIDMC, Neurology) in the study of traumatic brain injury (TBI), where we find that glia-expressed HO-1 are 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. We are studying the effects of TBI on arousal and behavior as it relates to athletes who experience multiple concussions. This work is funded with a five-year grant (2019-2024) from the National Football League as part of a multi-institutional program grant ($18M) to evaluate the effects of CO to alleviate brain injury, simulating what would occur as a result of multiple mild concussions that occur during football games. With Dr. Ping Lu (BIDMC, Medicine), and Dr. Fuller over the next five years we will test the ability of CO to limit injury and promote recovery in preclinical models of concussion. Exciting preliminary data in mice demonstrate the remarkable role of HO-1 in brain homeostasis.

Carbon Monoxide and Kidney Transplant

We are currently funded with a Phase 2 NIH SBIR grant (2018-2020; $1.5M) to study an exciting and innovative oral CO solution in rat and pig models of kidney transplant in collaboration with Hillhurst Biopharmaceuticals. These studies are ongoing, but complement and expand on those we have reported on with inhaled CO, which showed a benefit to reduce delayed graft function and triggered the first human trial. The oral formulation is simple and is being applied to multiple model systems including TBI and trauma. Proof of principal has been demonstrated and human testing will begin in early 2020.

HO-1 in Cancer

In collaboration and funded (2019-2021, $300K) with a company in Cambridge and we are studying the role of macrophages in tumor growth testing the hypothesis that the phenotype of the macrophage and neutrophil regulates its ability to direct T cell function. Using our regulated HO-1 null mice, we find that blockade of HO-1 significantly reduces tumor growth and are now exploring mechanisms of action using CyTOF and scRNAseq.

CO Prodrugs in Experimental Colitis

CO has been well described as a treatment for those suffering from inflammatory bowel disease. The challenge has been to define novel methods to deliver CO. Through a multi-PI R01 project with Georgia State University, we were recently funded with an R01 (2019-2024) to utilize sophisticated medicinal chemistry technology to develop new classes of molecules to influence both the host tissue response and the microbiome toward one promoting GI health.

Relationship Between the Microbiome, Glycome, and Tissue Damage

It has been known that the intestinal microbiome is important in numerous immune regulatory functions and that HO-1/CO can influence the intestinal flora in models of acute inflammation. Additionally, preliminary data show that injury leads to changes in cellular glycans, specifically in the neutrophil responding to bacteria. This finding is part of a new collaborative project with Richard Cummings, PhD (BIDMC, Surgery) and Carl Hauser, MD (BIDMC, Surgery), to integrate glycobiological changes that occur in response to injury comparing human and murine samples.

HO-1 and Exercise Metabolism

Rodrigo Souza, PhD (Instructor, HMS) was awarded an American Heart Association Career Development Award (2019-2022, $225K) to study how physical exercise influences HO-1 expression and contributes to skeletal muscle function and cardioprotection. Preliminary findings suggest that exercise metabolism is influenced by heme catabolism and the generation of CO.

ACCOMPLISHMENTS 2018-2019

We continue to be one of the leaders in the area of heme metabolism and the stress response, providing mechanistic insight into the role of HO-1 and its bioactive products carbon monoxide and the bile pigments. Our publications continue to provide important contributions toward the therapeutic use of these molecules in the clinic, which guided more than 10 ongoing clinical trials with CO.

- Invited presentation: 10th International Conference on Heme Oxygenases, Seoul, South Korea
- Invited presentation: Second Gasotransmitters Conference, University of Oregon
- Chair, BIDMC Institutional Animal Care and Use Committee
- 16th consecutive year as an NIH study section member for K01, K08, K02, K99, R25, and loan repayment, grant applications
- Director of Postgraduate Research Program, Department of Surgery

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. I am a preceptor for the Trauma T32 training grant and am currently mentoring a K08 awardee (Shazhad Shaefi, Anesthesia) and an AHA awardee (Rodrigo Souza, Surgery). As the BIDMC CIMIT site miner and 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 and liaison with the Technology Ventures Office. In addition, I advise on grant submissions, commercialization of ideas, interactions with the Technology Ventures Office, and various accelerator and venture opportunities.

SELECTED RESEARCH SUPPORT

DAMP-mediated innate immune failure and pneumonia after trauma; Department of Defense Focused Program Award, 2016-2021; Co-Director, Leo Otterbein, PhD

HBI-002 to treat delayed graft function in kidney transplant; NIH, 2016-2019; PI: Leo Otterbein, PhD

Immunomodulatory effects of bilirubin are mediated through the aryl hydrocarbon receptor, O_2 and purinergic pathways; NIH, 2017-2022; Co-Investigator: Leo Otterbein, PhD

Heme Oxygenase-1 and tumor growth; Agios Pharmaceuticals, 2017-2019; PI: Leo Otterbein, PhD

HBI-002 to treat traumatic injury; NIH, 2017-2019; Academic Site PI: Leo Otterbein, PhD (PI: Stephen Gomperts, MD, PhD)

Mechanisms of and potential treatments for repetitive concussions and chronic traumatic encephalopathy; National Football League, 2019-2024; Co-Investigator: Leo Otterbein, PhD

Examining carbon monoxide to treat inflammatory conditions using experimental colitis models; NIH 2019-2024; PI: Leo Otterbein, PhD

lncRNA regulates lung inflammation; NIH, 2019-2024; Co-Investigator: Leo Otterbein, PhD

SELECTED PUBLICATIONS

Correa-Costa M, Gallo D, Csizmadia E, Gomperts E, Lieberman J-L, Hauser CJ, Li X, Wang B, Camara N, Robson SC, Otterbein, LE. Carbon monoxide protects the kidney through the central circadian clock and CD39. Proc Natl Acad Sci 2018;E2302-E2310.

Zheng Y, Ji X, Yu B, Gallo D, Csizmadia E, Zhu M, Choudhury MR, De La Cruz K, Chittavong Z, Yuan Z, Wang B*, Otterbein, LE* Enrichment-triggered prodrug activation demonstrated through mitochondria-target delivery of doxorubicin and carbon monoxide. Nature Chemistry 2018;787-784. **equal contribution.*

Belcher JD, Gomperts E, Nguyen J, Chen C, Abdulla F, Kiser ZM, Gallo D, Levy H, Otterbein LE, Vercellotti GM. Oral carbon monoxide therapy in murine sickle cell disease: Beneficial effects on vaso-occlusion, inflammation and anemia. PLoS One 2018;13(10):e0205194.

Bisht K, Canesin G, Cheytan T, Li M, Nemeth Z, Csizmadia E, Woodruff TM, Stec DE, Bulmer AC, Otterbein LE, Wegiel B. Deletion of biliverdin reductase A in myeloid cells promotes chemokine expression and chemotaxis in part via a complement C5a-C5aR1 pathway. J Immunol 2019; 2982-2990.

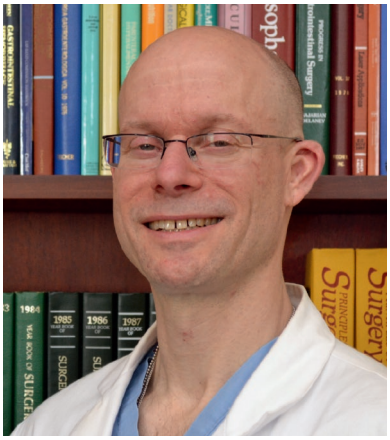
Itagaki K, Kaczmarek E, Kwon WY, Chen L, Vlková B, Zhang Q, Riça I, Yaffe MB, Campbell Y, Marusich MF, Wang JM, Gong WH, Gao JL, Jung F, Douglas G, Otterbein LE, Hauser CJ. Formyl peptide receptor-1 blockade prevents receptor regulation by mitochondrial danger-associated molecular patterns and preserves neutrophil function after trauma. Crit Care Med 2019; in press.

Lee GR, Shaefi S, Otterbein LE. HO-1 and CD39: It takes two to protect the realm. Front Immunol 2019;1765.

Lee H, Li C, Zhang Y, Zhang D, Otterbein LE, Jin Y. Caveolin-1 selectively regulates microRNA sorting into microvesicles after noxious stimuli. J Exp Med 2019;2202-2220.

A complete list of publications begins on page 15.

Acute Care Surgery, Trauma, and Surgical Critical Care*



Michael B. Yaffe, MD, PhD

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

RESEARCH GROUP

Christopher Barrett, MD
Molly Bird
Thomas Dietzel
Vasilena Gocheva, PhD
Robert Grant, PhD
Erika Handly
Brian Joughin, PhD
Yi Wen Kong, PhD
Alex Kruswick
Daniel Lim, PhD
Pau Creixell Morera, PhD
Tatiana Netterfield
Jesse Patterson, PhD
Ingred Goretti Rica, PhD
Samantha Rosenberg
Ganapathy Sriram, PhD
Shohreh Varmeh, PhD
Xueyang Yu, PhD

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

RESEARCH FOCUS

The goal of our research is to understand how cells respond to stress and injury at the molecular and systems biology level. We believe that in response to various types of damage, cells activate a common set of signaling pathways that control damage repair, recruit the innate immune system, and dictate the extent of tissue survival, inflammation and healing, or result in various types of cell death. We study the molecular components of these injury-induced signaling pathways and the manner in which these pathways communicate with each other to control the biological outcome after damage, using a combination of biochemistry, molecular cell biology, and systems-based computational approaches. We are particularly interested in cross-talk between: 1) stress, inflammation, blood clotting and immune function after trauma, 2) stress, inflammation, innate immune function, and cancer, and 3) targeting injury, DNA damage, and cell cycle control pathways for cancer treatment. Our lab has a longstanding interest in inventing new technologies to address these questions. These include novel proteomic methods; high-throughput signaling assays and peptide library screens; RNAi and CRISPR screens; and novel computational/bioinformatics methods. We use these together with more traditional techniques from cell biology, physical biochemistry, structural biology, and mouse genetic models.

Signaling Pathways and Cell Injury Networks That Control the DNA Damage Response, Cell Cycle Progression, 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 senescence or 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, phospho-binding domains, RNA-binding proteins, and epigenetic modulation of chromatin at the site of damage, and 2) examining whether cross-talk between various stress and injury signaling pathways and the DNA damage response can be pharmacologically manipulated to enhance the response of tumors to DNA damaging agents alone, or in combination with, immunotherapy.

We showed, for example, that p53-defective tumor cells become dependent on signaling through the stress-activated p38-MK2 pathway to resist killing by chemotherapy. We have now created a variety of standard and novel conditional MK2 knock-out mice, as well as nanoparticles delivering MK2-targeted RNAi and CRISPR, to target this pathway *in vivo* in ovarian, lung, and colon cancer models. We are continuing to explore the how the MK2 pathway cross-talks with several DNA repair pathways, as well as performing CRISPR-based screens to look for new modifiers of the DNA damage response that can be therapeutically targeted. This work has led to a new focus on the role of RNA damage and RNA-binding proteins as critical integrators of stress and DNA damage response pathways in the cell. We recently extended this work on DNA damage-induced cell injury to identify novel signaling mechanisms that enhance the response of cancers to

immunotherapy. Finally, we discovered that inhibitors of Polo-like kinases can synergize with both specific hormonal therapies or anti-microtubule drugs to cause severe mitotic injury and damage in cancer cells, but not in normal cells. This has led to an ongoing clinical trial in prostate cancer at BIDMC, in collaboration with Drs. Steve Balk and David Einstein (Hematology-Oncology, BIDMC) studying Abiraterone in combination with Plk1 inhibition in patients with progressive castrate-resistant prostate cancer.

Signaling Pathways and Networks That Control Inflammation and Immune Function in Trauma and Cancer

Stress and injury-induced activation of neutrophils and macrophages after massive tissue trauma results in an early systemic inflammatory response, inappropriate activation of the blood clotting cascade, and multiple organ failure, which is then followed by a state of immune deficiency with high susceptibility to infection. The molecular basis for these effects is poorly understood but involves dysregulation of key signaling pathways in neutrophils and macrophages.

Our research is focused on understanding the role of the p38-MK2 pathway in cytokine control and innate immune function, and on cross-talk between cytokines, clotting factors, and neutrophil NADPH oxidase-derived ROS in tissue damage, coagulopathy, and inflammation. We recently discovered a particularly important link between abnormal blood clotting and the complement pathway cytokine C5a, which causes excessive production of extracellular ROS and organ damage by neutrophils after traumatic injury. We discovered that the p38-MK2 pathway plays a critical role in controlling the phenotypic switch between M1 pro-inflammatory macrophages and M2 immunosuppressive macrophages after tissue injury and in inflammation-induced colon cancer.

ACCOMPLISHMENTS 2018-2019

- Chief Scientific Advisor and Academic Editor, *Science Signaling*
- One of eight investigators nationally to win the Revolutionizing Innovative Visionary Environmental Health Research (RIVER) award from the NIH
- Appointed Director, MIT Center for Precision Cancer Medicine

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 am designing a new course on quantitative physiology and molecular mechanisms of drug action. 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 in the genotoxic stress response; NIH, 2017-2025; PI: Michael Yaffe, MD, PhD

RNA-binding proteins as molecular integrators that control the response of HGSOC to anti-cancer therapies; NIH, 2018-2023; PI: Michael Yaffe MD, PhD

DAMP-mediated innate immune failure after trauma; Department of Defense, 2016-2021; Co-PI: Michael Yaffe, MD, PhD

SELECTED PUBLICATIONS

Patterson JC, Joughin BA, Prota AE, Mühlethaler T, Jonas OH, Whitman MA, Varmeh S, Chen S, Balk SP, Steinmetz MO, Lauffenburger DA, Yaffe MB. VISAGE reveals a targetable mitotic spindle vulnerability in cancer cells. Cell Systems 2019;9:74-92.

Walker CB, Moore EE, Kam A, Dexter-Meldrum J, Nydam TL, Chapman MP, Chandler J, Sauaia A, Barrett CD, Yaffe MB, Moore HB. Clot activators do not expedite the time to predict massive transfusion in trauma patients analyzed with tissue plasminogen activator thrombelastography. Surgery 2019;166:408-415.

van de Kooij B, Creixell P, van Vlimmeren A, Joughin BA, Miller CJ, Haider N, Simpson CD, Linding R, Stambolic V, Turk BE, Yaffe MB. Comprehensive substrate specificity profiling of the human Nek kinome reveals unexpected signaling outputs. Elife 2019;8. pii:e44635.

Barrett CD, Moore HB, Kong YW, Chapman MP, Sriram G, Lim D, Moore EE, Yaffe MB. Tranexamic acid mediates proinflammatory and anti-inflammatory signaling via complement C5a regulation in a plasminogen activator-dependent manner. J Trauma Acute Care Surg 2019;86:101-107.

Patterson JC, Joughin BA, van de Kooij B, Lim DC, Lauffenburger DA, Yaffe MB. ROS and oxidative stress are elevated in mitosis during asynchronous cell cycle progression and are exacerbated by mitotic arrest. Cell Systems 2019;8:163-167.

Creixell P, Pandey JP, Palmeri A, Bhattacharyya M, Creixell M, Ranganathan R, Pincus D, Yaffe MB. Hierarchical organization endows the kinase domain with regulatory plasticity. Cell Systems 2018;7:371-383.

Barrett CD, Hsu AT, Ellson CD, Miyazawa BY, Kong YW, Greenwood JD, Sanjeev Dhara S, Neal MD, Sperry JL, Park MS, Cohen MJ, Zuckerbraun BS, Yaffe MB. Blood clotting and traumatic injury with shock mediates complement-dependent neutrophil priming for extracellular ROS, ROS-dependent organ injury and coagulopathy. Clin Exp Immunology 2018;194:103-117.

Suarez-Lopez L, Sriram G, Kong YW, Morandell S, Merrick KA, Hernandez Y, Haigis KM, Yaffe MB. MK2 contributes to tumor progression by promoting M2 macrophage polarization and tumor angiogenesis. Proc Natl Acad Sci U S A 2018;115(18):E4236-E4244.

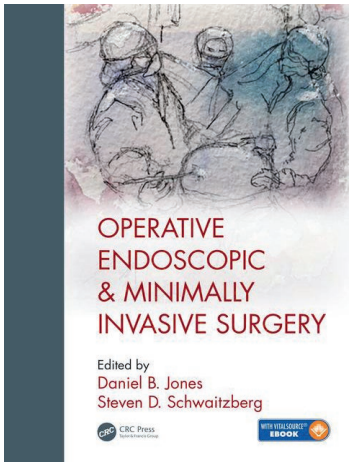
A complete list of publications begins on page 15.

Daniel B. Jones, MD, MS

Professor of Surgery
Vice Chairman, Surgery (Technology and Innovation)
Chief, Division of Bariatric and Minimally Invasive Surgery
Co-Director, Carl J. Shapiro Simulation and Skills Center

RESEARCH GROUP

Rassoul Abu-Nuwar, MD
Barbara Ainsley
Dale Bond, MD
Caroline Cao, PhD
Jaime Cudmore
Suvranu De, PhD
Michael Dombek, MD
Jody Dushay, MD
Emilie Fitzpatrick, MD
Cullen Jackson, PhD
Stephanie Jones, MD
Mojdeh Kappus, MD
Jaisa Olasky, MD
Brian Nguyen, MD
Blaine Phillips, MD
Ganesh Sankaranarayanan, PhD
Mandeep Sawhney, MD, MPH
Steven Schwaitzberg, MD
Stephanie Therrien
Linda Trainor, RN
Hung Truong, MD, MS
Christina Wee, MD, MPH



Jones DB, Schwaitzberg SD. Operative Endoscopic & Minimally Invasive Surgery, London, UK, CRC Press, 2019.

RESEARCH FOCUS

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

Simulation/Education

Since 2005, we have had continuous NIH funding to support collaborative projects among the Center for Modeling, Simulation and Imaging in Medicine (CeMSIM), Rensselaer Polytechnic Institute (RPI), and the Carl J. Shapiro Simulation and Skills Center, BIDMC. We are currently wrapping up three projects.

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

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

Virtual endoluminal surgery simulator (VESS) is used to teach advanced therapeutic endoscopy for the treatment of colorectal cancer.

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. In collaboration with Brown University we are funded by the NIH to better understand how we can use technology to help our bariatric surgery patients with lifestyle changes.

ACCOMPLISHMENTS 2018-2019

- President, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)
- Trustee-at-Large, Society for Surgery of the Alimentary Tract (SSAT)
- Past President, Association for Surgical Education (ASE)
- Chair, Essentials Task Force (www.Essentials.ASMBS.org)

Invited Presentations

It's Better to Be Lucky. Presidential Address, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), 16th World Congress of Endoscopic Surgery; Seattle, WA, 2018

Sparks, OR Fires, & Fiascos: Why the FUSE Program? 61st annual meeting of the International Surgical Group; Reykjavik, Iceland, 2018

Assuring Quality and Advancing Patient Safety for Bariatric Surgery. XI International Congress of Endoscopic Surgery; Lima, Peru, 2018

Bariatric Surgery—Primum Non Nocere. Anthony PC Yim Visiting Professorial Lecture in Minimally Invasive Surgery & Innovative Technology, 21st Chinese University of Hong Kong Surgical Symposium; China, 2018

Safer Surgery Using Virtual Reality and Simulation. T.E Udwadia Oration, Indian Association of Gastrointestinal Endoscopic Surgeons (IAGES); Bhubaneseswar, Odhisa, India, 2019 (https://vimeo.com/315766371)

Recognition and Awards

- Honorary Member, Korean Society of Endoscopic &Laparoscopic Surgeons
- Honorary Member, Sociedad Peruana De Cirugia Endoscopica
- Anthony PC Yim Visiting Professor in Minimally Invasive Surgery & Innovative Technology, The Chinese University of Hong Kong
- Harvard Medical School Excellence in Mentoring Award, Nominee
- Award of Honour, T.E Udwadia Oration, Indian Association of Gastrointestinal Endoscopic Surgeons (IAGES)
- Best Doctors in America; Top Doctors, *Boston Magazine,* America's Top Surgeons

Editorial Roles

Editorial Board: *UpToDate, Bariatric Times* and *Surgery for Obesity and Related Disorders*

TEACHING, TRAINING, AND EDUCATION

- ASE/ACS Skills-based Simulation Curriculum for Medical School Years 1-3; Released national curriculum for medical students using educational theory and assessment metrics
- Fundamental Use of Surgical Energy (FUSE): International curriculum and certification to advance OR safety
- Essentials: Multidisciplinary curriculum for management of bariatric surgery patient
- SAGES MASTERS program: Curriculum for deliberate learning after fellowship
- Co-Director: Carl J. Shapiro Simulation and Skills Center, BIDMC
- Site Director: OR CRICO Team Training with Simulation
- Course Director: BIDMC Surgery Grand Rounds, weekly CME lecture series

SELECTED RESEARCH SUPPORT

Ecological momentary assessment of behavioral and psychological predictors of weight loss following bariatric surgery; NIH, 2015-2019; PI: Daniel Jones, MD, MS

Development and validation of virtual endoluminal surgery simulator (VESS) for the treatment of colorectal cancer; NIH, 2016-2021; PI: Suvranu De, PhD; Co-Investigator: Daniel B. Jones, MD, MS

Virtual Airway Simulation Trainer (VAST); NIH, 2014-2018; PI: Stephanie Jones, MD; Co-Investigator: Daniel B. Jones, MD, MS

SELECTED PUBLICATIONS

Jones DB (ed). Pocket Surgery, Second Edition. Philadelphia: Wolters Kluwer, 2018.

Nguyen B, Fitzpatrick E, Jones DB. Barriers to implementation of the FUSE Program. Surg Endosc 2018;32(1): 466-471.

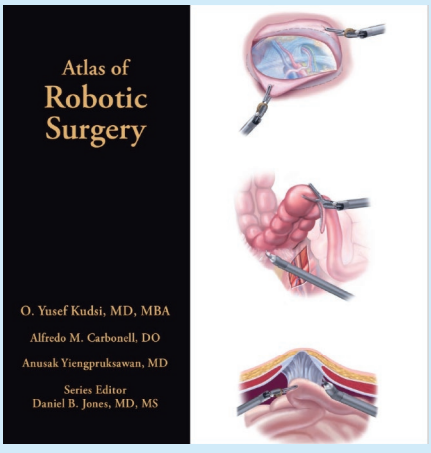
Sankaranarayanan G, Wooley L, Hogg D, Dorozhkin D, Olasky J, Chauhan S, Fleshman JW, De S, Scott D, Jones DB. Immersive virtual reality-based training improves response in a simulated operating room fire scenario. Surg Endosc 2018;32: 3439-3449.

Telem DA, Qureshi A, Edwards M, Jones DB. SAGES climate survey: Results and strategic planning for our future. Surg Endosc 2018, 32(10): 4105-4110.

Goldstein AP, Thomas JG, Vithiananthan S, Blackburn GA, Jones DB, Webster J, Jones R, Evans EW, Dushay J, Moon J, Bond DS. Multi-sensor ecological momentary assessment of behavioral and psychological predictors of weight loss following bariatric surgery: Study protocol for a multicenter prospective longitudinal evaluation. BMC Obesity 2018;5(27):1-12.

Cetinsaya B, Gromski MA, Lee S, Xia Z, Doga D, Halic T, Bayrak C, Cullen J, De S, Hegde S, Cohen J, Sawhney M, Stavropoulos S, Kantsevov SV, Jones DB. A task and performance analysis of endoscopic submucosal dissection (ESD) surgery. Surg Endosc 2019;33(2):592-606.

Wee CC, Fleischman A, Bourland AC, Hess DT, Apovian C, Jones DB. Decision regret up to four years after gastric bypass and gastric banding. Obes Surg 2019;29(5):1624-1631.



Kudsi YO, Carbonell AM, Yiengpruksawan A, Jones DB. Atlas of Robotic Surgery. Cine-Med Inc., Woodbury, CT, 2019.

A complete list of publications begins on page 15.

Kamal Khabbaz, MD

David S. Ginsburg Associate Professor of Surgery
Chief, Cardiac Surgery

RESEARCH GROUP

Louis Chu, MD
David Liu, MD
Feroze-ud-Den Mahmood, MD

RESEARCH FOCUS

The multidisciplinary 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 Dr. Feroze Mahmood and a multidisciplinary Valve Research Group, normal and abnormal size, shape, and geometric parameters pertaining to the mitral, tricuspid, and aortic valves are being researched. In addition, we are studying 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 software programs 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.

The Valve Research Group is involved with multiple national and international universities, 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, which include the following:

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

Clinical trial of the On-X valve using low dose anticoagulation: The purpose of this study is to define the lowest level of required antithrombotic therapy for mitral or aortic valve replacement using the On-X Valve.

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

Early Feasibility Study of the CardiAQ™ Transcatheter Mitral Valve (TMV) System with Transseptal Delivery System for the Treatment of Moderate to Severe Mitral Regurgitation

REPRISE III: REpositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System-Randomized Clinical Evaluation

ACCOMPLISHMENTS 2018-2019

Several studies are 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 describe the workflow in development and use of a customizable left-sided pulsatile heart model in which patient-specific, 3-dimensionally printed patient valves can be modeled under physiological intracardiac pressures. The model allows for TEE visualization and promotes familiarization of heart anatomy, surgical equipment, and imaging workflow for trainees.

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.

The Valve Research Group has been recognized and granted the status of a hospital "core laboratory" for 3D printing, establishing a state-of-the-art 3D printing laboratory. We have recently begun 3D printing patient-specific mitral valves for creation of silicone replicas to be placed in our state-of-the-art pulse duplicator device, which generates realistic pulsatility and allows for TEE visualization. Additionally, multiple echocardiography simulators serve as a dedicated simulation laboratory.

TEACHING, TRAINING, AND EDUCATION

I teach residents in our ACGME-accredited Cardiothoracic Surgery Residency Program as well as postgraduate fellows. I also teach BIDMC General Surgery residents (PGY-3) in cardiac surgery techniques, and continue to teach a course on echocardiography at Harvard Medical School (HMS). 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.

SELECTED RESEARCH SUPPORT

Multi-Center Experience with the Rapid Deployment EDWARDS INTUITY Valve System for Aortic Valve ReplaceMent (TRANSFORM Trial); Edwards Lifesciences, 2014-2024; PI: Kamal Khabbaz, MD (Co-Investigator: David Liu, MD)

SELECTED PUBLICATIONS

Baribeau Y, Sharkey A, Mahmood E, Feng R, Chaudhary O, Baribeau V, Mahmood F, Matyal R, Khabbaz K. Three-dimensional printing and transesophageal echocardiographic imaging of patient-specific mitral valve models in a pulsatile phantom model. J Cardiothorac Vasc Anesth 2019;Jul 31 (Epub ahead of print).

Hosler QP, Maltagliati AJ, Shi SM, Afilalo J, Popma JJ, Khabbaz KR, Laham RJ, Guibone K, Kim DH. A practical two-stage frailty assessment for older adults undergoing aortic valve replacement. J Am Geriatr Soc 2019;Jun 18 (Epub ahead of print).

Kundi H, Popma JJ, Khabbaz KR, Chu LM, Strom JB, Valsdottir LR, Shen C, Yeh RW. Association of hospital surgical aortic valve replacement quality with 30-day and 1-year mortality after transcatheter aortic valve replacement. JAMA Cardiol 2019;1;4(1):16-22.

Shi SM, Sung M, Afilalo J, Lipsitz LA, Kim CA, Popma JJ, Khabbaz KR, Laham RJ, Guibone K, Lee J, Marcantonio ER, Kim DH. Delirium incidence and functional outcomes after transcatheter and surgical aortic valve replacement. Am Geriatr Soc 2019;67(7):1393-1401.

Kim DH, Afilalo J, Shi SM, Popma JJ, Khabbaz KR, Laham RJ, Grodstein F, Guibone K, Lux E, Lipsitz LA. Evaluation of changes in functional status in the year after aortic valve replacement. JAMA Intern Med 2019;179(3):383-391.

Mahmood E, Jeganathan J, Feng R, Saraf M, Khabbaz K, Mahmood F, Venkatachalam S, Liu D, Chu L, Parikh SM, Matyal R. Decreased PGC-1α post-cardiopulmonary bypass leads to impaired oxidative stress in diabetic patients. Ann Thorac Surg 2019;107(2):467-476.

A complete list of publications begins on page 15.

Colon and Rectal Surgery

Evangelos Messaris, MD, PhD

Associate Professor of Surgery
Chief of Colon and Rectal Surgery

RESEARCH GROUP

Benjamin Allar, MD
Thomas Cataldo, MD
Gabrielle Cervoni, MD
Carlos Cordova, MD
Anne Fabrizio, MD
Michelle Fakler, MD
Israel Gaytan, MD
Ana Sofia Ore, MD
Jonathan Pastrana Del Valle, MD
Claire Sokas, MD
Alessandra Storino, MD
Daniel Wong, MD

RESEARCH FOCUS

The Division of Colon and Rectal Surgery focuses on outcomes research for patients undergoing colorectal surgery for colorectal cancer and inflammatory bowel diseases. The research is based on our own data from our busy clinical practice of 500 major colorectal resections a year or from national databases such as the NSQIP or NCDB.

Areas of emphasis are the development and critical analysis of clinical pathways and other systems initiatives for optimal patient care. Enhanced recovery pathways and improvement of these pathways have been a long ongoing project for the division. Separate investigations are centered on perioperative management of pain in patients undergoing surgery.

Ongoing clinical projects:

- Outcomes in rescue therapy for ulcerative colitis
- Impact of NSAIDs in Crohn's disease recurrence after ileocolectomy
- Effect of carbohydrate gels on diabetics undergoing colorectal resections
- Ventral mesh rectopexy versus standard rectopexy
- Impact of rectal cancer tumor board on decision making
- Impact of ethnicity on patient outcomes

ACCOMPLISHMENTS 2018–2019

- Established Colorectal Surgery Research Group: This group meets monthly and collaborates with multiple other divisions/departments at BIDMC, such as gastroenterology; basic science labs (Richard Cummings, PhD, and Efi Kokkotou, MD, PhD); and the FIRST Program.
- Reviewer's Education for the journal *Diseases of the Colon & Rectum:* A program for mentoring young surgeons on how to become reviewers for *Diseases of the Colon & Rectum*
- 2018 Castle Connolly Top Doctor
- Award: Publons Top Peer-Reviewer
- American Society of Colon and Rectal Surgeons, Committee on Continuous Education
- American Society of Colon and Rectal Surgeons Research Foundation, Research Committee
- Moderator, Colon and Rectal Surgery Session IV, American College of Surgeons Clinical Congress, Boston, MA
- Moderator, Critical Review of Scientific Manuscripts; Annual Scientific Meeting, American Society of Colon and Rectal Surgeons Conference, Cleveland, OH
- From Instructor to Chair: Academic Development and Promotion; Invited Lecture, American Society of Colon and Rectal Surgeons Conference, Cleveland, OH
- Moderator, e-poster Presentations on Quality; Annual Scientific Meeting, American Society of Colon and Rectal Surgeons Conference, Cleveland, OH
- Moderator, e-Poster Presentations on Basic Science; Annual Scientific Meeting, American Society of Colon and Rectal Surgeons Conference, Cleveland, OH

TEACHING, TRAINING, AND EDUCATION

The entire division is invested in education:

- First year of the Colorectal Surgery Fellowship at BIDMC (Program Director: Thomas Cataldo, MD)
- Didactics to Harvard Medical School students and BIDMC residents
- Harvard Medical School Surgery Clerkship tutorials throughout the year
- Advanced Anatomy Class, Department of Surgery
- Mock oral examiner for BIDMC and New England Society of Colon and Rectal Surgeons

ABSTRACTS, POSTERS, AND EXHIBITS

Elective colon resection for cancer in end-stage liver disease patients. New England Society of Colon and Rectal Surgeons Conference, Bretton Woods, NH

Impact of lack or poor response to chemoradiotherapy on radical margin positivity rates in locally advanced rectal cancer. New England Society of Colon and Rectal Surgeons Conference, Bretton Woods, NH (3rd award of best podium presentation)

Effect of enhanced recovery protocol on length of stay and readmission rate in patients undergoing a colectomy with or without stoma creation: Does type of stoma matter? American Society of Colon and Rectal Surgeons Conference, Cleveland, OH

Minimal effect of universal extended prophylaxis on rates of venous thromboembolic events after colorectal surgery in a tertiary care center: Is compliance the problem? American Society of Colon and Rectal Surgeons Conference, Cleveland, OH

Does cessation of the preoperative antibiotic prophylaxis in loop ileostomy closure reduce postoperative readmissions for *c. difficile* infection? American Society of Colon and Rectal Surgeons Conference, Cleveland, OH

Oncotype Dx® testing does not affect clinical practice in stage IIA colon cancer. American Society of Colon and Rectal Surgeons Conference, Cleveland, OH

SELECTED PUBLICATIONS

Dickson EA, Penna M, Cunningham C, Ratcliffe FM, Chantler J, Crabtree NA, Tuynman JB, Albert MR, Monson JRT, Hompes R; International TaTME Registry Collaborative. Carbon dioxide embolism associated with transanal total mesorectal excision surgery: A report from the international registries. Dis Colon Rectum 2019;62(7):794-801.

Kulaylat AS, Schaefer EW, Messaris E, Hollenbeak CS. Truven Health Analytics MarketScan databases for clinical research in colon and rectal surgery. Clin Colon Rectal Surg 2019;32(1):54-60.

Kulaylat AS, Pappou E, Philp MM, Kuritzkes BA, Ortenzi G, Hollenbeak CS, Choi C, Messaris E. Emergent colon resections: Does surgeon specialization influence outcomes? Dis Colon Rectum 2019;62(1): 79-87.

Kulaylat AS, Boltz MM, Moyer M, Mathew A, McKenna K, Messaris E. Management of large cecal polyps: When can the ileo-cecal valve be spared? Dis Colon Rectum 2018;61(9):1089-1095.

Wong DJ, Curran T, Poylin VY, Cataldo TE. Surgeon-delivered laparoscopic transversus abdominis plane blocks are non-inferior to anesthesia-delivered ultrasound-guided transversus abdominis plane blocks: A blinded, randomized non-inferiority trial. Surg Endosc 2019;Sep 4 (Epub ahead of print).

A complete list of publications begins on page 15.

Susan J. Hagen, PhD

Associate Professor of Surgery
Associate Vice Chair for Research
Director, BIDMC Microscopy and Histology Cores
Director, Harvard Digestive Diseases Center Microscopy and Histopathology Core

RESEARCH GROUP

Lay-Hong Ang, PhD
Mahnoor Baqai, MD
Aniket Gad, MS
Wenting He, PhD
Yue Li, PhD
Lena Liu
Kyle Smith, BS
Suzanne White

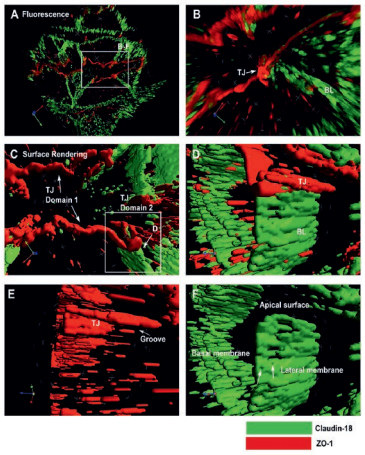
RESEARCH FOCUS

The focus of my laboratory is to understand how barrier dysfunction facilitates gastric cancer development. We approach our work by studying the details of gastric barrier function in general and its disruption during *Helicobacter pylori* infection using genetic, advanced microscopy, and genomic approaches. Our aims have two important goals: one is to understand basic science principles and the other is translational.

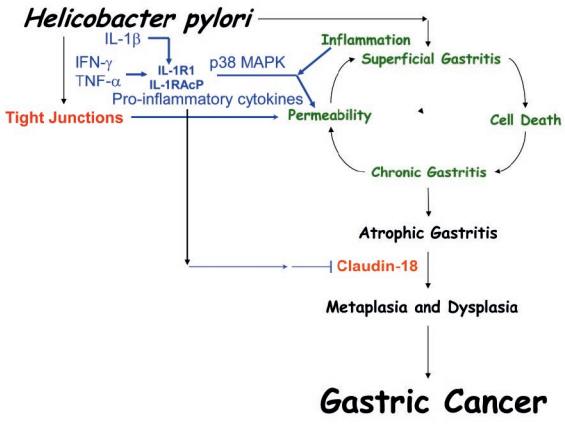
Although the stomach expresses a specific subset of claudin molecules, which are proteins that confer barrier properties to epithelial cells at the tight junction, it highly expresses one particular claudin, claudin-18 (*CLDN18*). *CLDN18* is a cation-selective tight junction protein that is transcriptionally down-regulated in *H. pylori* infection in mice as well as in human patients with gastric cancer. Because *CLDN18* protein and its gene, *CLDN18,* are attenuated in disease, we made *CLDN18* knockout mice to study its role in mucosal barrier function in general and in gastric cancer pathogenesis in particular. Our recent work demonstrates that *CLDN18* is: 1) most highly expressed as a basolateral membrane protein (Figure 1). This work was done using super-resolution microscopy techniques by Dr. Ang; 2) an important signaling molecule that regulates gastric homeostasis; and 3) a potent tumor suppressor in the stomach.

We recently demonstrated that knockout of *CLDN18* promotes gastric cancer development. Due to these results, we created two gastric cell-specific conditional knockout mouse lines to genetically dissect the role of *CLDN18* 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, or gastric organoids. We have work in progress to evaluate the role of cytokines in down-regulation of *CLDN18* using the reductionist models, with the hypothesis that interleukin-1beta down-regulates *CLDN18,* leading to gastric cancer development (Figure 2). With collaborators, we hope to use human samples from gastritis through gastric cancer to evaluate gene-expression patterns for novel biomarkers and cancer drivers that may inform patient management, drive biomarker development for early screening, and/or uncover therapeutic opportunities for novel drug development targeting gastric cancer.

A second project in the lab involves a close collaboration with Dr. David Cohen, Chief of Gastroenterology and Hepatology at Weill Cornell in New York, to study the role of thioesterase superfamily member 1 (Them1) in hepatic steatosis/NAFDL. We became involved with this project due to our expertise in microscopy, specifically in correlative light and electron microscopy (CLEM). Using CLEM techniques, we showed that Them1 *in vivo* and *in vitro* forms novel membraneless organelles (we call "puncta") that represent the functionally active form of Them1. Upon stimulation, the puncta dissolve so that Them1 is dispersed via phosphorylation of one specific serine at the amino terminus. We are currently working to isolate puncta, determine scaffold and client proteins that constitute puncta, and understand mechanisms that regulate the phase transition from puncta to diffuse Them1 intracellular states.



▲ FIGURE 1: *CLDN18* is highly expressed as a basolateral membrane protein.



◀ FIGURE 2: We are evaluating the role of cytokines in down-regulation of *CLDN18* using the reductionist models, with the hypothesis that interleukin-1beta down-regulates *CLDN18*, leading to gastric cancer development.

ACCOMPLISHMENTS 2018-2019

- Susan Hagen, PhD, sat on NIH study section 2019/01 ZRG1 DKUS-T (90) S "Topics in Gastroenterology," an ad hoc study section assembled while the NIH reviewed the Cellular and Molecular Gastroenterology study section. November 2018.
- Susan Hagen, PhD, joined the editorial board of *Tissue Barriers.*
- Wenting He, PhD, an Associate Researcher at the Second Hospital of Lanzhou University in China, received a faculty fellowship from the China Scholarship Council to do a sabbatical year in Boston studying gastric cancer pathogenesis in the Hagen lab. Dr. He worked to understand interacting binding partners of claudin 18.
- Mahnoor Baqai, MD, a new postdoctoral fellow in the lab, was accepted to attend the Mount Desert Island Biological Laboratory course for GI Fellows, "Origins and Frontiers of Hepatobiliary and Gastrointestinal Physiology," in September 2019. Attendance was awarded competitively to a small number of applicants.

TEACHING, TRAINING, AND EDUCATION

In addition to teaching students, technicians, and postdoctoral fellows in the research laboratory, I taught investigators to use the electron microscope in the EM facility at BIDMC.

Resident Courses

Module Leader: BIDMC resident's course in Comparative Physiology at Mount Desert Island Biological Laboratory. Approximately 12 medical/surgical residents rotated through the module, "Gastric Acid Secretion," during the one-week course.

GI Fellows Courses

Module Leader: "Origins and Frontiers of Hepatobiliary and Gastrointestinal Physiology" at Mount Desert Island Biological Laboratory. Approximately 12 GI fellows or PhD research fellows rotated through the module, "Gastric Acid Secretion," during the one-week course.

SELECTED RESEARCH SUPPORT

Gastric Cancer Research Fund; 2015-ongoing; PI: Susan J. Hagen, PhD

Them1-mediated metabolic regulation and pathogenic role in NAFLD; NIH, 2015-2020; Multi-PI R01 with David Cohen, MD, PhD, Weill Cornell Medical College and Eric Ortlund, PhD, Emory University

Biology of alimentary epithelia in health and disease; NIH, 2015-2020; PI and Director, Microscopy and Histopathology Core B: Susan J. Hagen, PhD (PI: Wayne Lencer, MD)

Biomedical research training for veterinary scientists; NIH, 2013-2019; Academic Mentor: Susan J. Hagen, PhD (PI: James G. Fox, DVM)

Airyscan (super-resolution) upgrade for the Live-cell LSM 880 confocal microscope; BIDMC Capital Investment Award, 2019

SELECTED PUBLICATIONS

Muthupalani S, Ge Z, Joy J, Feng Y, Dobey C, Cho HY, Langenbach R, Wang TC, Hagen SJ, Fox JG. Muc5ac null mice are predisposed to spontaneous gastric antro-pyloric hyperplasia and adenomas coupled with attenuated *H. pylori*-induced corpus mucous metaplasia. Lab Invest 2019;Aug 9 (Epub ahead of print).

Hagen SJ. Unraveling a new role for claudins in gastric tumorigenesis. Cell Mol Gastroenterol Hepatol 2019;8(1):151-152.

Hagen SJ, Ang LH, Zheng Y, Karahan SN, Wu J, Wang YE, Caron TJ, Gad AP, Muthupalani S, Fox JG. Loss of tight junction protein claudin 18 promotes progressive neoplasia development in mouse stomach. Gastroenterology 2018;155(6):1852-1867.

A complete list of publications begins on page 15.

Tara S. Kent, MD, MS

Associate Professor of Surgery
Vice Chair for Education
Program Director, General Surgery Residency

RESEARCH GROUP

Courtney Barrows, MD
Rodrigo Calvillo-Ortiz, MD
Manuel Castillo-Angeles, MD, MPH
Eiman Ghaffarpasand, MD
John Polanco, MD
Alessandra Storino, MD, MS
Ammara A. Watkins, MD

RESEARCH FOCUS

Research in Pancreaticobiliary Surgery

Our group's work focuses on patient-centered outcomes research in pancreaticobiliary surgery. A prospective database of more than 4,000 operations and 750 pancreatic resections has been developed and maintained from a robust clinical practice, providing the substrate for our investigations. In addition, we have utilized national large databases. Areas of emphasis are investigation into the transition from inpatient to post-discharge care and prediction of post-discharge needs. Based on earlier work, we developed a discharge informational tool for patients and evaluated its utility after pancreatectomy.

Recent efforts have focused on investigation of the means by which patients process information about their pancreatic cancer diagnosis and treatment options, with a goal of improving patient understanding of, and contribution to, their care. We have assessed the readability, accuracy, and suitability of available online information on pancreatic cancer, the communication between the care team and patients and families, and the use of health literacy assessments. We are now investigating the relationship between designated language and time to definitive treatment. We are currently developing a process to assess health literacy and cultural expectations in patients with new pancreas cancer diagnoses in order to evaluate the impact of these factors on patient progression to care. In addition, our group has collaborated with colleagues around the world through our AHPBA and IHPBA networks.

Surgical Education Research

Our surgical education research effort includes the study of factors influencing resident acquisition of knowledge and skills, as well as development of novel curricula. In addition, with support from a Shapiro Institute grant, we developed and evaluated a curriculum on the learning environment and mistreatment. Currently, we are completing a survey of the resident-perceived optimal reporting mechanisms for learning environment concerns. Additionally, we are involved in an NIH-funded multicenter study of the impact of a surgical resident curriculum on cultural dexterity as well as providing technical assistance via a USAID grant to help restructure surgical residency in Vietnam.

ACCOMPLISHMENTS 2018-2019

- Associate Editor, *HPB,* 2018
- Editorial Board member, *Journal of Gastrointestinal Surgery,* 2019

TEACHING, TRAINING, AND EDUCATION

- I continue as Program Director of the General Surgery Residency, a position I have held since September 2012. I administer the training of our 45 categorical and 10 preliminary trainees
- As Vice Chair for Education (since 2014), I oversee the department's educational programs at the student, resident, and fellow levels
- I serve on the Entrustable Professional Activities (EPA) working group, representing the Americas Hepato-Pancreato-Biliary Association (AHPBA) on this Fellowship Council-based group, developing EPAs as standards for fellowship-level training. I am also a member of the International Hepato-Pancreato-Biliary Association (IHPBA) Education and Training Committee as well as Chair of the AHPBA Education and Training Committee

SELECTED RESEARCH SUPPORT

The provider awareness and cultural dexterity toolkit for surgeons trial; NIH R-01, 2018-2022; Co-Investigator: Tara Kent, MD, MS (PIs: Adil Haider, MD, MPH, Douglas Smink, MD)

Improving Access, Curriculum and Teaching in Medical Education and Emerging Diseases (IMPACT MED) Alliance; USAID Cooperative Agreement, 2019-2022; Technical Advisor: Tara Kent, MD, MS (PI: Lisa Cosimi, MD)

SELECTED PUBLICATIONS

Storino A, Guetter C, Castillo-Angeles M, Watkins AA, Mancias JD, Bullock A, Moser A, Kent TS. What patients look for when browsing online for pancreatic cancer: The bait behind the byte. World J Surg 2018;Jul 3 (Epub ahead of print).

Calvillo-Ortiz R, Raven KE, Castillo-Angeles M, Watkins AA, Barrows CE, James BC, Boyd CG, Critchlow JF, Kent TS. Using individual clinical evaluations to assess residents' clinical judgment: Feasibility and residents' perception. J Surg Educ 2018;Nov-Dec (Epub ahead of print).

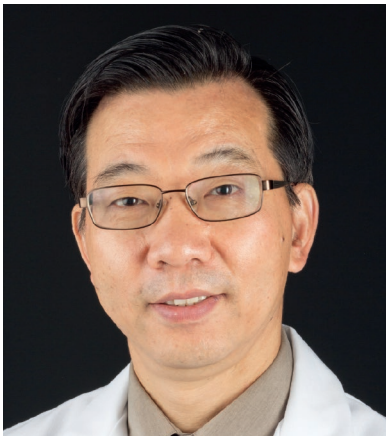
Castillo-Angeles M, Calvillo-Ortiz R, Acosta D, Watkins AA, Evenson A, Atkins KM, Kent TS. Mistreatment and the learning environment: A mixed methods approach to assess knowledge and raise awareness amongst residents. J Surg Educ 2019;Mar-Apr (Epub ahead of print).

Watkins AA, Castillo-Angeles M, Calvillo-Ortiz R, Guetter CR, Eskander MF, Ghaffarpasand E, Anguiano-Landa L, Tseng JF, Moser AJ, Callery MP, Kent TS. Braden scale for pressure ulcer risk predicts rehabilitation placement after pancreatic resection. HPB 2018;Dec (Epub ahead of print).

Castillo-Angeles M, Calvillo-Ortiz R, Barrows C, Chaikof EL, Kent TS. The learning environment in surgery clerkship: What are faculty perceptions? J Surg Educ 2019;July (Epub ahead of print).

Ecker BL, Vollmer CM Jr, Behrman SW, Allegrini V, Aversa J, Ball CG, Barrows CE, Berger AC, Cagigas MN, Christein JD, Dixon E, Fisher WE, Freedman-Weiss M, Guzman-Pruneda F, Hollis RH, House MG, Kent TS, Kowalsky SJ, Malleo G, Salem RR, Salvia R, Schmidt CR, Seykora TF, Zheng R, Zureikat AH, Dickson PV. Role of adjuvant multimodality therapy after curative intent resection of ampullary carcinoma. JAMA Surg 2019;May 29 (Epub ahead of print).

A complete list of publications begins on page 15.



Jin-Rong Zhou, PhD

Associate Professor of Surgery
Director, Nutrition/Metabolism Laboratory

RESEARCH GROUP

Hamid Abdolmaleky, MD
Suthakar Ganapathy, PhD
Yi Ji, PhD
Kehuan Lin (undergraduate)
Chao Sun (PhD candidate)
Sheng Yin (PhD candidate)

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 and other metabolic disorders. 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. Additionally, we have investigated the effects of bioactive components on blood glucose management, alleviation of chronic kidney disease, promotion of gut health, prevention of osteoporosis, and improvement of cognition. In the past year, my laboratory has focused on the following projects.

Synergistic Combinations of Tanshinones for Potent Anti-Cancer and Anti-Cancer Stem Cells

Our studies have shown that tanshinones, which include cryptotanshinone (CT), tanshinone I (T1), and tanshinone IIA (T2A), have potent anti-growth and anti-cancer stem cell (CSC) self-renewal activities against several types of cancer cell lines. Further mechanism studies demonstrated that downregulation of Aurora A and B kinases was an important mechanism shared by all three tanshinones. To further improve the anti-cancer activities of bioactive agents with additive and/or synergistic combination, we found that the combination between CT and T1 or T2A had synergistic effect against prostate cancer in part via downregulation of aurora kinases. Our animal studies by applying orthotopic tumor models further verified that the combination of T1 and CT inhibited the growth and progression of prostate cancer in a synergistic manner.

Bioactive Components Delay the Development and Progression of Chronic Kidney Injury and Improve Cognition

We have also studied the effects of bioactive components, activated lactic acid (ALA), and a soy germ extract (SGE), on chronic kidney disease and associated cognitive impairment *in vivo*. ALA or SGE delayed the progression of adenine-induced chronic kidney injury in mice by inhibiting inflammation and reducing toxicity in the kidney that was associated with modulating inflammation biomarkers in blood and kidney samples, and could significantly improve cognition. We are investigating the possible underlying mechanisms of action of these bioactive components.

Effects of Bioactive Components on Controlling Blood Glucose/Anti-Diabetes and Delaying Diabetes-Associated Cognitive Decline

In this project, we evaluated the effects of a novel dietary ingredient, nostoc, on metabolic disorders and associated cognitive decline by applying both the db/db and high-fat diet-induced obesity (DIO)/prediabetic animal models. We found that nostoc components significantly reduced fasting blood glucose levels in both animal models and delayed diabetes-associated cognitive impairment. We are investigating possible mechanisms of action of nostoc components especially on regulating beta-cell production.

Effects of Epimedium Components on Osteoporosis Prevention

In this project, we evaluated the effects of an epimedium flavonoids extract (EFE) and the major component in epimedium, icariin, on bone metabolism both *in vitro* and in animal systems. *In vitro* studies indicated that EFE and icariin could stimulate osteoblast differentiation, but inhibit osteoclast differentiation. The animal study using ovariectomized mice showed that EFE and icariin reduced osteoporosis. We are in the process of identifying molecular biomarkers that are responsive and responsible for the activity of bioactive components in preventing osteoporosis.

ACCOMPLISHMENTS 2018-2019

Grant Review Activities

- Review panel, Key Programs, National Science Foundation of China, 2019
- Review panel, General Research Fund, Research Grant Council, Hong Kong, 2019
- Ad hoc member, ZRG1 OTC-T (02) M, NCI/NIH, 2019
- Review panel, Function and Efficacy of Nutrients Review Panel of National Institute of Food and Agriculture, U.S. Department of Agriculture, 2018

Editorial Services

- Editorial board member: *Health, Digital Chinese Medicine, Journal of Genetic, Molecular and Cellular Biology, Journal of Disease and Global Health, Single Cell Biology, World Journal of Clinical Oncology, International Journal of Tropical Disease & Health, Hepatobiliary Surgery and Nutrition*
- Editor: *Frontiers in Biosciences*
- Associate Editor: *Integrative Oncology and Rehabilitation*
- Editor-in-Chief: *Nutrition and Metabolic Insights* (2012-present), *Journal of Health Sciences* (2013-present)

Invited Presentations

- Tanshinones and Their Synergistic Combination for Prostate Cancer Therapy; 1st International Conference on the Forefront of Complementary and Integrative Medicine, Boston, MA, 2018
- The current status of body constitution research in the US; Tizhi, Nutrition, and Health for Chinese Forum, Beijing, China, 2018
- Collaborative opportunities for promoting a healthy China via scientific research and development; Boston-Nanjing Twin Cities Summit Forum, Boston, MA, 2019
- Research priorities in nutrition and cancer prevention; The China International Forum at Nutrition 2019, Baltimore, MD, 2019

Other

- Co-Chair, Organizing Committee; Co-Chair, Biomarkers, Bioinformatics, Bioactive Molecules for Development of Functional Foods Session, 24nd International Conference of Functional Foods Center (FFC), 12th International Symposium of Academic Society for Functional Foods and Bioactive Components (ASFFBC)
- Vice Chairperson, the First Board of Specialty Committee of Breast Diseases, World Federation of Chinese Medicine Societies
- Organizing Committee Member; International Conference on Diet and Nutrition, Berlin, Germany

TEACHING, TRAINING, AND EDUCATION

I have been training two postdoctoral fellows and one undergraduate student on a daily basis for the past year. In addition, I served as the co-supervisor of graduate students and thesis defense committee member at the Nanjing University of Chinese Medicine, China, and at the Institute of Food Science Research in Spain.

SELECTED RESEARCH SUPPORT

Effects of epimedium flavonoids extract (EFE) on osteoporosis and breast cancer; Kanion Pharmaceutical Co., China, 2017-2020; PI: Jin-Rong Zhou, PhD

Effects of Wang-Shi-Bo-Chi-Wan (WSBCW) on gastrointestinal functions and its mechanisms of action; Jinghua Pharmaceuticals Co., China, 2017-2020; PI: Jin-Rong Zhou, PhD

Effects of Nostoc on blood glucose management, digestive health and cognitive improvement; Yandi Biotechnology Co, LTD, China, 2018-2020; PI: Jin-Rong Zhou, PhD

Evaluation of anti-oxidative activities of Acai preparations; Vitamin World (China) Limited, 2018-2020; PI: Jin-Rong Zhou, PhD

SELECTED PUBLICATIONS

Cheng Y, Gao XH, Li XJ, Cao QH, Zhao DD, Zhou J-R, Wu HX, Wang Y, You LJ, Yang HB, He YL, Li YR, Bian JS, Zhu QY, Birnbaumer L, Yang Y. Depression promotes prostate cancer invasion and metastasis via a sympathetic-cAMP-FAK signaling pathway. Oncogene 2018;37(22):2953-66.

He L-X, Zhang Z-F, Zhao J, Li L, Xu T, Sun B, Ren J-W, Liu R, Chen Q-H, Wang J-B, Salem M, Pettinato G, Zhou J-R, and Li Y. Ginseng oligopeptides protect against irradiation-induced immune dysfunction and intestinal injury. Sci Reports 2018;8:13916.

Abdolmaleky HM, Gower AC, Wong CK, Cox JW, Zhang X, Thiagalingam A, SHafa R, Zhou J-R, Sivaraman V, Thiagalingam S. Aberrant transcriptomes and DNA methylomes define pathways that drive pathogenesis and loss of brain laterality/asymmetry in schizophrenia and bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 2019;180:138-49.

Ji Y, Li L, Ma YX, Li WT, Li L, Zhu HZ, Wu MH, Zhou J-R. Quercetin inhibits growth of hepatocellular carcinoma by apoptosis induction in part via autophagy stimulation in mice. J Nutr Biochem 2019;69:108-119.

Sun C, Yang J, Cheng HB, Shen W-X, Jiang Z-Q, Wu M-J, Li L, Li W-T, Chen T-T, Rao X-W, Zhou J-R, Wu M-H. 2-Hydroxy-3-methylanthraquinone inhibits lung carcinoma cells through modulation of IL-6-induced JAK2/STAT3 pathway. Phytomedicine 2019;28(61):152848.

A complete list of publications begins on page 15.

Richard D. Cummings, PhD

S. Daniel Abraham Professor of Surgery
Vice Chair, Basic and Translational Research
Director, National Center for Functional Glycomics
Director, Harvard Medical School Center for Glycoscience

RESEARCH GROUP

Rajindra Aryal, PhD
Gabrielle E. Cervoni, MD
Jane Cheng, MD
Sandra Cummings
Sucharita Dutta, PhD
Deniz Eris, PhD
Chao Gao, PhD
Jamie Heimburg-Molinaro, PhD
Nan Jia, PhD
Mark Jones, PhD
Sylvain Lehoux, PhD
Yasuyuki Matsumoto, PhD
Tanya McKitrick, PhD
Alyssa McQuillan
Robert Mealer, MD, PhD
Akul Mehta, PhD
Nandini Mondal, PhD
Maxence Noel, PhD
Steven Siegel, MD, PhD
Kathrin Stavenhagen, PhD
Mohui Wei, PhD
Junwei Zeng, PhD

RESEARCH FOCUS

A key quest of my research during the past 35 years has been to understand the structure and function of glycoconjugates in cell adhesion and signaling, studying the molecular and biochemical functions of surface and secreted glycoproteins in normal biological processes and disease. We study the molecular nature and specificity of protein-glycan interactions and their roles in biology, and how glycans are recognized by glycan-binding proteins (GBPs). My laboratory has been instrumental in developing new technologies in glycoscience, discovering novel functions of glycans in immune recognition and modulation, viral (influenza), parasitic (helminth) and bacterial infections, cell adhesion, selectin biology and leukocyte trafficking, inflammation, new enzymes, and molecular chaperones that regulate protein glycosylation, as well as educating students in the field of glycoscience.

Early work in our laboratory established the identities and specificities of many glycosyltransferases and glycan-binding proteins and plant lectins. In our translational studies, we are exploring glycoimmunology, and the roles of adaptive and innate immune responses to pathogens, as well as human diseases that are both heritable and acquired, and that involve altered glycosylation. We have developed novel techniques in the field for glycan analysis and for exploring the structure/function relationships of glycans using genetic/molecular approaches, biophysical and biochemical strategies, and multiple glycan microarray and glycan bead strategies. We are also developing semi-synthetic methods for making glycoconjugates and for isolating, characterizing, and derivatizing glycans. Such technologies are revolutionary and are growing at a rapid pace; thus, I expect such microarray (and flow cytometry-based arrays) to be a major contributor to the field of glycoscience going forward.

I currently hold 31 patents in the field of glycoscience, and have been the founder or cofounder of three biotechnology companies. My laboratory is the headquarters of the National Center for Functional Glycomics (NCFG), of which I am the Director, and the Protein-Glycan Interaction Resource of the Consortium for Functional Glycomics (CFG), of which I am the Chair, and offers glycan microarray services to hundreds of laboratories worldwide. We also have a strong effort in promoting and developing bioinformatics and databases related to glycoscience. My laboratory and the NCFG moved to Harvard Medical School (HMS) and Beth Israel Deaconess Medical Center (BIDMC) in the fall of 2015, where I founded and was appointed Director of the new Harvard Medical School Center for Glycoscience. My research goals are centered on identifying the structures, functions, and biosynthesis of complex glycoconjugates in a variety of normal and pathologic biological processes.

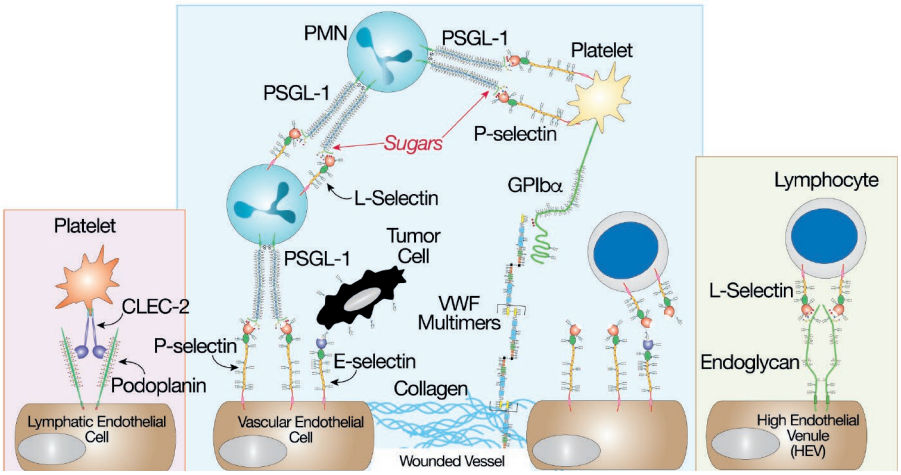


FIGURE 1: Glycoprotein interactions regulate platelet, endothelial cell, leukocyte, and metastatic tumor cell adhesion and trafficking

PINK BOX: Platelet interactions with lymphatic endothelial cells

BLUE BOX: Polymorphonuclear (PMN) leukocytes interacting with vascular endothelial cells, platelets, and other PMNs; Tumor cells interact with vascular endothelial cells; Platelet and VWF interactions at wound sites; Lymphocyte interactions with vascular endothelial cells

YELLOW BOX: Lymphocyte interactions with high endothelial venules

ACCOMPLISHMENTS 2018-2019

- Director, National Center for Functional Glycomics (NCFG), 2015-Present
- Awarded the IGO Award 2019 from the International Glycoconjugate Organization (IGO) for exceptional contributions to the field of glycobiology, Milan, Italy, 2019
- Invited to join Editorial Board of *Nature Scientific Reports,* 2019
- Organizer and Chair, 13th Jenner Glycobiology and Medicine Symposium on "Glycoimmunology – Roles of Sugars in Immune Functions and Medicine," Cambridge, MA, 2019
- Co-Organizer and Co-Chair, NHLBI/NIH Working Group on "Integration of Glycoscience into Bioinformatics and Personalized Medicine," Bethesda, MD, 2018
- Distinguished Alumnus Award from the University of Montevallo, 2019
- Named Scientific Director of the Feihe Nutrition Laboratory, 2018
- Appointed S. Daniel Abraham Professor of Surgery, 2018
- Co-Organizer and Co-Director of the Human Glycome Project, 2018-Present
- Invited Lecture, Molecular Biology of the Cell Course, Institute Pasteur, Paris, France, 2019
- Invited Seminar, Institute Curie, Paris, France, 2019
- Medical Grand Rounds Presentation, BIDMC, Harvard Medical School, Boston, MA, 2019
- Invited Speaker, Scientific Symposium in Honor of Prof. Em. Dr. Beat Ernst, University of Basel, Switzerland, 2019
- Invited Speaker, 13th Jenner Glycobiology and Medicine Symposium, Boston, MA, 2019
- Commencement Speaker, spring graduation ceremony, University of Montevallo, Montevallo, AL, 2019
- Invited Speaker, Beilstein Glyco-Bioinformatics Symposium, Limburg, Germany, 2019
- IGO Award Presentation, 25th International Symposium on Glycoconjugates, Milan, Italy, 2019
- Plenary Lecture, Midwest Carbohydrate & Glycobiology Symposium 2019, University of Notre Dame, IN, 2019

TEACHING, TRAINING, AND EDUCATION

In 2017, I was inducted into the BIDMC Academy of Medical Educators. I am also the co-PI and help direct the NIH-supported K12 program entitled "Harvard Career Development Program in Translational Glycobiology (ProTG): Bridging Glycoscience and Clinical Medicine."

I mentored three doctoral students, all of whom completed their degrees. In 2016, Alexander Noll received his PhD from Emory University with a thesis entitled "Human milk glycan interactions with glycan-binding proteins of the gastrointestinal tract." He published three original peer-reviewed publications and has a comprehensive review ready for submission. In 2017, Matthew Kudelka received his PhD from Emory University with a thesis entitled "Cosmc is an X-linked inflammatory bowel disease risk gene that spatially regulates gut microbiota and contributes to sex-specific risk." He published three original peer-reviewed publications and three reviews. In 2019 Chris Cutler received his PhD under my direction for his doctoral work at BIDMC, granted from Emory University. His thesis was entitled "An investigation into the role of Cosmc in T cell biology and as a key to exploring the O-glycoproteome."

SELECTED PUBLICATIONS

Byrd-Leotis L, Jia N, Dutta S, Trost JF, Gao C, Cummings SF, Braulke T, Müller-Loennies S, Heimburg-Molinaro J, Steinhauer DA, Cummings RD. Influenza binds phosphorylated glycans from human lung. Sci Adv 2019;5(2):eaav2554.

Lu LL, Smith MT, Yu KKQ, Luedemann C, Suscovich TJ, Grace PS, Cain A, Yu WH, McKitrick T, Lauffenburger D, Cummings RD, Mayanja-Kizza H, Hawn TR, Boom WH, Stein CM, Fortune SM, Seshadri C, Alter G. IFN-γ-independent immune markers of *Mycobacterium tuberculosis* exposure. Nat Med 2019;25(6):977-987 (publisher correction 6/20/19).

Tuccinardi D, Farr OM, Upadhyay J, Oussaada SM, Klapa MI, Candela M, Rampelli S, Lehoux S, Lazaro I, Sala-Vila A, Brigidi P, Cummings RD, and Mantzoros CS. Mechanisms underlying the cardiometabolic protective effect of walnut consumption in obese subjects: A cross-over, randomized, double-blinded, controlled inpatient physiology study. Diabetes Obes Metab 2019;21(9):2086-2095.

Pettinato G, Lehoux S, Ramanathan R, Salem MM, He L-X, Muse O, Flaumenhaft R, Thompson MT, Rouse EA, Cummings RD, Wen X, Fisher RA. Generation of fully functional hepatocyte-like organoids from human induced pluripotent stem cells mixed with endothelial cells. Sci Rep 2019;9(1):8920.

Jandus P, Boligan KF, Smith DF, de Graauq E, Grimbacher B, Jandus C, Abdelhafez MM, Despont A, Bovin, N, Simon D, Rieben R, Simon H-U, Cummings RD, von Gunten S. The architecture of the IgG anti-carbohydrate repertoire in primary antibody deficiencies (PADs). Blood 2019; in press.

Takagi J,Turner BS, Kim C, Lehoux S, Cummings RD, Ribbeck K. Mucin glycans attenuate the virulence of Pseudomonas aeruginosa in infection. Nature Microbiol 2019; in press.

A complete list of publications begins on page 15.

SELECTED RESEARCH SUPPORT

Glycoproteomics and the glycosylation code of the brain in asymptomatic and symptomatic Alzheimer's disease; NIH/NIA, 2018-2023; PI: Richard D. Cummings, PhD

National Center for Functional Glycomics; NIH/NIGMS, 2013-2018; PI: Richard D. Cummings, PhD

Modulation of inflammatory responses by helminth glycans; NIH/NIGMS, 2013-2018; PI: Richard D. Cummings, PhD

Facile synthesis of glycosulfopeptides and related bioconjugates; NIH/NIGMS, 2015-2019; Co-PI: Richard D. Cummings, PhD

Smart anti-glycan reagents to generate the human glycome atlas; NIH/NCI, 2015-2018; MPI: Richard D. Cummings, PhD (Co-PI: Ray Mernaugh, PhD, Vanderbilt University)

Discovery platform of mycobacterium tuberculosis glycans; Gates Foundation, 2016-2018; PI: Richard D. Cummings, PhD

Human milk glycan research; Abbott Laboratories, 2015-2018; PI: Richard D. Cummings, PhD

RESEARCH GROUP

Jea Eun Cheong, PhD
Elisa Liardo, PhD

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 provides a platform and expertise in medicinal chemistry to promote bench-to-bedside translation. My laboratory has studied the optimal integration of molecular simulations into the generation of bioactive molecules. In collaboration with investigators at Harvard Medical School, we have applied this research methodology for the discovery of novel inhibitors of the protein-protein interaction (PPI) between interleukin (IL)-18 and its receptor (collaborator: Dr. Leena Pradhan-Nabzdyk, BIDMC), the CDC-like kinase (CLK) in highly aggressive cancers (collaborator: Dr. Bruce Zetter, Boston Children's Hospital), the mast cell degranulation (collaborator: Dr. Aristidis Veves, BIDMC), the ORAI ion channel, the dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), as well as the arylhydrocarbon receptor (AhR) (collaborator: Dr. Elliot Chaikof, BIDMC).

IL-18 plays a significant role in driving the inflammatory processes responsible for the development of intimal hyperplasia (IH). Via molecular simulation and *in silico* screening, we recently identified small molecule compounds that inhibit IL-18 signaling with low micromolar potency. Preliminary data suggest the small molecules elicit IL-18 antagonistic activity by inhibiting the PPI between IL-18 and its receptor. We are actively engaged in the characterization and improvement of the novel inhibitors.

Overly activated mast cells are implicated in the pathology of a number of diseases, including diabetic neuropathy and diabetic foot ulcer. Mast cell activation and the release of a spectrum of proinflammatory mediators are controlled by calcium channels. We have synthesized a new class of calcium channel blockers that effectively inhibit channel function and mast cell degranulation. We have demonstrated efficacy in mouse models of diabetic wound healing and the multidisciplinary study led to a publication in the *Journal of Investigative Dermatology*.

CLKs are a class of kinases that regulate the alternative splicing of messenger RNA and are considered attractive drug targets for cancer as well as neurodegenerative disorders. We have discovered a class of benzimidazoles as highly selectively CLK inhibitors that inhibited cancer growth *in vitro* and *in vivo*. Structure-activity relationship study is currently one focus of our research, which has resulted in newly identified highly active CLK inhibitors (IC_{50}: 1-10 nM).

DYRK1A is a kinase that phosphorylates amyloid precursor and tau proteins, two major pathological effectors involved in the formation of amyloid plaques and neurofibrillary tangle, and consequentially neuroinflammation in Alzheimer's disease (AD). Our SAR and structure-based designs led to the identification of a number of highly active DYRK1A inhibitors with <1 nanomolar (nM) binding affinity (Kd) and potent inhibition of tau phosphorylation (IC_{50}: 20-50 nM).

AHR is a ligand activated transcription factor and controls the expression of IL-22, which plays a critical role in the maintenance and regeneration of barrier tissues of the gastrointestinal tract, respiratory system, and skin. Our computational and SAR studies of a series of novel 3-acylindoles revealed structural attributes important for AHR activation. Orally bioavailable AHR agonists were achieved via improvement of metabolic stability and permeability. We demonstrated in a murine model of inflammatory bowel disease that oral administration of the potent AHR agonists significantly reduced disease severity and protected animals from tissue damages in the gut.

ACCOMPLISHMENTS 2018–2019

We have successfully established a number of collaborative research programs that are supported by extramural funding provided by a federal agency or by other sources. Our research has started to bear fruit in a number of dimensions. In addition to the discovery and dissemination of new knowledge (including eight peer-reviewed publications), one major objective of our center is to promote technological and therapeutic innovations that address highly unmet patients' needs. One of the technologies invented in our laboratory was licensed by a venture capital firm, which formed the cornerstone platform technology in a biotech startup focusing on the discovery and development of novel anticancer and anti-inflammatory therapies. Further, we are in active discussions for multiple funding or licensing opportunities to advance our innovations toward improving patient care. In 2018 and 2019, we have filed three U.S. provisional patent applications, and have planned to submit multiple additional applications based on the inventions from our center:

- Compounds, pharmaceutical compositions, and methods of their use in the inhibition of interaction between Il18 and Il18r. Application #62/881,679
- ORAI channel inhibitors. Application #62/813,402
- Arylhydrocarbon receptor modulators and uses thereof. Application #62/653,257

I reviewed grant proposals for the Medical Research Council (UK), European Research Council, and the Auckland Medical Research Foundation (New Zealand). I also served as a reviewer for journals including *Nature Communication, European Journal of Medicinal Chemistry, Journal of Cancer, Journal of Molecular Medicine,* and *Bioorganic and Medicinal Chemistry.* We have regularly presented our research at national and international conferences.

TEACHING, TRAINING, AND EDUCATION

I have been committed to the training of next-generation scientists who are passionate about translational biomedical research. My laboratory has welcomed visiting scholars from medical centers and industrial research institutes to work alongside research fellows. In addition, we also provided internship opportunities for high school graduates who plan to enter college in basic and biological science. On numerous occasions, I have provided technical expertise to research fellows from collaborators' laboratories, guided their study designs, and had an impactful influence on their scientific development and professional careers. I am inspired by the success of the talented fellows and motivated to transform the center to become a platform of excellence for training and biomedical innovation.

SELECTED RESEARCH SUPPORT

Development of small molecule inhibitors of IL-18 to prevent intimal hyperplasia; NIH, 2016–2018; Co-PI: Lijun Sun, PhD (Contact PI: Leena Pradhan-Nabzdyk, PhD, MBA)

Facile synthesis of glycosulfopeptides and related bioconjugates; NIH, 2015–2019; Co-Investigator: Lijun Sun, PhD (PI: Elliot Chaikof, MD, PhD)

A PSGL-1 glycopeptide mimetic for treatment of metabolic syndrome; NIH, 2016–2020; Co-Investigator: Lijun Sun, PhD (PI: Elliot Chaikof, MD, PhD)

SELECTED PUBLICATIONS

Cheong JE, Zaffagni M, Chung, I, Xu Y, Wang Y, Jernigan FE, Zetter BR, Sun L. Synthesis and anticancer activity of novel water soluble benzimidazole carbamates. Eur J Med Chem 2018;144:372–385.

Cheong JE, Sun L. Targeting IDO1/TDO2-KYN-AhR pathway for cancer immuno-therapy: Challenges and opportunities. Trends Pharmacol Sci 2018;39:307–325.

Cheong JE, Ekkari A, Sun L. A patent review of IDO1 inhibitors for cancer. Expert Opin Ther Pat 2018;28:317–330.

Tellechea A, Bai S, Dangwal S, Theo-charidis G, Nagai M, Koerner S, Cheong JE, Bhasin S, Shih T-Y, Zheng Y, Zhao W, Zhang C, Li X, Kounas K, Panagiotidou S, Theoharides T, Mooney D, Bhasin M, Sun L (co-corresponding author), Veves A. Topical application of a mast cell stabilizer improves impaired diabetic wound healing. J Invest Dermatol 2019; in press.

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

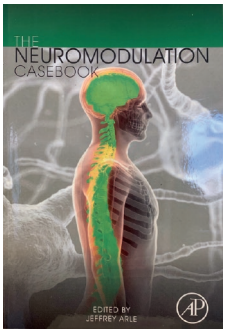
RESEARCH FOCUS

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, we have focused on mechanisms of action to treat chronic pain using high frequency and burst-type spinal cord stimulation as well as work showing how computational models of neural circuitry can be used to help streamline new drug development in major depressive disorder. We have also worked on a new analysis of theoretical changes in information processing in axons of passage through regions using deep brain stimulation in Parkinson's disease and other disorders.

Our work has been presented this past year at the International Neuromodulation Society meeting in Sydney, Australia; the International Society of Intraoperative Neurophysiology in Madrid, Spain; the North American Neuromodulation Society meeting in Las Vegas, NV; the American Association of Neurological Surgeons in San Diego, CA; and the Spine Intervention Society meeting in San Francisco, CA.

In recent efforts, we have further developed and refined our hypothesis on how high-frequency stimulation systems modulate axons, both in suppressing or blocking them as well as in stimulating them. 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 in addition to internal funding through the Beth Israel Deaconess Medical Center Department of Surgery.



◀ Jeffrey Arle, MD, PhD, Editor. *The Neuromodulation Casebook,* Elsevier, Academic Press, 2020.

ACCOMPLISHMENTS 2018-2019

Organizational and Academic Work

- Appointed Co-chair of the Research and Scientific Policy Committee for the International Neuromodulation Society
- Appointed board member of the International Society of Intraoperative Neurophysiology
- Continued as a member of the North American Neuromodulation Society (NANS) Policy and Advocacy Committee
- Appointed as member of the Epilepsy Foundation of New England Patient Advisory Board
- Continued as Associate Editor of *Neurosurgery* and Associate Editor of *Neuromodulation*

Invited Presentations and Meetings

- Moderator, International Society of Intraoperative Neurophysiology, Madrid, Spain
- Moderator, IEEE-EMBC, Honolulu, HI
- Just When You Thought You Had It All Figured Out....North American Neuromodulation Society, Las Vegas, NV
- Mechanism of Action in BurstDR Waveforms. North American Neuromodulation Society, Las Vegas, NV
- Integrating Neuromodulation Devices for Managing Pain into Your Practice: Spine, Head and Face, Post-Stroke, Periphery, and Other. American Association of Neurological Surgeons, Practical Course, San Diego, CA
- Computational Modeling Insights into Mechanisms of Action in Ultra-High Frequency Spinal Cord Stimulation. IEEE-EMBC, Honolulu, HI
- Controlling Spinal Cord Activation During Delivery of SCS Therapy in Patients With High Degree of Movement in the Spinal Canal. International Neuromodulation Society, Sydney, Australia
- Neuromodulation: Can It Make Use Smarter? International Neuromodulation Society, Sydney, Australia
- The Human Spinal Cord Connectome. International Neuromodulation Society, Sydney, Australia
- Robustness in Complex Neural Circuitry Simulations. IEEE-EMBC, Berlin, Germany

SELECTED RESEARCH SUPPORT

The Sydney Family Foundation, 2005-present

SELECTED PUBLICATIONS

Arle JE, Mei LZ, Carlson KW, Shils JL. Theoretical effect of DBS on axonal fibers of passage: Firing rates, entropy, and information content. Stereotact Funct Neurosurg 2018;96(1):1-12.

Arle JE, Mei LZ, Carlson KW. Fiber threshold accommodation as a mechanism of burst and high frequency spinal cord stimulation. Neuromodulation 2019;Nov 27 (Epub ahead of print).

Arle JE, Carlson KW. Novel waveform and method to automatically program spinal cord stimulation for pain therapy. Neuromodulation 2019; in press.

Deer TR, Falowski S, Arle JE, Vesper J, Pilitsis J, Slavin KV, Hancu M, Grider JS; Mogilner A. A systematic literature review of brain neurostimulation therapies for the treatment of pain. Pain Medicine 2019; in press.

Maragkos GA, Gomez-Paz S, Salem MM, Baum P, Arle JE. Non-invasive testing for trigeminal branch stimulation to treat atypical facial pain. J Neurosurgery 2019; in review.

Arle JE, Carlson KW. Medical Diagnosis is NP-Complete 2019; J Exp Theor AI 2019; in press.

Maragkos GA, Motiei-Langroudi R, Arle JE. Safety and efficacy of the VariLift-C® cervical standalone interbody fusion device with emphasis on multiple-level and prior fusion cases. Cureus 2019;11(10):e5885.

Arle JE, Mei, LZ. Robustness in neural circuitry simulations, 2019; in preparation. (Also as a book chapter in Brain and Human Body Modeling; Eds. Springer, Makarov, Horner, Noetscher.)

Arle JE, editor. The Neuromodulation Casebook, Elsevier, Academic Press, London, Jan 2020.

Arle JE, Shils JL, editors. Essential Neuromodulation, 2nd ed. Elsevier – Academic Press, London, 2019; in preparation.

A complete list of publications begins on page 15.

RESEARCH GROUP

Luis Ascanio-Cortez, MD
Kohei Chida, MD
Alejandro Enriquez-Marulanda, MD
Franciele Kipper, PhD
Melissa Lee, BSci
Georgios Maragkos, MD
Mat Robinson, MD
Mohamed Salem, MD
David Vergara, MD

Christopher S. Ogilvy, MD
Professor of Neurosurgery
Director, BIDMC Brain Aneurysm Institute

Ajith J. Thomas, MD
Associate Professor of Neurosurgery
Co-Director, BIDMC Brain Aneurysm Institute

Justin Moore, MD, PhD, MPH
Assistant Professor of Neurosurgery
Director of Research and Radiosurgery, BIDMC Brain Aneurysm Institute
Director of Neuro-Oncology Skull Base, BIDMC

RESEARCH FOCUS

Clinical Research

Flow diverter technology The Brain Aneurysm Institute has been at the forefront of introducing cutting-edge technology such as flow diverters, including Surpass and the Woven EndoBridge (WEB) device. We have one of the largest experiences with flow diverter technology in the world and have added substantially to the understanding of the safety and efficacy of these devices. We have also initiated prospective studies looking at symptomatic improvement with the use of flow diverters and the affect aneurysm characteristics (e.g., thrombosis) have on treatment outcomes. We are also launching a multi-center effort to delineate options when flow diverters fail to obliterate aneurysms. Our publications in peer-reviewed literature (about 20 in 2019), are a reflection of the utility of these devices and techniques.

Cavernous malformations Cavernous malformation are common, yet there is a paucity of data on the natural history of these lesions or treatment options. We have gathered the largest published cohort of cavernous malformations to shed light on these lesions. Furthermore, we have investigated our antiplatelet and statin medication influence on these lesions as potential therapeutic options.

Management of subdural hematoma We are at the forefront of utilizing embolization techniques to treat subdural hematomas. We are co-leading a number of multi-center trials to determine the safety and efficacy of this novel treatment technique. We are currently defining the population that will most benefit from this technique, as well as characterizing patients who may benefit from this technique post-surgical treatment.

Subarachnoid hemorrhage We have multiple projects covering many aspects of subarachnoid hemorrhage (SAH). Our work includes utilizing large databases to provide the first evidence that treating unruptured aneurysms leads to a reduction in SAH. We have also made the startling discovery that treated migraine appears protective for SAH, which suggests some possible drug treatments. Our clinical research has identified the importance of maintaining a minimal blood pressure to avoid poor outcomes in SAH. We have also initiated imaging studies to determine new biomarkers of SAH complications.

Artificial intelligence (AI) We have partnered with companies to design new AI-powered algorithms. Current projects focus on aneurysm and hydrocephalus detection.

Microsimulations We have developed microsimulation techniques to help optimize the most appropriate follow-up strategies following aneurysm treatment. Microsimulations leverage our large datasets to help determine the safest and most cost-effective follow-up treatment options.

Technological and Other Scientific Innovations

In collaboration with a number of international AI firms, we have been pioneering AI software development to identify aneurysms with non-invasive imaging. We have also developed software algorithms to enable identification of hydrocephalus in neurosurgical patients.

Basic Laboratory Science

In the laboratory, we have been exploring the hypothesis that some of the limitations surrounding neural stem cell transplantation can be overcome by the addition of periventricular endothelial cells (PvECs) from the embryonic brain. This novel concept is the outgrowth of several recent studies in the area of angiogenesis and neurogenesis, where it is postulated that PvECs migrate in the embryonic brain in a similar manner to neurons, and have a reciprocal relationship in the development of neuronal networks and the vasculature that supports them. We have also been studying the blood-brain barrier (BBB), a major barrier that has implications from chemotherapy drug administration to traumatic head injury. This work has identified novel mechanisms associated with BBB permeability and will provide the basis for the development of novel treatments to facilitate and amplify BBB permeability. We have also been studying the underlying molecular alternation in endothelial cells in normal and pathological tissue. We aim to delineate the genetic and molecular signature of these cells as a way to enhance treatment of CNS disease including aneurysms, gliomas, and cerebral metastasis. This work is currently being done as an interdisciplinary team and includes collaborations with oncologists and bioinformaticians.

ACCOMPLISHMENTS 2018-2019

- 2018 Physician Champion Award, Brain Aneurysm Foundation (Dr. Thomas)
- Invited Speaker: Controversies in Cerebrovascular and Endovascular Neurosurgery. American Association of Neurological Surgeons annual scientific meeting, San Diego, CA. (Dr. Ogilvy)

TEACHING, TRAINING, AND EDUCATION

- BIDMC Site Director, combined BIDMC/ Boston Medical Center Neurosurgical Residency Program (Dr. Thomas)
- Fellowship Director, Endovascular and Operative Neurovascular Fellowship, BIDMC (Dr. Thomas)

ABSTRACTS, POSTERS, AND EXHIBITS

Gomez-Paz S, Maragkos GA, Ascanio LC, Salem MM, Enriquez-Marulanda A, Orrego-Gonzalez E, Foreman P, Moore JM, Ogilvy CS, Thomas AJ. Anatomic-based hemorrhagic behavior of cerebral cavernous malformations: A retrospective cohort analysis. AANS/CNS Joint Cerebrovascular Section annual meeting, Honolulu, HI (oral presentation)

Salem MM, Enriquez-Marulanda A, Ascanio LC, Jordan N, Gomez-Paz S, Foreman P, Ogilvy CS, Thomas AJ, Moore JM. Pipeline embolization device vs. stent-assisted coiling for intracranial aneurysms treatment: A retrospective and propensity score-matched study. AANS, San Diego CA

Enriquez-Marulanda A, Salem M, Ascanio L, Maragkos G, Gomez-Paz S, Ravindran K, Alturki A, Ogilvy C, Thomas A, Moore J. Effect of admission antiplatelets medications on aneurysmal subarachnoid hemorrhage discharge outcomes: A retrospective and propensity score-matched study. AANS, San Diego, CA

Gomez-Paz S, Salem MM, Maragkos GA, Ascanio LC, Enriquez-Marulanda A, Lee M, Kicielinski K, Moore JM, Thomas AJ, Ogilvy CS. Role of antiplatelet and statin therapy in patients with cerebral cavernous malformations. CNS 2019 annual meeting, San Francisco, CA

SELECTED PUBLICATIONS

Salem MM, Maragkos GA, Enriquez-Marulanda A, Ascanio L, Ravindran K, Alturki AY, Ogilvy CS, Thomas AJ, Moore JM. Statin therapy and diabetes do not affect aneurysm occlusion or clinical outcomes following Pipeline embolization device treatment: A preliminary study. World Neurosurgery 2018;120:e525-e532.

Ogilvy CS, Jordan NJ, Ascanio LC, Enriquez-Marulanda AA, Salem MM, Moore JM, Thomas AJ. Surgical and endovascular comprehensive treatment outcomes of unruptured intracranial aneurysms: Reduction of treatment bias. World Neurosurg 2019;126:e878-e887.

Enriquez-Marulanda A, Ravindran K, Salem MM, Ascanio LC, Kan P, Srinivasan VM, Griessenauer CJ, Schirmer CM, Jain A, Moore JM, Ogilvy CS, Thomas AJ, Alturki AY. Evaluation of radiological features of the posterior communicating artery and their impact on efficacy of saccular aneurysm treatment with the Pipeline embolization device: A case series study. World Neurosurg 2019;125:e998-e1007.

Ravindran K, Salem MM, Alturki AY, Thomas AJ, Ogilvy CS, Moore JM. Endothelialization following flow diversion for intracranial aneurysms: A systematic review. Am J Neuroradiol 2019;40(2):295-301.

Dmytriw AA, Phan K, Salem MM, Adeeb N, Moore JM, Griessenauer CJ, Foreman PM, Shallwani H, Shakir H, Siddiqui AH, Levy EI, Davies JM, Harrigan MR, Thomas AJ, Ogilvy CS. The Pipeline embolization device: Changes in practice and reduction of complications in the treatment of anterior circulation aneurysms in a multicenter cohort. Neurosurgery 2019;Mar 12 (Epub ahead of print).

A complete list of publications begins on page 15.

RESEARCH GROUP

Mary Buss, MD, MPH
Jonathan Edlow, MD
Carl Hauser, MD
Carlo Rosen, MD

Martina Stippler, MD

Assistant Professor of Neurosurgery
Director of Neurotrauma
Neurosurgery Clerkship Director

RESEARCH FOCUS

My research focuses on triage of complicated mild traumatic brain injury (TBI). As the quality of head CT scans has improved dramatically over the last two decades we now can detect minor brain hemorrhage. However, this leads to the over-triage and over-diagnosis of complicated mild TBI. Routine follow-up head CT has not been shown to improve patient outcome or lead to a change in treatment but is still performed at many institutions. Under the leadership of myself, Carlo Rosen, MD (Emergency Medicine, BIDMC) and Carl Hauser, MD (Acute Care Surgery, Trauma, and Surgical Critical Care, BIDMC) a new protocol has been initiated and is currently being investigated with the goal of avoiding routine follow-up head CTs. Within the first year we could reduce the number of follow-up head CTs in the complicated mild TBI population by 75%.

As our society is aging, increasing numbers of elderly people present with TBI. While in this patient population goal-concordant care is very important, it has been shown that few surgeons take the patient's and family's care goals into account. One of my other areas of research is to understand whether training for goal-of-care discussions improves goal-concordant care and also reduces burn-out among surgeons.

ACCOMPLISHMENTS 2018-2019

- Inducted as a Fellow of the American College of Surgeons
- Completed Palliative Care Education and Practice (PCEP) Fellowship
- Selected as a recipient of a Rabkin Fellowship for 2019-2020
- Became Chair for the BIDMC Department of Surgery Wellness Committee
- Voted onto the Board of "Think First," a national nonprofit injury-prevention organization
- Named Neurotrauma Section Editor of *Neurosurgery Open*
- Advanced to Chair-Elect of Women in Neurosurgery Joint Section of the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS)
- Continued as *ex officio* member of the CNS Executive Committee
- Named Neurosurgery Clerkship Director

TEACHING, TRAINING, AND EDUCATION

- Led Communication Care Workshop for surgery, critical care, and emergency medicine residents
- Established Harvard Medical School Neurosurgery Clerkship
- Presented neurosurgery lecture to Harvard Medical School general surgery clerkship students
- Facilitated Outcome, Palliative Care, and Ethical Considerations in Neurosurgical Care Seminar at Congress of Neurological Surgeons meeting
- Co-led (with Alexandra Stillman, MD, BIDMC Neurology) first-ever interdisciplinary and inter-professional TBI symposium held during TBI Awareness Month

ABSTRACTS, POSTERS, AND EXHIBITS

Nelton E, Maragkos G, Richter S, Filippidis A, Stippler M. Clinical course of intracranial bleeding in patients anticoagulated with Factor Xa inhibitors without the use of specific reversal agent. Annual Congress of Neurological Surgeons meeting, San Francisco, CA

Maragkos G, Papavassiliou E, Stippler M, Filippidis A. Meta-analysis of functional outcomes in 5508 patients sustaining a gunshot wound to the head. Annual Congress of Neurological Surgeons meeting, San Francisco, CA

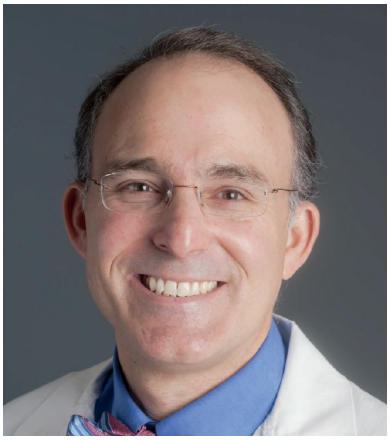
SELECTED PUBLICATIONS

Wagner KE, Binyamin TR, Colley P, Chiluwal AK, Harrop JS, Hawryluk GW, Hickman ZL, Margetis K, Rymarczuk GN, Stippler M, Ullman JS. Trauma. Oper Neurosurg (Hagerstown) 2019;17(Supplement 2): S45-S75.

Maragkos GA, Papavassiliou E, Stippler M, Filippidis AS. Civilian gunshot wounds to the head: Prognostic factors affecting mortality: Meta-analysis of 1774 patients. J Neurotrauma 2018;35(22):2605-14.

Motiei-Langroudi R, Alterman RL, Stippler M, Phan K, Alturki AY, Papavassiliou E, Kasper EM, Arle J, Ogilvy CS, Thomas AJ. Factors influencing the presence of hemiparesis in chronic subdural hematoma. J Neurosurg 2019;11:1-5.

A complete list of publications begins on page 15.



Jorge G. Arroyo, MD, MPH

Associate Professor of Ophthalmology

RESEARCH GROUP

Purva Atreay
Mohamed Elmasry, MD
Efren Gonzalez, MD
Rachelle Koch
Mark Kuperwaser, MD
Brendan Seto
Sinjin Swartz, MS
Keiko Yamada, MD

RESEARCH FOCUS

Our research focuses on the development and evaluation of novel ophthalmologic surgical techniques and less invasive treatment options. We also collaborate with a diverse group of scientists who analyze our large ophthalmic tissue repository, develop algorithms predicting visual and anatomical success using retinal imaging, and conduct multi-centered clinical trials for novel therapeutics.

Surgical Techniques

Much of this past year has been focused on two novel techniques: Endoscopic visualization of the peripheral retina and ciliary body and scleral-fixated intra-ocular lenses. Endoscopic visualization is a valuable tool in vitreoretinal surgery as it provides a unique view that is not limited by media or anterior segment opacities. We recently were invited to author a chapter in the first edition of the *Duke Manual for Vitreoretinal Surgery* based on this topic and have demonstrated its efficacy in a series of complicated cases. Moreover, we are currently working on a project comparing a posterior approach to endoscopic photocoagulation (ECP) treatment for glaucoma vs an anterior approach. This project, like many others in our clinic, takes advantage of the supportive and collaborative relationships we share with the other ophthalmologists in our clinic that synthesize our various specialties into the best possible care for our patients.

Scleral-fixated intra-ocular lenses are our newest surgical innovation, which aims to reduce the number of subluxed or dislocated artificial lenses. With cataract surgeries continuing to be the most common procedure in the country, methods to deal with their complications are of continuous interest. Our method builds on others' work to better secure the artificial lens in a way that does not expose the intra-ocular space to outside elements. For more detailed information, watch our video: www.youtube.com/watch?v=aTeMDZvNDBY.

Less-Invasive Treatment Options

Much of our work this past year has focused on less-invasive alternatives to surgery. Our first treatment is for vitreomacular traction (VMT), a condition that occurs when abnormally strong vitreomacular adhesions (VMA) between the vitreous and retina cause tugging of the retina as the vitreous contracts, resulting in distortion of the neurosensory retina. The medical goal of intervention is to stimulate the point of traction until it releases. While surgery is a viable, effective and relatively safe procedure, there are other potential approaches. We have worked on and publicized one of these methods extensively in the past. Pneumatic vitreolysis (PV) is a procedure involving the intravitreal injection of an expansile gas coupled with intermittent face-down positioning. The gas bubble massages the adhesion point, facilitating its release. This year, we have added an in-depth look at the long-term outcomes of combining this treatment with intravitreal ocruplasmin (IVO), a recombinant protease with activity against the main components of the vitreoretinal interface. In complex cases, this FDA-approved but rarely prescribed drug may provide the last bit of stimulus needed to relieve VMT.

Most retinal conditions originate from a common source: ischemia. As such, we are currently working on a novel intervention aimed at restoring retinal oxygen levels and combatting the root cause of patients' symptoms. While our work is still in its infancy, we hope to soon supplement care with a non-invasive and inexpensive therapy.

ACCOMPLISHMENTS 2018-2019

Presentations

- Anti-VEGF Non-Responders In Age-Related Macular Degeneration. New England Ophthalmologic Society
- Artificial Intelligence in Ophthalmology: A Look into the Future. New England Ophthalmologic Society
- Interesting Surgical Cases and the Use of the Endoscope in Vitrectomies. Grand Rounds Visiting Professor; New York Eye and Ear Infirmary
- Advances in Care for Ocular Trauma. Surgical Grand Rounds, Cambridge Health Alliance

Posters

The research team also presented posters at the International Association for Research in Visual Outcomes conference, Harvard Surgery Research Day, and BIDMC Research Assistant Grand Rounds.

Leadership

I am the Director of Retinal Services at BIDMC. Among my other leadership roles are serving on the Board of Directors of the New England Ophthalmologic Society. I also hold teaching positions as the Associate Chief of Resident and Fellowship Education in the BIDMC Division of Ophthalmology, Co-Director of the BIDMC-Lahey Surgical Retina Fellowship, and instructor at the Massachusetts Eye and Ear Vitrectomy Surgical Course.

TEACHING, TRAINING, AND EDUCATION

We have continued to train rotating residents, fellows, and medical school students from around the world in clinical, surgical, and research settings. We have welcomed several new members to our Retina Service and clinical research team, including BIDMC-Lahey Hospital surgical fellows Dr. Michael Lewen and Dr. Megan Nichols, as well as BIDMC-Joslin Diabetes Center medical retina fellows Drs. Omar Abdelal, Siamak Shokrollahi, Michael Gilbert, and Mohamed Elmasry. Dr. Keiko Yamada of the Kyoto Prefectural University of Medicine is completing an International Retina Research Fellowship in our department. We have also been joined by eight Boston University master's students conducting their clinical research theses with our group. Brendan Seto is our clinical research assistant.

ABSTRACTS, POSTERS, AND EXHIBITS

Yamada K, Seto B, Dingillo G, Hsu C, Arroyo J. Retinal vascular blood flow measurements in healthy patients. Association for Research in Vision and Ophthalmology (ARVO), Vancouver, Canada (poster)

Minturn R, Seto B, Zeng K, Yamada K, Arroyo J. Short-term normobaric hyperoxia therapy for retinal vein occlusion. ARVO, Vancouver, Canada (poster)

Seto B, Zeng K, Minturn R, Yamada K, Tandias R, Arroyo J. Nocturnal normobaric hyperoxia in patients with diabetic macular edema: A case series. Harvard Surgery Research Day (poster)

Seto B, Shahi M, Arroyo J. ECP: A Comparison of an anterior vs posterior approach. BIDMC Research Assistant Grand Rounds (poster)

SELECTED PUBLICATIONS

Seto B, Arroyo J. Endoscopic-assisted vitrectomy. Duke Manual of Vitreoretinal Surgery, First Edition, Ed: Fekrat, S. Lippincott Williams & Wilkins; in press.

Sun P, Tandias RM, Yu G, Arroyo JG. Spectral domain optical coherence tomography findings and visual outcomes after treatment for vitreomacular traction. Retina 2019;39(6):1054-1060.

Wang S, Sun P, Tandias R, Seto B, Arroyo J. Mineralocorticoid receptor antagonists in central serous chorioretinopathy: A meta-analysis of randomized controlled trials. Ophthalmol Retina 2019;3(2):154-60.

Yu G, Sun P, van Zyl T, Tandias R, Arroyo JG. Bilateral central retinal vein occlusions in a young patient with a history of eosinophilic pneumonia and thalamic stroke. Retin Cases Brief Rep 2018;12(4):300-304.

A complete list of publications begins on page 15.

Nurhan Torun, MD

Chief of Ophthalmology
Assistant Professor of Ophthalmology

RESEARCH GROUP

Marc A. Bouffard, MD
Edsel Ing, MD

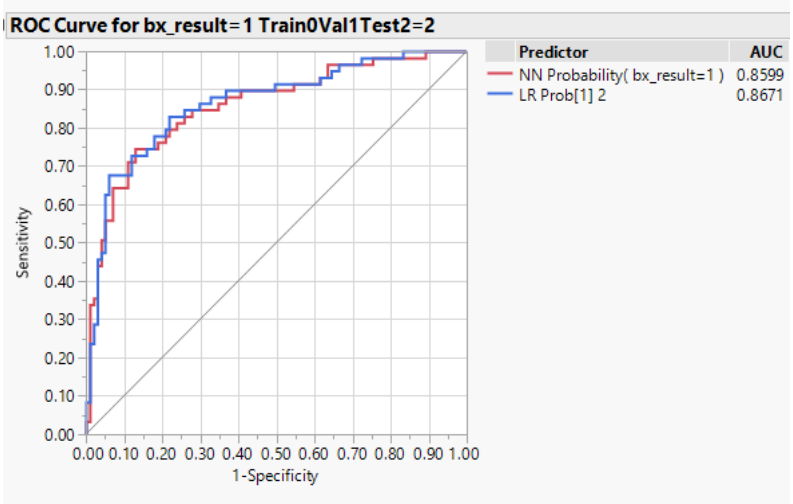
RESEARCH FOCUS

My research continued to focus on investigating newer non-invasive methods for the diagnosis of giant cell arteritis (GCA), the most common vasculitis in the elderly, which can cause irreversible blindness. GCA can be a diagnostic conundrum when it presents in an atypical or occult fashion. Although temporal artery biopsy (TABx) is an invasive and time-consuming test, most authorities feel that it remains the gold standard for the diagnosis of GCA. The primary treatment of GCA, systemic glucocorticoids, has many potential complications. As such, the decision to perform TABx and initiate glucocorticoids can be difficult when there are multiple risk factors of varying importance. Therefore it is advantageous to have an objective, accurate prediction model based on commonly used clinical criteria to estimate the risk of GCA prior to TABx.

It has been argued that statistical models can outperform clinical experts. Humans are prone to making biased predictions based on heuristic methods, and may have difficulty synthesizing the cumulative risk of, and interactions between, multiple predictor variables. Properly formulated regression equations uniformly surpass human experts because the mathematical algorithms can better calculate the appropriate weights that should be placed on individual predictor variables. We wanted to develop and validate neural network (NN) versus logistic regression (LR) diagnostic prediction models in patients with suspected GCA.

LR and artificial neural networks or neural networks NN are two of the most commonly used clinical prediction models for data classification. LR is the most widely applied prediction model for binary classification. LR is a parametric method in which coefficients and intercepts are explicable, and is best applied to "linearly separable" classes. The coefficients from this parametric method show the association of the input variables with the outcome and can suggest a causal inference. NN are processing algorithms modeled after the neural connections of the brain. Just as neuronal connections can be bolstered or decreased through repeated activation, NN can perform an analogous process through mathematical weighting to activate pathways that connect with the desired output. NN is a semi-parametric "black box" method the multiple weights from which are difficult to interpret. The advantages of NN over LR include the "ability to implicitly detect complex nonlinear relationships between dependent and independent variables" and the "ability to detect all possible interactions between predictor variables."

▼ FIGURE 1: ROC curves, complete case analysis, NN vs LR



We conducted a retrospective chart audit of consecutive adult patients who had TABx for suspected GCA at 14 secondary and tertiary care medical centers in Canada, the U.S., and Switzerland. Our outcome variable for this study was biopsy-proven GCA, i.e., the pathologic diagnosis from TABx was considered the final diagnosis. We retrieved the records of 1,833 patients who underwent TABx at the 14 centers, 465 (25%) of whom had biopsy-proven GCA.

The predictor variables were age, gender, headache (HA), clinical temporal artery abnormality (TAabn), jaw claudication (JC), vision loss (VL), diplopia, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet level. The data were divided into three groups to train, validate, and test the models. Of 1,833 patients

who underwent TABx, there was complete information on 1,201 patients, 300 (25%) of whom had a positive TABx. On multivariable LR age, platelets, JC, VL, log CRP, logESR, HA and TAabn were statistically significant predictors of a positive TABx (p<=.05). The NN had higher sensitivity and accuracy than the LR, with a 17% lower false negative rate. The discrimination of the LR and NN models was good at 0.867 (0.794, 0.917) and 0.860 (0.786, 0.911), respectively. The AUC difference was 0.007 higher for the LR than the NN, but not statistically significant on comparison of the ROC curves (p=0.317) (Figure 1). The NN and LR prediction models both had good discrimination, but the NN model had fewer false negatives. While they are not a substitute for TABx, prediction models aid in the objective triage of patients with suspected GCA and can improve the diagnostic yield of TABx.

ACCOMPLISHMENTS 2018-2019

- In July 2019, I delivered the following talks at the Lancaster Course, one of the largest ophthalmology review courses given to national and international ophthalmologists and residents:
  - Neuro-ophthalmic Examination: Pearls and Pitfalls
  - Neuro-ophthalmic Emergencies
  - Central Processing Disorders of Vision
- Since 2018 I have served on the Executive Committee of the BIDMC Academy
- I was invited as the guest of honor to the 52nd National Congress of the Turkish Ophthalmological Association (TOA) in November 2018 in Antalya, Turkey for the following:
  - Frontiers in Optic Neuritis (keynote lecture)
  - An Approach to Nystagmus (course on extraocular motility)
  - Moderator, panel: Sudden Vision Loss
  - Co-moderator, interactive panel: Neuro-ophthalmology and Strabismus
- I presented my research "Diagnostic Prediction Models for Giant Cell Arteritis" at the Harvard Department of Ophthalmology annual meeting in 2019
- I accepted an invitation to give a keynote lecture and participate in the "Ask an Expert" session on ocular motility at the 55th Turkish National Neurology Congress in Antalya, Turkey in 2019

TEACHING, TRAINING, AND EDUCATION

I am involved in didactic and bedside teaching of residents. I developed a curriculum of 11 core neuro-ophthalmology lectures that I deliver each year to neurology residents at BIDMC. I supervise ophthalmology residents in my comprehensive ophthalmology clinics and while doing on-call duty. I am also one of the instructors teaching the Core Medicine Ophthalmology Course to Harvard Medical School students in the Longwood Medical Area, which involves eight to 10 two-hour lectures each year.

Since 2015, I have been one of the Neuro-ophthalmology Fellowship preceptors for the Harvard Neuro-ophthalmology Fellowship. Since 2019, I have taught fellows of BIDMC and Tufts University Combined Neuroradiology Fellowship by presenting two one-hour lectures on "clinicoanatomical correlation in neuro-ophthalmology."

SELECTED RESEARCH SUPPORT

Establishing the endocrine and metabolic profile of idiopathic intracranial hypertension; Department of Neurology Research Grant; PI: Marc A. Bouffard, MD

SELECTED PUBLICATIONS

Ing E, Su W, Schonlau M, Torun N. Support vector machines and logistic regression to predict temporal artery biopsy outcomes. Can J Ophthalmology 2019;54(1):116-118.

Ing EB, Miller NR, Nguyen A, Su W, Bursztyn LLCD, Poole M, Kansal V, Toren A, Albreki D, Mouhanna JG, Muladzanov A, Bernier M, Gans M, Lee D, Wendel C, Sheldon C, Shields M, Bellan L, Lee-Wing M, Mohadjer Y, Nijhawan N, Tyndel F, Sundaram ANE, Ten Hove MW, Torun N. Neural network and logistic regression diagnostic prediction models for giant cell arteritis: Development and validation. Clin Ophthalmol 2019;13: 421-430.

Zhao B, Torun N, Elsayed M, Cheng AD, Brook A, Chang YM, Bhadelia RA. Diagnostic utility of optic nerve measurements with MRI in patients with optic nerve atrophy. AJNR Am J Neuroradiol 2019;40(3):558-561.

Ing E, Kam J, Weisbrod L, Wong SWK, Strungaru MH, Cheng J, Torun N. The incidence of non-arteritic ischemic optic neuropathy following topical clear corneal cataract surgery: Survey and meta-analysis. Can J Ophthalmol 2019; in press.

Jastrzembski B, Torun N. A 45-year-old man with unilateral optic disc edema and vision loss. Digit J Ophthalmol 2019;25(1): 16-20.

Ing E, Pagnoux C, Torun N. Advances in the diagnosis of giant cell arteritis. Current Opin Ophthalmol 2019;30(6):407-411.

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Otolaryngology/Head and Neck Surgery

Ernest (Ted) Gomez, MD, MTR

Instructor in Otolaryngology/Head and Neck Surgery

RESEARCH GROUP

David Caradonna, MD, DMD
Scharukh Jalisi, MD
Pavan Mallur, MD
James Naples, MD
Stephanie Teng, MD

RESEARCH FOCUS

My clinical research is centered on head and neck cancer, with specific interest in treatment outcomes, discovery of quality metrics, and patient risk stratification, especially in patients treated with primary surgery. I work with single-institution data as well as databases including the National Cancer Database (NCDB) and the National Surgical Quality Improvement Program (NSQIP) to provide useful information to both providers and patients.

I also conduct translational research at the intersection of surgical simulation, device development, and human performance. I have studied the effects of vibrotactile haptic feedback (and its lack thereof) in robotic surgery on surgical learning in the simulation and live operative room settings. I have also developed technology for the provision of haptic awareness for electrosurgical systems. My current work examines the role of haptic intelligence for surgical performance and learning curves, and I have ongoing collaborations with engineers to develop technologies that can both assess and enhance surgical skill.

ACCOMPLISHMENTS 2018–2019

- Completed the Head and Neck Oncology/Microvascular Reconstruction/Transoral Robotic Surgery fellowship at the University of Pennsylvania
- Appointed to the American Association of Medical Colleges Program Planning Committee for 2020
- Elected to the Administrative Board of the American Association of Medical Colleges Organization of Resident Representatives (ORR)
- Awarded U.S. patent #10,292,752, entitled Electrocautery Tactile Feedback Systems and Methods, for a device that provides haptic feedback for surgical energy devices in minimally invasive surgery

TEACHING, TRAINING, AND EDUCATION

- Served as course faculty for the Worst-Case Scenarios Simulation Course at the American Academy of Otolaryngology – Head and Neck Surgery Annual Meeting, September 2019
- Performed a validation study for a microvascular anastomosis simulation protocol for early trainees
- Served as course faculty for the 7th Annual Otorhinolaryngology PGY3 SimFest in Philadelphia, PA, May 2019
- Mentored a 2019 Penn Engineering Senior Design team for their project entitled ArcAlert – a system that identifies and warns surgeons of conditions at high-risk for operating room fires

ABSTRACTS, POSTERS, AND EXHIBITS

Gomez ED, Brody RM, Brant, JA, Weinstein GS, Rassekh CH, Newman JG. Nodal yield impacts survival in surgically treated oropharyngeal cancer. American Academy of Otolaryngology – Head and Neck Surgery Annual Meeting, New Orleans, LA, 2019 (oral presentation)

Chao T, Gomez ED, Kearney JJ. Graduated simulation curriculum in Otorhinolaryngology training for teaching and skills assessment. AAMC Northeastern Group on Educational Affairs (NEGEA) Annual Conference, Philadelphia, PA, 2019 (poster)

Gomez ED, Brody RM, Haugen TW, Sheth NP, Shanti RM, Rajasekaran K, Chalian AA, Newman JG, Cannady SB. The anterolateral thigh osteocutaneous (ALTO) free flap: A clinical update and lessons learned. American Head and Neck Society Annual Meeting, Austin, TX, 2019 (poster)

Gomez ED, Brant JA, Cannady SB, Newman JG, Rassekh CH, O'Malley, Jr. BW, Weinstein GS. The role of clinical volume on margin status in transoral surgery for oropharyngeal squamous cell carcinoma: How many cases is enough? American Head and Neck Society Annual Meeting, Austin, TX, 2019 (poster)

SELECTED PUBLICATIONS

Gomez ED, Thaler ER, O'Malley BW, Rassekh CH, Weinstein GS, Newman JG, Brody RM. Techniques for developing and viewing stereoscopic three-dimensional teaching videos for transoral robotic surgery (TORS). J Robot Surg 2019;13(4):581-584.

Thomas WW, Calcagno HE, Azzi J, Petrisor D, Cave T, Barber B, Miles B, Gomez ED, Cannady S, Bhadkamkar M, Hanasono MM. Incidence of inadequate perforators and salvage options for the anterior lateral thigh free flap. Laryngoscope 2019;Jul 4 (Epub ahead of print).

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Otolaryngology/Head and Neck Surgery

James G. Naples, MD

Instructor in Otolaryngology

RESEARCH FOCUS

Repurposing of Therapies as Otoprotective Agents

My main research focus has been in repurposing diltiazem as a novel intratympanic agent to protect against cisplatin ototoxicity. I have studied the effects in various animal models, where I have found preservation of hearing thresholds compared to animals that do not receive the treatment. The aim of this work is to continue to understand the mechanism underlying these protective effects and apply it for use in the clinical setting. I am currently working with the Division of Hematology/Oncology to streamline ototoxicity monitoring in the clinical setting with the hopes of translating this otoprotective research to clinical medicine.

Otologic Biomarkers

I have worked in collaboration with teams at the University of Connecticut and the University of Pennsylvania to identify proteins specific to the inner ear that may have utility as an otologic blood biomarker. Early work suggests that this biomarker may identify inner ear injury prior to permanent audiometric changes in various ototoxicity models, thus offering an opportunity for treatment. I am interested in applying this biomarker to clinical ototoxicity and vertigo. I have initiated a study evaluating the role of this protein in differentiating vertigo caused by the ear from the central nervous system and will be working to initiate this research at BIDMC.

Cochlear Implant and Olfaction

My recent research aims to understand how we can predict outcomes for cochlear implant (CI) users. Currently there are few factors that can predict how well CI recipients will use their device. Rehabilitation with CI requires a significant amount of central processing and cognitive function to "hear" again. In fact, the association of cognitive decline and hearing loss are gaining recognition. Coincidentally, it is well established that olfaction (smell) is an early indicator of memory loss and cognitive decline. Thus, I have initiated a study in collaboration with the University of Pennsylvania and Ohio State University that aims to evaluate whether olfaction correlates with CI outcomes. Ultimately, the goal of this work would be to apply it as a predictor of CI outcomes for patients.

ACCOMPLISHMENTS 2018–2019

- Invited as guest editor to an issue of *Otolaryngologic Clinics of North America*
- Moderated two panel presentations at American Academy of Otolaryngology–Head and Neck Surgery National Meeting
- Selected to Editorial Board of *World Journal of Otolaryngology–Head and Neck Surgery*
- Awarded Fellow Research Award from American Neurotology Society
- Awarded 2nd place for Poster Blitz Presentation at Association for Research in Otolaryngology

TEACHING, TRAINING, AND EDUCATION

- Member of the Otology and Neurotology Education Committee of the American Academy of Otolaryngology
- Selected to participate in two mini-seminar panel discussions at the annual American Academy of Otolaryngology annual meeting
- Fellow instructor at the bi-annual University of Pennsylvania temporal bone dissection course
- Initiated and developed otolaryngology interest groups for medical students while at the University of Connecticut and the University of Pennsylvania
- Initiated and developed a weekly otology journal club for resident/student trainees at the University of Pennsylvania
- Mentored over 15 students through clinical research projects while at the University of Pennsylvania
- Presented quarterly lectures to the otolaryngology residents at the University of Pennsylvania
- Presented yearly lectures to the neurosurgery residents at the University of Pennsylvania

ABSTRACTS, POSTERS, AND EXHIBITS

Naples JG, Cox BC, Singh J, Ruckenstein MJ, Li D. Intratympanic diltiazem-chitosan hydrogel as a novel otoprotectant against cisplatin-induced ototoxicity in a mouse model. 54th Annual Spring Meeting, American Neurotology Society, Austin, TX (podium presentation)

Naples JG, Henry L, Brant JA, Eliades SJ, Ruckenstein MJ. Comparison of Failure Rates for Intratympanic Dexamethasone and Gentamicin in Meniere's Disease. 53rd Annual Spring Meeting, American Neurotology Society, National Harbor, MD (podium presentation)

Naples JG. Integrating the role of history, social science, and technology in understanding hearing loss. 42nd Annual Mid-Winter Meeting, Association of Research in Otolaryngology, Baltimore, MD (podium presentation)

Lee D, Naples JG, Lerner D, Brant JA, Bigelow DC, Alonso-Basanta M, Lee JYK, Ruckenstein MJ. Vestibular schwannoma tumor size is associated with acute vestibular symptoms after Gamma Knife therapy. 54th Annual Spring Meeting, American Neurotology Society, Austin, TX (podium presentation)

Kaufman A, Naples JG, Kaufman H, Brant JA, Eliades SJ, Bigelow DC, Ruckenstein MJ. Lateral wall electrodes increase the rate of post-activation non-auditory percepts. 152nd Annual Spring Meeting, American Otological Society, Austin, TX (podium presentation)

SELECTED PUBLICATIONS

Naples JG, Shah RR, Ruckenstein MJ. The evolution of presenting signs and symptoms of lateral skull base cerebrospinal fluid leaks. Curr Opin Otolaryngol Head Neck Surg 2019;Jul 22.

Naples JG, Henry L, Brant JA, Eliades SJ, Ruckenstein MJ. Intratympanic therapies in Ménière disease: Evaluation of outcomes and early vertigo control. Laryngoscope 2019;129(1):216-221.

Naples JG, Ruckenstein MJ, Cox BC, et al. Intratympanic diltiazem-chitosan hydrogel as a novel otoprotectant against cisplatin-induced ototoxicity in a mouse model. Otology & Neurotology; in press.

Naples JG, Canfarotta M, Tabtabai R, Sparks D, Parham K, Falcone T. Otolaryngology interest groups: A potential solution to the residency match crisis. Laryngoscope Investig Otolaryngol 2018;4(1):24-29.

Gautam A, Naples JG, Eliades SJ. Control of speech and voice in cochlear implant patients. Laryngoscope 2019, Jan 6.

Torres Maldonado S, Naples JG, Fathy R, Eliades SJ, Lee JYK, Brant JA, Ruckenstein MJ. Recent Trends in Vestibular Schwannoma Management: An 11-Year Analysis of the National Cancer Database. Otolaryngol Head Neck Surg 2019 Jul;161(1):137-143.

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Otolaryngology/Head and Neck Surgery

RESEARCH GROUP

David Caradonna, MD, DMD
Ernest Gomez, MD, MTR
Scharukh Jalisi, MD
Pavan Mallur, MD
James Naples, MD

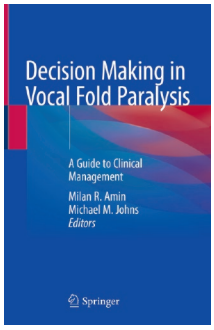
Stephanie E. Teng, MD

Instructor in Otolaryngology

RESEARCH FOCUS

My research focus is related to clinical outcomes in laryngology with recent work on peri-operative and airway management in the professional voice population, as well as the safety and efficacy of jet ventilation for the management of a variety of laryngotracheal pathologies. I am currently working on building a database compiling validated quality-of-life measures collected from patients with voice, airway, and swallowing issues to assess the efficacy of our interventions.

Throughout my training I was involved in pre-clinical investigations using animal models to evaluate laryngeal pathologies including laryngeal burn injury and recurrent respiratory papillomatosis. This is an area that I have a continued interest in, and hope to build toward in the future.



Drs. Stephanie E. Teng and Gregory Postma, Augusta University, contributed a chapter entitled "Static Medialization: Fat Injection vs. Medialization Laryngoplasty," to this book, published in 2019.

ACCOMPLISHMENTS 2018-2019

- Completion of my fellowship in laryngology with Dr. Gregory N. Postma at the Medical College of Georgia at Augusta University (June 2019)
- Invited laryngology panelist, 17th Annual Porubsky Symposium and Alumni Event for the Department of Otolaryngology-Head and Neck Surgery, Medical College of Georgia, Augusta University (June 2019)
- Completion of the Charleston Pharyngoesophageal Manometry Training Program, Medical University of South Carolina (January 2019)

TEACHING, TRAINING, AND EDUCATION

I am involved in the teaching and training of the Combined Harvard Otolaryngology residents, including weekly journal clubs and teaching sessions.

I am mentoring interested Harvard Medical School students through the provision of shadowing opportunities and engagement in research, along with participation in the medical school's otolaryngology interest group meetings.

ABSTRACTS, POSTERS, AND EXHIBITS

CW Myint, SE Teng, JV Griffeth, MA Fritz, SE Meiler, GN Postma. Low frequency, low pressure jet ventilation: Patient selection, safety, and complications. Combined Otolaryngology spring meetings, Austin, TX.

SE Teng, JR Booth, MA Fritz, MW Groves, GN Postma. Airway management in vocal professionals. Combined Otolaryngology spring meetings, Austin, TX.

SELECTED PUBLICATIONS

Irizarry R, Shatzkes DR, Teng S, Kohli N, Har-El G. Osteoradionecrosis of the sternoclavicular joint after laryngopharyngeal radiation. Laryngoscope 2019;129(4): 865-870.

Iftikhar IH, Teng S, Schimmel M, Duran C, Sardi A, Islam S. A network comparative meta-analysis of percutaneous dilatational tracheostomies using anatomic landmarks, bronchoscopic, and ultrasound guidance versus open surgical tracheostomy. Lung 2019;197(3): 267-275.

Teng SE, Postma G. (2019) Static medialization: Fat injection versus medialization laryngoplasty. In: Amin M, Johns M (eds). Decision Making in Vocal Fold Paralysis. Springer.

A complete list of publications begins on page 15.

RESEARCH GROUP

Miguel Bravo, MD
Ryan Cauley, MD, MPH
Danielle Chuang
Diana Del Valle, MD
Christine Kang, MD, MHS
Brady Sieber, MD
Anamika Veeramani (Harvard Medical School)

Bernard T. Lee, MD, MBA, MPH

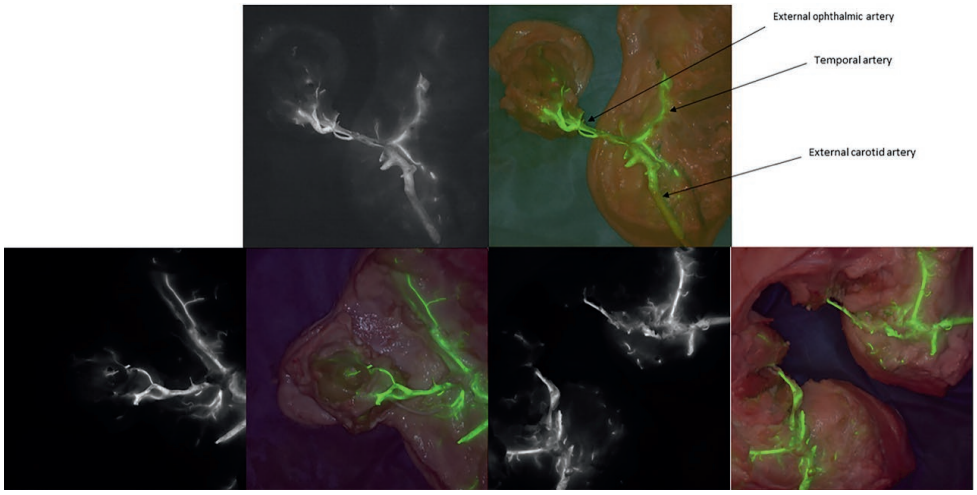
Professor of Surgery
Chief, Plastic and Reconstructive Surgery
Director, Peter Jay Sharp Microsurgery Fellowship Program

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. Using two imaging modalities, Fluorescence-Assisted Resection and Exploration (FLARE) system and Spatial Frequency Domain Imaging (SFDI), we have successfully translated this technology from large animal models to first-in-human clinical trials.

In addition, we have collaborated with Dr. Hak Soo Choi (Massachusetts General Hospital) in examining vascularized composite allotransplantation (VCA) and combining immunohistochemically techniques with our well-developed NIR technologies in order to detect early signs of graft rejection. We are working to develop small and large animal protocols to start our research in this field for reconstructive surgery.

Finally, 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. Most recently, we have been examining patient access, health literacy, and readability of resources for plastic surgery working with collaborators such as Dr. Rima Rudd (Harvard T. H. Chan School of Public Health).



▲FIGURE 1: Near infrared imaging of a composite whole-eye transplant in a swine model. Perfusion of the external ophthalmic artery.

Near Infrared Imaging Systems

Our most recent studies have focused on using the FLARE system to examine perfusion in large animal models. Using a novel liquid latex-indocyanine green combination in a cadaver swine model, we have delineated the vascular anatomy for composite whole-eye transplantation.

In a separate face transplantation model, we have used FLARE and SFDI to determine perfusion in large animals. During these swine studies, we have altered the face transplant constructs to determine feasibility and, ultimately, perfusion. 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.

Patient Access and Health Literacy in Plastic and Reconstructive Surgery

Our clinical outcomes research team has extensively examined the area of health literacy and patient access. The AMA and NIH guidelines are for patient-directed health literature to be written at a sixth-grade level. Unfortunately, most patient resources are well above this level. Our group has examined online patient resources and their readability for patients not only in the English-speaking population but also in the Spanish-speaking population. We are also working to examine health literacy in OpenNotes and how this impacts health communication. Finally, our group is designing new patient materials and patient apps at the appropriate reading levels for patient education.

ACCOMPLISHMENTS 2018-2019

I am the Chief of the Division of Plastic and Reconstructive Surgery at BIDMC. I serve on multiple national committees at the American Society of Plastic Surgeons and serve as the Board Vice President for Academic Affairs. I was recently a visiting professor for the American Society of Plastic Surgeons and visited five sites during that time. At the American Society for Reconstructive Microsurgery, I serve as the Treasurer. I am also a Director for the American Board of Plastic Surgery.

I am currently the Editor-in-Chief of the *Journal of Reconstructive Microsurgery* and serve on the editorial boards of *Annals of Plastic Surgery, Journal of Plastic, Reconstructive, & Aesthetic Surgery,* and *ePlasty.* I am also an editor of a two-volume textbook on reconstructive surgery, *Encyclopedia of Flaps.*

Invited Presentations

- Health Literacy in Surgery. American Society of Plastic Surgeons/Plastic Surgery Foundation Visiting Professor, UNLV, U. Colorado, U. Missouri-Columbia, U. Cincinnati, U. Florida, MD Anderson Cancer Center
- Improving Outcomes in Breast Reconstruction. American Society of Plastic Surgeons/ Plastic Surgery Foundation Visiting Professor, UNLV, U. Colorado, U Missouri-Columbia, U Cincinnati, U Florida, MD Anderson Cancer Center
- What's Trending at the *Journal of Reconstructive Microsurgery.* American Society of Plastic Surgeons/Plastic Surgery Foundation Visiting Professor, UNLV, U. Colorado, U. Missouri-Columbia, U. Cincinnati, U. Florida, MD Anderson Cancer Center
- Academic Plastic Surgery Practice: Strategies for Success and Avoiding Burnout. American Society of Plastic Surgeons/Plastic Surgery Foundation Visiting Professor, UNLV, U. Colorado, U. Missouri-Columbia, U. Cincinnati, U. Florida, MD Anderson Cancer Center
- The Value of an Additional Degree. Plastic Surgery Research Council
- Demonstrating the Value of Breast Reconstruction to Your Hospital. American Society of Plastic Surgeons meeting

TEACHING, TRAINING, AND EDUCATION

I have been training medical students, general surgery and plastic surgery residents, clinical fellows, and research fellows for over 15 years. We have had multiple students from Harvard Medical School (HMS) as well as international students working on our research team. I serve as the course director for the plastic surgery medical student clerkship at BIDMC, a mentor in the Holmes Society, and a mentor for medical students and residents applying to plastic surgery residency programs. I was awarded the Young Mentor Award by HMS in 2012, the Harvard Plastic Surgery Residency Teaching Award in 2013, and the BIDMC Department of Surgery Clinical Research Mentorship Award in 2017.

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, MPH

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

SELECTED PUBLICATIONS

Siddiqui A, Ueno C, Agarwal J, Chang EI, Chrysopoulo M, Davidson C, Khuthaila D, Manahan MA, Matros E, Newman LA, Newman M, Sowden M, Tessler O, Whitacre E, Lee BT. Evidence-based performance measures of autologous breast reconstruction: An American Society of Plastic Surgeons quality performance measure set. Plast Reconstr Surg 2019; in press.

Bravo MG, Granoff MD, Johnson AR, Lee BT. Development of a new large animal model for composite face and whole-eye transplantation: A novel application for anatomical mapping using indocyanine green and liquid latex. Plast Reconstr Surg 2019; in press.

Johnson AR, Bravo MG, Granoff MD, Lee BT. Cultural insensitivity pervasive in Spanish online cosmetic surgery resources: A call to action. Ann Plast Surg 2019; in press.

Johnson AR, Doval AF, Granoff MD, Egeler SA, Bravo MG, Dowlatshahi AS, Lin SJ, Lee BT. A comparative multimetric assessment of English and Spanish carpal tunnel syndrome materials. J Surg Res 2019; in press.

Karinja SJ, Lee BT. Advances in flap monitoring and impact of enhanced recovery protocols. J Surg Onc 2018;118(5):759-767.

Egeler SA, Johnson AR, Ibrahim AMS, Bucknor A, Chen A, Malyar M, Tobias AM, Lin SJ, Mureau MAM, Lee BT. Reconstruction of Mohs defects located in the head and neck: An analysis of 418 patients. J Craniofac Surg 2019; in press.

Epstein S, Tran BN, Cohen JB, Lin SJ, Singhal D, Lin BT. Racial disparities in postmastectomy breast reconstruction: National trends in utilization from 2005-2014. Cancer 2018;124(13):2774-2784.

A complete list of publications begins on page 15.

Samuel J. Lin, MD

Associate Professor of Surgery
Program Director, BIDMC/Harvard Medical School Plastic Surgery Residency

RESEARCH GROUP

Ahmed Ibrahim, MD, PhD
Darya Kazei, MD
Nargiz Seyidova, MD
Catherine Wu, BS

RESEARCH FOCUS

Over the past year, my focus continues to be both basic and clinical research across a spectrum of disciplines in plastic and reconstructive surgery. These are collaborative projects utilizing the expertise and experiences of scientists, engineers, and clinicians. Our main collaborators include: Massachusetts Institute of Technology (MIT), Tufts University, and Massachusetts General Hospital/Wellman Center for Photomedicine.

Electrochemical Activation and Inhibition of Neuromuscular Systems with Modulation of Ion Concentrations Using Ion-Selective Membranes

This project is an ongoing collaborative effort with MIT since 2008. Our pilot data was published in *Nature Materials* in October 2011. 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 for conditions such as facial nerve paralysis, chronic pain, and nerve dysfunction syndromes.

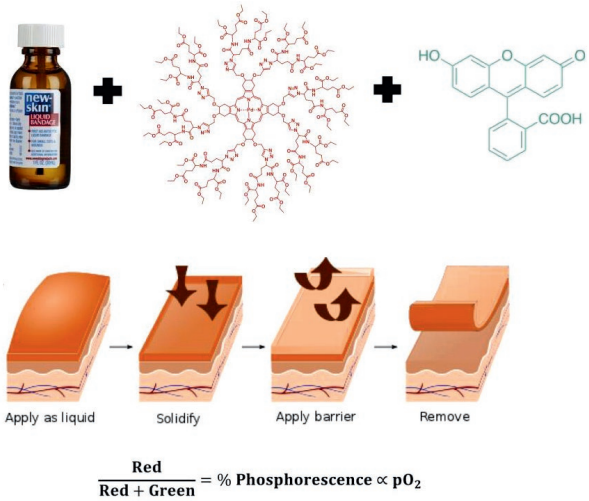
Use of Silk-Based Orthopedic Devices to Modulate Healing

I am co-principal investigator on this R01 funded project. 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). 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.

Use of Novel Oxygen-Sensing, Paint-On Liquid Bandage for Tissue-Oxygenation Monitoring

This project is a collaborative effort with the Massachusetts General Hospital/Wellman Center for Photomedicine in which we are developing a novel oxygen-sensing, paint-on liquid bandage (see Figure 1) for use in perioperative tissue-oxygenation monitoring following microvascular free-tissue reconstruction. Our pilot animal model data was published in *Plastic and Reconstructive Surgery* in July 2017, and we have since conducted a first in-human trial. This technology may be able to address limitations of the gold standard in tissue oxygenation monitoring. It has the potential to improve flap failure rates by providing timely and accurate data to guide decision making.

▼FIGURE 1: A novel oxygen-sensing paint-on liquid bandage is being tested for use in perioperative tissue-oxygenation monitoring.



3D Printing in Plastic Surgery

We have been also focused on other applications of 3D printing, e.g. 3D printed surgical tools for use in plastic surgery either through customized implants or surgical planning. Potential applications in regards to our other basic science research include the use of 3D printing for the production of silk screws and plates.

Outcomes Research in Plastic Surgery

We also have an active clinical research group examining outcomes, techniques, and patient satisfaction following reconstructive and aesthetic plastic surgery procedures, including the head and neck, breast, and abdominal areas. Using institutional databases at BIDMC, as well as national databases from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Healthcare Cost and Utilization Project (HCUP), we have been able to explore risk factors that lead to complications, trends over time, healthcare disparities, and cost analysis.

ACCOMPLISHMENTS 2018-2019

- Over the last year, I have been focused upon the continued development of medical devices that derive from our research in electrical stimulation and neural blocking, bioresorbable devices, and oxygen-sensing paint-on liquid bandage.
- I served as a study section grant reviewer of the Netherlands Organization for Scientific Research, Zon MW, and Small Business (SBIR), National Institutes of Health, Musculoskeletal Oral and Skin Sciences (NIH/MOSS).
- I continued writing plastic and reconstructive surgery books, atlases, and book chapters, with recent projects in the past year.
- My editorial activities include continuing to serve as an Associate Editor of *Plastic and Reconstructive Surgery,* and Associate Editor of *Plastic and Reconstructive Surgery-Global Open*. I was recently selected to serve as Section Editor for the outcomes section in *Plastic and Reconstructive Surgery.*
- I also continued as 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.*
- I was also an invited speaker at a number of regional, national, and international meetings.

Awards

- 2018, Warren B. Davis Circle (*Plastic and Reconstructive Surgery* Reviewer Recognition)
- 2018, Robert Ebert Prize for Health Care Delivery Research or Service. 78th Annual Soma Weiss Student Research Day: Racial Disparities in Complication Occurrence Among Lower Extremity Trauma and Flap Reconstruction Patients
- 2018, Department of Surgery Annual Award for Excellence in Clinical Research Mentorship
- 2019, Harvard Plastic Surgery Residency Program Julian J. Pribaz Teacher of the Year Award
- 2019, Harvard Plastic Surgery Residency Program Lecturer of the Year Award

TEACHING, TRAINING, AND EDUCATION

I have been training medical students, general surgery and plastic surgery residents, and clinical and research fellows for the past 13 years at BIDMC. Currently, I serve as the Program Director of the BIDMC/Harvard Medical School Plastic Surgery Residency Program. In this role, I oversee the medical education and experience of residents who rotate on plastic surgery, organizing a microsurgery lab for the residents and presenting on a range of topics for didactics. 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 and other U.S. and international medical schools.

SELECTED RESEARCH SUPPORT

Degradable orthopedic hardware; NIH/NIAMS, 2015-2020; R01 Co-PI: Samuel J. Lin, MD

Lateral canthotomy and cantholysis training system; Defense Health Program (DHP) and Triton Systems, Inc., SBIR Phase 1 and 2, 2017-2019; Expert Consultant: Samuel J. Lin, MD

Are plastic surgeons participating in the national opioid crisis?; American Association for the Accreditation of Ambulatory Surgical Facilities grant, 2018-2019; PI: Samuel J. Lin, MD

SELECTED PUBLICATIONS

Branford O, Kamali P, Rohrich RJ, Song DH, Mallucci P, Liu DZ, Lang D, Sun K, Stubican M, Lin SJ. #PlasticSurgery. Plast Reconstr Surg 2016;138(6):1354-1365.

Li C, Hotz B, Ling S, Guo J, Haas DS, Marelli B, Omenetto F, Lin SJ, Kaplan DL. Regenerated silk materials for functionalized silk orthopedic devices by mimicking natural processing. Biomaterials 2016;110:24-33.

Rodriguez MJ, Brown J, Giordano J, Lin SJ, Omenetto FG, Kaplan DL. Silk based bioinks for soft tissue reconstruction using 3-dimensional (3D) printing with in vitro and *in vivo* assessments. Biomaterials 2017;117:105-115.

Koolen P, Li Z, Roussakis E, Ibrahim A, Matyal R, Huang T, Evans CL, Lin SJ. Oxygen sensing paint-on bandage: Calibration of a novel approach in tissue perfusion assessment. Plast Reconstr Surg 2017;140(1):89-96.

van Veldhuisen CL, Kamali P, Wu W, Becherer BE, Sinno HH, Ashraf AA, Ibrahim AMS, Tobias A, Lee BT, Lin SJ. Prospective, double-blind evaluation of umbilicoplasty techniques using conventional and crowdsourcing methods. Plast Reconstr Surg. 2017;140(6):1151-1162.

Chattha A, Bucknor A, Chen AD, Lee BT, Lin SJ. Indocyanine green angiography use in breast reconstruction: A national analysis of outcomes and cost in 110,320 patients. Plast Reconstr Surg 2018;141(4):825-832.

A complete list of publications begins on page 15.

Dhruv Singhal, MD

Associate Professor of Surgery
Director, BIDMC Lymphatic Center

RESEARCH GROUP

Hao Wei Chen, BS
Diana Del Valle, MD
Aaron Fleishman, MPH
Melisa Granoff, BA
Anna Rose Johnson, MPH
Christine Kang, MD
Leo Magrini, BS
Chris Mistretta, RN
Jaime Pardo, MD

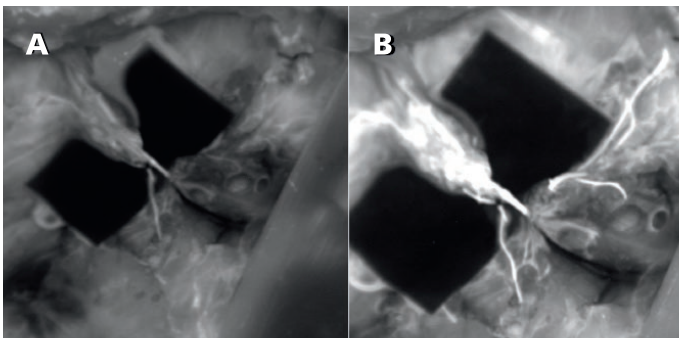
RESEARCH FOCUS

Over the last several years my clinical and basic science research has primarily been focused on the surgical prevention and treatment of lymphedema.

During the past year, as the BIDMC Lymphatic Center became a formalized entity, our research program continued to grow with the unparalleled support from the BIDMC FIRST (Facilitating Innovative Research & Surgical Trials) Program team. Our robust quality improvement database includes more than 700 new patients who have presented to our center for a lymphedema evaluation in the past three years. Similarly, our biorepository currently houses more than 300 samples of healthy and diseased lymphatic tissue. Working closely with Dr. Timothy Padera at the Steele Laboratories at Massachusetts General Hospital (MGH), we have ongoing protocols for tissue investigation.

In the laboratory, we have worked to further refine our animal model to investigate the physiology of preventing lymphedema surgically at the time of lymphadenectomy. Specifically, working in collaboration with Dr. Hak Soo Choi, Gordon Center for Imaging at MGH, we are utilizing unique lymphatic-specific dyes to report real-time changes in lymphatic flow from an extremity. This past year we have focused on noninvasive imaging approaches to measure real-time clearance.

ACCOMPLISHMENTS 2018–2019



▲ **(A)** FLARE image of a lymphaticovenous bypass in the swine groin prior to hind limb lymphatic injection with fluorophore. **(B)** Post injection image demonstrating free passage of dye from lymphatic channels into the venous system. Note that the exposure time (400 ms) was the same in images A and B.

I am the Director of the BIDMC Lymphatic Center.

In the fall of 2018, we held our second annual Lymphatic Symposium at BIDMC (harvardlymphaticsurgery.org). Dr. Sumner Slavin serves as the Honorary Chair of the symposium. The meeting was a tremendous success with 400 participants who traveled from around the world to attend. The two-day event included a separate pathway for clinicians and patients. The highlight of the event was the keynote address from Academy Award-winning actress and Lymphatic Education & Research Network (LE&RN) national spokesperson Kathy Bates. In the fall of 2019, we held our third annual lymphatic symposium, which was geared to patients. Highlights of the sold-out conference included a talk from Chuck Ehrlich, author of "Lymphedema and Lipedema Nutrition Guide" and a keynote address from Cam Ayala, a contestant on last year's "Bachelorette" show on ABC and LE&RN Celebrity Ambassador, who shared his personal journey with primary lymphedema.

I am an ad hoc reviewer for: *Plastic and Reconstructive Surgery, Annals of Plastic Surgery, Journal of Reconstructive Microsurgery,* and the *International Microsurgery Journal.*

Invited Presentations

How to Start a Lymphatic Surgery Program; A Novel Animal Model for the Surgical Prevention of Lymphedema: The Power of Molecular Imaging; Dyes and Lymphatic Surgery. International Course of Supermicrosurgery, Jinan, China

Immediate Lymphatic Reconstruction; Clinical Assessment of Lymphatic Contractility; Hydrodissection to Facilitate DIEP Flap Perforator Dissections. Red Sea Plastic Surgery Meeting, Eilat, Israel

Lymphedema Risk Reducing Surgery in Breast Cancer; What Do You Do With an Idea? Keynote Lecture; How To Build Your Research Work in Supermicrosurgery. European School of Reconstructive Microsurgery, Barcelona, Spain

Immediate Lymphatic Reconstruction; Improving Aesthetic Outcomes in Breast Reconstruction. Barcelona Breast Meeting, Barcelona, Spain

Immediate Lymphatic Reconstruction: Current Results; Live Surgery: Immediate Lymphatic Reconstruction. 8th World Symposium for Lymphedema Surgery, Taipei, Taiwan

Lymphatic Surgery Research: An Update. 53rd Spanish National Plastic Surgery Congress, Madrid, Spain

Immediate Lymphatic Reconstruction: Current Results; Immediate Lymphatic Reconstruction: Update on Research. World Society for Reconstructive Microsurgery, Bologna, Italy

TEACHING, TRAINING, AND EDUCATION

I have been training medical students, general surgery residents, and plastic surgery residents, clinical fellows, and research fellows for the past five years.

SELECTED RESEARCH SUPPORT

Lymphatic reconstitution in microvascular breast reconstruction; BIDMC FIRST Program, 2019-2020; PI: Dhruv Singhal, MD

Evaluating real-time changes in lymphatic flow utilizing optical imaging; Lymphatic Education and Research Network (LE&RN) and the American Society for Reconstructive Microsurgery (ASRM), 2018-2019; PI: Dhruv Singhal, MD

Evaluating real-time changes in lymphatic flow utilizing optical imaging; Plastic Surgery Foundation, 2018-2019; PI: Dhruv Singhal, MD

SELECTED PUBLICATIONS

Johnson AR, Singhal D. Immediate lymphatic reconstruction. J Surg Oncol 2018;118(5):750-757.

Doval AF, Lamelas AM, Daly LT, Tobias AM, Lin SJ, Singhal D, Dowlatshahi AS, Lee BT. Deep inferior epigastric artery perforator flap breast reconstruction in women with previous abdominal incisions: A comparison of complication rates. Ann Plast Surg 2018;81(5):560-564.

Tran BN, Celestin AR, Lee BT, Critchlow J, Tsai L, Toskich B, Singhal D. Quantifying lymph nodes during lymph node transplantation: The role of intraoperative ultrasound. Ann Plastic Surg 2018;81(6):675-678.

Johnson AR, Doval AF, Egeler SA, Lin SJ, Lee BT, Singhal D. A multimetric evaluation of online Spanish health resources for lymphedema. Ann Plast Surg 2019;82(3):255-261.

Johnson AR, Granoff MD, Lee BT, Padera TP, Bouta EM, Singhal D. The impact of taxane-based chemotherapy on the lymphatic system. Ann Plast Surg 2019;82(4S Suppl 3):S173-S178.

Johnson AR, Kimball S, Epstein S, Recht A, Lin SJ, Lee BT, James TA, Singhal D. Lymphedema incidence after axillary lymph node dissection: Quantifying the impact of radiation and the lymphatic microsurgical preventive healing approach. Ann Plast Surg 2019;82(4S Suppl 3):S234-S241.

Ruan QZ, Chen AD, Tobias AM, Fukudome EK, Lin SJ, Lee BT, Singhal D. Referrals of plastic surgery patients to integrative medicine centers: A review of resource utility. Ann Plast Surg 2019;83(1):3-6.

Tran BNN, Chen AD, Granoff MD, Johnson AR, Kamali P, Singhal D, Lee BT, Fukudome EY. Surgical outcomes of sternal rigid plate fixation from 2005 to 2016 using the American College of Surgeons-National Surgical Quality Improvement Program database. Arch Plast Surg 2019;46(4):336-343.

Johnson AR, Bravo MG, Granoff MD, Kang CO, Critchlow JF, Tsai LL, Lee BT, Singhal D. Flow-through omental flap for vascularized lymph node transfer: A novel surgical approach for delayed lymphatic reconstruction. Plast Reconstr Surg Glob Open 2019;7:e2436.

A complete list of publications begins on page 15.

Aristidis Veves, MD, DSc

Rongxiang Xu, MD, Professor of Surgery in the Field of Regenerative Medicine
Director of the BIDMC Rongxiang Xu, MD, Center for Regenerative Therapeutics

RESEARCH GROUP

Navin Jayaswal
George Theocharidis, PhD
Weijie Zhang, MD, PhD

RESEARCH FOCUS

I am 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. Approximately 90 percent of my effort is dedicated to research, five percent for teaching and an additional five percent for administrative and other relevant professional activities.

Translational research 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 impairment of wound healing. This work has been supported by the NIH and nonprofit organizations. I collaborate with investigators from various departments at BIDMC, and investigators from other institutions, such as Brigham and Women's Hospital, to conduct additional translational research.

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

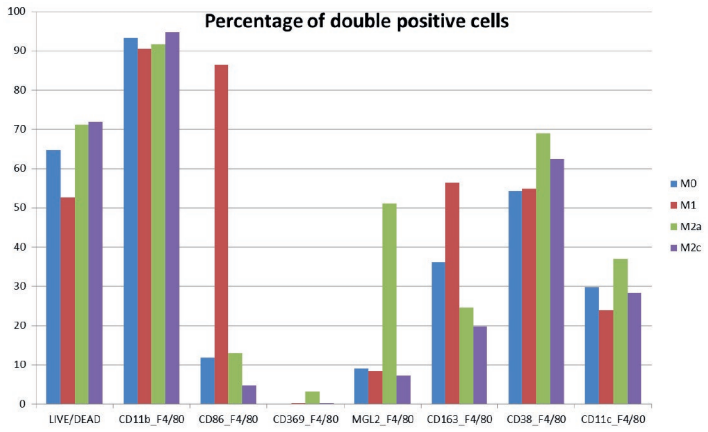


FIGURE 1: Flow cytometry analysis of primary mouse macrophages after 24 hours inside the bandages

I also run my own basic research laboratory that mainly explores the findings of this translational research and tries to identify mechanisms underlying the observed results. My laboratory works closely with other laboratories in BIDMC and is funded by NIH grants. I also collaborate with Dr. David Mooney's laboratory at the Wyss Institute and Harvard Engineering School and Dr. Jonathan Garlick's at Tufts Medical School. The main aim of our collaboration is the development of new wound-healing products. This collaboration has resulted in NIH funding of our grant applications.

The results of my research have been published in prestigious medical journals, including *Lancet, Diabetes,* and *Circulation.* My work, according to Google Scholar as of August 2019, has resulted in more than 19,500 citations; an h-index of 69 and i10-index of 170.

I am also the Director of the Rongxiang Xu, MD, Center for Regenerative Therapeutics since its establishment in December 2015. The center was established after a generous donation from the National Rongxiang Xu Foundation to help further its mission to advance the treatment of patients throughout the world with chronic wounds, burns, and other conditions resulting from a failure of tissue repair and regeneration. As part of its mission, the Center provides resources for collaborative bench-to-bedside research with investigators worldwide, as well as the education of physicians and scientists internationally.

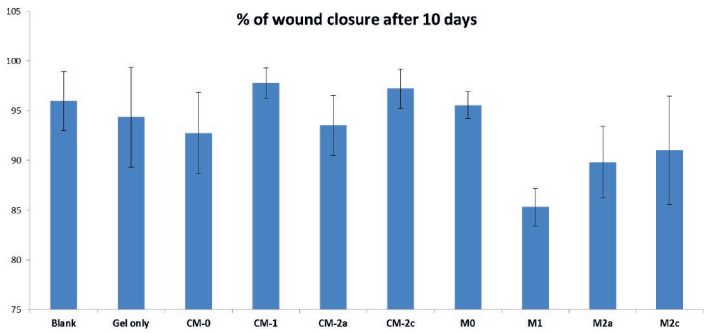


FIGURE 2: Wound healing analysis of mice with bandages covering their wounds

ACCOMPLISHMENTS 2018-2019

A major aim of our work this year was to further understand the pathophysiology of impaired diabetic wound healing. To this end, it is mandatory not only to understand the transcriptional state of individual cells at the skin and blood level but also their proteome state. A combined understanding of single cell transcriptome and proteome levels has the potential to greatly enhance our understanding in an agnostic way regarding the interaction of individual cells in the expression of various genes and production of proteins associated with wound healing. In this project, which is funded by DiaComp, we are comparing single cell transcriptome and proteome profiling of cells from forearm and foot skin biopsies and blood from healthy, non-DM subjects and DM patients with healed and non-healed DFU. We also evaluate single cell protein expression, mainly the expression of proteins known to be expressed in specific cells and involved in the wound-healing process. In addition, in an agnostic way, we compare the expression of the most highly expressed proteins among the various groups.

In addition to the above, we have already performed transcriptomic analysis in a portion of the collected samples. Our preliminary results show that our techniques are working very well and provide reliable data. Also, our data indicate that there are similarities in the gene expression between the forearm and foot skin specimens of the same subjects. Analysis is currently ongoing and we hope to have additional data soon.

We also continue subject recruitment in another NIH-funded study that aims to investigate the association between dermal macrophage infiltration/polarization and mast cell activation with systemic inflammation, oxidative stress, and cardiovascular remodeling in elderly diabetic patients. This work is progressing well and we expect the first results soon.

Finally, we are in the final stages of data analysis of another NIH-funded project that investigates how the tissue microenvironment modulates the functional activation of inflammatory (M1) or pro-regenerative macrophages (M2) to direct wound healing in 3D, *in vitro* skin-like tissues, the propensity of immune cells from diabetic mice to polarize to the M1 versus M2 phenotype *in vivo,* and their impact on diabetic wound healing. This project also aims to develop and test the ability of biomaterials capable of localized, sequential release of factors to first recruit macrophages, and then direct these cells to the M2 phenotype to enhance diabetic wound healing.

TEACHING, TRAINING, AND EDUCATION

My teaching responsibilities include participation in the training of podiatry residents, supervision of the fellows and junior faculty in my laboratory, and participation in mentorship committees of junior faculty members from other units. I am also involved in educational activities of the Center for Education at BIDMC, which provides guidance to candidates for NIH K-series awards. Finally, I participated as series editor, book editor or co-editor and author in numerous textbooks. One of these textbooks *(Diabetes and Cardiovascular Disease)* has been already translated into Italian and another one *(Diabetic Foot)* into Greek.

SELECTED RESEARCH SUPPORT

Role of macrophages in impaired wound healing in diabetes; NIH, 2015-2018; Co-PI/Contact PI: Aristidis Veves, MD, DSc

Skin inflammatory phenotypes as biomarkers of myocardial and vascular remodeling; NIH, 2016-2021; Co-PI/Contact PI: Aristidis Veves, MD, DSc

Single cell transcriptome sequencing of diabetic foot skin; DiaComp 2017-2019; PI: Aristidis Veves, MD, DSc

Proteomic and transcriptomic single cell analysis In DFU patients. DiaComp 2018-2020; PI: Aristidis Veves, MD, DSc

SELECTED PUBLICATIONS

Kashpur O, Smith A, Gerami-Naini B, Maione A, Calabrese R, Tellechea T, Theocharidis T, Liang L, Pastar I, Tomic-Canic M, Mooney D, Veves A, Garlick J. Differentiation of diabetic foot ulcer-derived iPS cells reveals distinct cellular and tissue phenotypes. FASEB 2019;Jan;33(1):1262-1277.

Ana Tellechea A, Bai S, Dangwal S, Theocharidis G, Nagai M, Koerner S, Cheong JE, Bhasin S, Shih TU, Zheng Y, Zhao W, Zhang Z, Li X, Kounas K, Panagiotidou S, Theoharides T, Mooney D, Bhasin M, Sun L, Veves A. A novel mast cell stabilizer improves impaired diabetic wound healing. J Invest Dermatol; in press.

Didangelos T, Veves A. Treatment of diabetic cardiovascular autonomic, peripheral and painful neuropathy. Focus on the treatment of cardiovascular autonomic neuropathy with ACE inhibitors. Curr Vasc Pharmacol 2019;May 20 (Epub ahead of print).

A complete list of publications begins on page 15.

Benjamin C. James, MD, MS

Assistant Professor of Surgery
Section Chief, Endocrine Surgery
Associate Surgery Clerkship Director, BIDMC

RESEARCH GROUP

Hao Wei Chen, BA
Richard D. Cummings, PhD
Sarah Duncan, BA
Per-Olof Hasselgren, MD, PhD
Sylvain Lehoux, PhD
Chun Li, MD
Anthony Maeda, MD
Michiya Nishino, MD, PhD

RESEARCH FOCUS

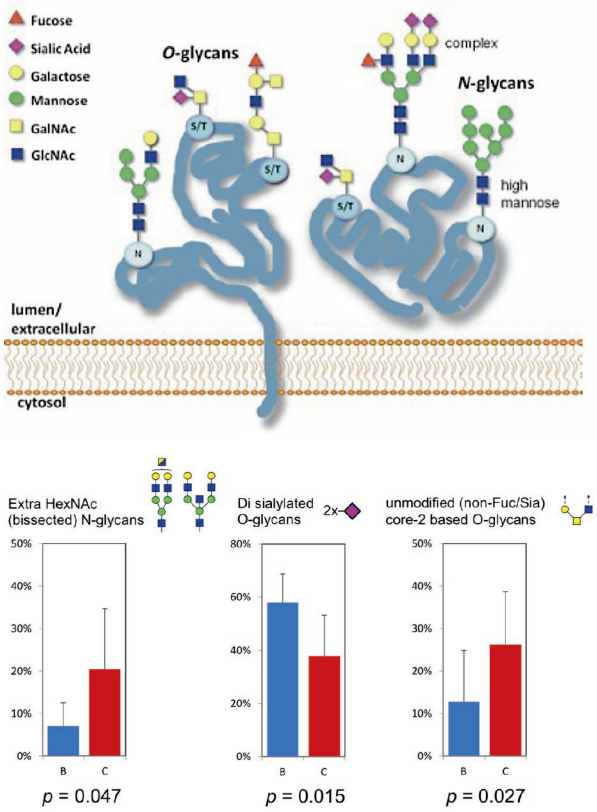
Over the past several decades there has been a substantial increase in the diagnosis and treatment of differentiated thyroid cancer. This rise has largely been attributed to increased detection of nonaggressive and nonlethal thyroid cancers. It has been suggested that this rise has resulted in an epidemic of overtreatment of thyroid cancer. My research has focused on a combination of population-level analysis of thyroid cancer incidence and treatment patterns; an evaluation of the surgical, financial and quality of life impact of surgical treatment of thyroid cancer; and the development of new translational approaches to the evaluation of thyroid nodules.

Differential Glycosylation Patterns in Papillary Thyroid Cancer

Thyroid nodules are a common clinical encounter, found in as high as 68% of the population by ultrasound detection. When evaluated by fine needle aspiration, roughly 2-5% are diagnosed as malignant and 55-74% are classified as benign. However, the remaining biopsies are reported as cytologically indeterminate. The risk of malignancy in these indeterminate categories can range anywhere from 10-30%. As a result, a large number of patients may be subjected to surgery solely for the purpose of obtaining a diagnosis, which is often benign.

The focus of investigations over the past 15 years aimed at delineating cases of indeterminate pathology has revolved almost exclusively around finding clinically-relevant molecular markers capable of distinguishing between benign and malignant tissue. These commercially available tests have proven beneficial as rule-out tests. However, their positive predictive value has been as low as 50%, making their clinical utility, when positive, not as useful.

Recent research aimed at understanding cancer pathogenesis and progression has focused on the topic of glycosylation, the post-translational process of adding glycan moieties to non-carbohydrate structures such as proteins or lipids. More important is the promise that by understanding differences in glycosylation patterns, glycobiomarkers for human cancers can be identified. Differences in glycosylation have been studied in virtually all types of cancers, including brain and lung; however, this has yet to be systemically studied for papillary thyroid cancer. Our lab has begun to evaluate glycosylation patterns in benign thyroid tissue and papillary thyroid cancer. Preliminary unpublished results of N- and O-glycans suggest a large difference in glycosylation in papillary thyroid cancer compared to benign thyroid tissue. Specifically, markedly elevated levels of unmodified (non-Fuc/Sia) core-2 based O-glycans, Di sialylated O-glands and Extra HexNAc (bisected) N-glycans were seen in papillary thyroid cancer. Based on these findings, we will continue to evaluate these differences by validating our initial findings and expanding our evaluation of the glycosylation profile in cancerous thyroid nodules. Our hope is that over the coming years, we may be able to develop a diagnostic tool that may aid in definitely distinguishing benign from malignant thyroid nodules.



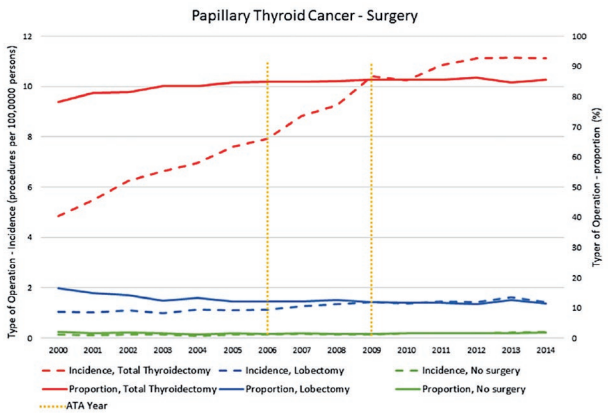
▲FIGURE 1: *N*- and *O*- Glycosylation

Economic Impact of a Diagnosis of Thyroid Cancer

Cancer care expenditure in the United States continues to rise yearly and is projected to surpass $150 billion by 2020. Although thyroid cancer has a generally high survival rate, it is associated with a potential long-term financial and psychological impact, which has not previously been rigorously studied. We aimed to evaluate the comparative prevalence of financial and psychological hardship among U.S. thyroid cancer and non-thyroid cancer survivors. In an ongoing evaluation using the Agency for Healthcare Research and Quality Medical Expenditure Panel Survey (MEPS), we have found that thyroid cancer survivors experience a significantly higher level of both material and psychological financial hardship compared to non-thyroid cancer survivors. These findings suggest that financial hardship may be under-recognized in the medical community and warrants further investigation into the etiology behind the financial burden associated with a diagnosis of thyroid cancer. Our findings are currently in submission.

Treatment Patterns in Thyroid Cancer

Over the past 15 years, there has been a growing body of literature suggesting a rising incidence of thyroid cancer without a rise in mortality. As a result, there has been a shift in guidelines to offer less aggressive surgical intervention. These recommendations have come as multiple studies have shown that patients with thyroid cancer may have a similar prognosis when undergoing less aggressive surgical intervention such thyroid lobectomy. Our group hypothesized that despite evidence of equivalent survival with less aggressive treatment, patients are still undergoing aggressive surgeries for the treatment of thyroid cancer regardless of the size of the cancer. Our findings have shown that the incidence of total thyroidectomy has not decreased over the past 15 years despite recommendations encouraging consideration of lobectomy for patients with small papillary thyroid cancers.



▲FIGURE 2: Treatment patterns in thyroid cancer

ACCOMPLISHMENTS 2018-2019

- Elected to the Editorial Board of the *Journal of Surgical Research*
- Elected to the Research Committee for the American Association of Endocrine Surgeons
- Appointed Director of the Advanced Surgery Elective, BIDMC
- Appointed Co-Chair of the Postgraduate Research Scholarship Committee
- Graduate of the HMS Academy Fellowship

Invited Presentations

- Panelist, Academic Surgical Congress

TEACHING, TRAINING, AND EDUCATION

I developed an endocrine surgery teaching series for residents rotating on the endocrine surgery service. This series was developed to prepare residents for both the written and oral general surgery boards. As a result of my dedication to education, I was given the "Outstanding Faculty Mentor Award" by BIDMC in June of 2019. I have also taken on a new role in the BIDMC Department of Surgery as Director of the Advanced Surgery Sub-Internship.

SELECTED PUBLICATIONS

James BC, Mitchell JM, Jeon HD, Vasilottos N, Grogan RH, Aschebrook-Kilfoy B. An update in international trends in incidence rates of thyroid cancer, 1973-2007. Cancer Causes and Control 2018;29(4-5):465-47.

James BC, Aschebrook-Kilfoy B, White MG, Applewhite MK, Kaplan SP, Angelos P, Kaplan EL, Grogan RH. Quality of life in thyroid cancer-assessment of physician perceptions. J Surg Research 2018;226: 94-99.

Calvillo-Ortiz R, Raven KE, Castillo-Angeles M, Watkins AA, Barrows CE, James BC, Boyd CG, Critchlow JF, Kent TS. Using individual clinical evaluations to assess residents' clinical judgement; Feasibility and residents' perception. J Surg Educ 2018;75(6):e31-e37.

Rappaport M, Skierczynski P, Dungy-Poy-thress L, Benjamin T, Saunders BD, Wagner AA, James BC. Chromaffin-cell tumors in pregnancy: A case series and systematic review. World J Endoc Surg 2018;10(3): 163-169.

James BC, Timsina L, Graham R, Angelos P, Haggstrom DA. Changes in total thyroidec-tomy versus thyroid lobectomy for papillary thyroid cancer during the past 15 years. Surgery 2019;166(1):41-47.

Nagarur A, McEvoy JW, Hirsh DA, James BC. Words Matter: Removing the word pimp from medical education discourse. Am J Med 2019 (Epub ahead of print).

DeLacey S, Liu Z, Broyles A, El-Azab SA, Guandique CF, James BC, Imel EA. Hyper-parathyroidism and parathyroidectomy in X-linked hypophosphatemia patients. Bone 2019 (Epub ahead of print).

Roth EM, Barrows CE, Nishino M, Sacks B, Hasselgren PO, James BC. Papillary thyroid cancer with extrathyroidal exten-sion of desmoid-type fibromatosis. A case report of an aggressive presentation of an uncommon pathologic entity. Int J Surg Case Rep 2019 (Epub ahead of print).

A complete list of publications begins on page 15.

Ted A. James, MD, MHCM

Associate Professor of Surgery
Chief, Breast Surgical Oncology
Co-Director, BreastCare Center
Vice Chair, Academic Affairs

RESEARCH GROUP

Leah Beight, MPH
Isha Emhoff, MD
Betty Fan, DO
Leo Magrini, BS
Alessandra Mele, MD
Jamie Pardo, MD
Stephanie Serres, MD, PhD
Monica Valero, MD

RESEARCH FOCUS

Our Breast Cancer Surgery Outcomes Research and Innovation (BCSORI) Program is focused on assessing the effectiveness, quality, and value of specific care practices and interventions in the surgical management of breast cancer. The goal is to derive best practices, determine optimal pathways, and develop innovations in care delivery that improve quality for patients with breast cancer. The program integrates health care services research, quality improvement, health care delivery science, and implementation science. Innovations in decision-support, patient care models, and patient education are employed to advance care and outcomes. We use a variety of clinical databases, patient-reported outcomes, and real-world data sources to critically appraise results and establish best practices.

Outcomes include traditional clinical metrics in breast cancer (e.g., survival, complications, local recurrence), as well as patient well-being, satisfaction, functional status, and impact on the health-care system. The results then "translate" into practice and policy by working with clinicians, professional societies, patients, and health-care system leaders.

Outcomes research seeks to understand the end results of particular health-care practices and interventions. By linking the care people get to the outcomes they experience, outcomes research has become the key to developing better ways to monitor and improve the quality of care.

ACCOMPLISHMENTS 2018-2019

- National Institutes of Health grant funding to support research initiatives
- National Cancer Database research awards
- Harvard research awards
- Invited podium presentations at multiple national surgical research meetings
- Peer-reviewed publications in high-impact surgical journals

TEACHING, TRAINING, AND EDUCATION

Our research fellow completed a Master of Science in Epidemiology degree program, a 42.5 credit program with the goal of training clinicians with the quantitative skills needed for a clinical research career. Students in this program are required to complete a research thesis under the joint supervision of a local research advisor and a member of the faculty of the Department of Epidemiology at the Harvard T. H. Chan School of Public Health. Additional research training is provided through a series of local and national courses, as well as one-on-one mentorship with experienced senior research faculty.

Our research team receives formal mentoring in the areas of clinical outcomes research, quantitative and qualitative methods, designing high-level observational studies, assessing validity, working with clinical registries, managing and analyzing large datasets, mixed methods research, implementation science, manuscript preparation, grant-writing skills, and academic career development.

Our Clinical Scholarship Program pairs all first-year categorical general surgery residents with a faculty research mentor who guides the residents throughout the year as they acquire the skills to develop and implement a clinical research project. The objectives of the Clinical Scholarship Program are to provide residents with a robust foundation for scholarship early in their training, increase their academic productivity, and enhance their opportunities to compete for national grants.

SELECTED RESEARCH SUPPORT

Breast cancer research project: Analysis of claims in breast cancer surgery; CRICO Data Use agreement, 2019-2020; Co-Investigator: Ted James, MD, MHCM

Identifying strategies for comprehensive survivorship care plan implementation; Alliance for Clinical Trials in Oncology: Cancer Care Delivery Research Committee ($250,000), 2018-2019; Co-PI: Ted James, MD, MHCM

Translating research into practice: A regional collaborative to reduce disparities in breast cancer care; NIH, 2017-2022 ($444,281); Collaborating PI: Ted James, MD, MHCM

SELECTED PUBLICATIONS

Johnson AR, Fleishman A, Tran BNN, Shillue K, Carroll B, Tsai LL, Donohoe KJ, James TA, Lee BT, Singhal D. Developing a lymphatic surgery program: A first-year review. Plast Reconstr Surg 2019;144(6):975e-985e.

Li S, Alapati A, Riba L, Fleishman A, James TA, Sharma R. Delayed adjuvant hormonal therapy and its impact on mortality in women with breast cancer. Breast J 2019;Oct 11 (Epub ahead of print).

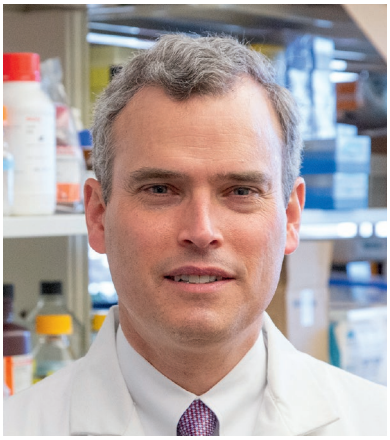
James TA, Zhang JQ. ASO author reflections: A closer look at burnout and professional fulfillment in breast surgery. Ann Surg Oncol 2019;Aug 29 (Epub ahead of print).

Freund KM, Haas JS, Lemon SC, Burns White K, Casanova N, Dominici LS, Erban JK, Freedman RA, James TA, Ko NY, LeClair AM, Moy B, Parsons SK, Battaglia TA. Standardized activities for lay patient navigators in breast cancer care: Recommendations from a citywide implementation study. Cancer 2019;Aug 26 (Epub ahead of print).

Johnson AR, Bravo MG, James TA, Suami H, Lee BT, Singhal D. The all but forgotten Mascagni-Sappey pathway: Learning from immediate lymphatic reconstruction. J Reconstr Microsurg 2019;Aug 9 (Epub ahead of print).

Zhang JQ, Riba L, Magrini L, Fleishman A, Ukandu P, Alapati A, Shanafelt T, James TA. Assessing burnout and professional fulfillment in breast surgery: Results from a national survey of the American Society of Breast Surgeons. Ann Surg Oncol 2019;26(10):3089-3098.

A complete list of publications begins on page 15.



A. James Moser, MD, AM

Professor of Surgery, Harvard Medical School
Co-Director, BIDMC Pancreas and Liver Institute
Director, BIDMC Pancreatic Cancer Research Program
Director, PLI Disease Registry and Biorepository Core

RESEARCH GROUP

Project Survival
Corinne DeCicco
Wendy Hori, RN
Kevin Kennedy, PhD
Genesis Malara
Koenraad Mortele, MD
John Putzke, PhD, MSPH
Khoschy Schawkat, MD

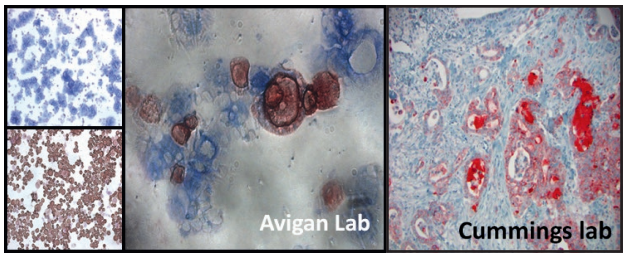
Biomarkers, Causal Inference, and Outcomes of Pancreatic Cancer
Carlos Cordova, MD
Michiel Francken
William E. Gooding, MS
Juanita Rodriguez, MD
Wald Van der Vliet, MD
Koen Verkoulen

The Role of Tn Antigen in Pancreatic and Duodenal Cancers
Richard D. Cummings, PhD
Gabrielle Dombek, MD
Jonathan Glickman, MD, PhD
Kathryn Stackhouse, MD

RESEARCH FOCUS

Our research program to discover and validate novel diagnostic and therapeutic biomarkers for pancreatic cancer spans an increasing number of expert collaborators at international centers of excellence. Project Survival remains the core of this effort and incorporates leaders in the fields of biomarker discovery, including artificial intelligence algorithms, experts in GI oncology, cancer biology, genetic target selection, diagnostic platform development, and novel imaging assessment of treatment outcome. In concert with the PLI Biorepository Core, these programs, and data support collaborations with Helsinki University Hospital, Masstricht University Medical Center, and the Academic Medical Center Amsterdam. These collaborations enable the training of BIDMC surgery research fellows, medical students, and Dutch MD/PhD candidates obtaining advanced degrees in clinical science and translational research through a unique trans-Atlantic collaborative of which Dr. Moser is the Harvard co-promoter.

Here at BIDMC, we are working with Dr. David Avigan and the Immunooncology Institute to develop and enrich a novel autologous DC fusion vaccine for pancreatic cancer in parallel to the use of Tn antigen (Dr. Richard Cummings) as a method to sort and enrich the fused construct in the preclinical phase of a therapeutic clinical trial for metastatic pancreatic cancer.



These efforts are supported through large industry and society grants and the enduring generosity of numerous grateful patient family foundations whose vision and partnership are critical to developing the critical mass of people required to enable this level of interdisciplinary cooperation within the academic spheres of numerous centers of excellence.

ACCOMPLISHMENTS 2018-2019

- Elected Chairman of the Project Survival Joint Steering Committee
- Director of the PLI Disease Registry and Biorepository Core
- Listed in "Boston's Best Doctors"

SELECTED RESEARCH SUPPORT

Project Survival: Multisite identification and validation of prognostic biomarkers for pancreatic cancer detection and treatment. Berg Pharma, LLC: 2015-2022; PI: ($5,150,000 total costs) and Chairman of the Joint Steering Committee: A. James Moser, MD, AM

Phase II study of pancreatic enzyme replacement therapy (Zenpep) on completion rates of adjuvant therapy among subjects with resected pancreatic ductal adenocarcinoma; Allergan, Inc., 2016-2019; PI ($418,500 total cost): A. James Moser, MD, AM

Systematic intraoperative assessment of robotic technology during high-complexity HPB surgery; Investigative robotic surgery grant, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), 2019-2020; PI ($50,000 total grant): A. James Moser, MD, AM

Computational modeling of pancreatic cancer biology and development of prognostic algorithms; Alliance of Families Fighting Pancreatic Cancer (affpc.org), 2014-2019; PI ($100,000 annually): A. James Moser, MD, AM

TEACHING, TRAINING, AND EDUCATION

- Co-promoter for MD/PhD candidates studying Clinical Surgery and Innovation at Maastricht University Medical Center and Academic Medical Center, Amsterdam, Netherlands
- Co-Director of Pancreaticobiliary Multidisciplinary Management Conference, a weekly CME-approved course of Harvard Medical School (50 hours)

SELECTED PUBLICATIONS

Klompmaker S, Peters NA, van Hilst J, Bassi C, Boggi U, Bushc OR, Nieses W, Van Gulik TM, Javed Garces-Descovich A, Morrison TC, Beker K, Jaramillo-Cardoso A, Moser AJ, Mortele KJ. DWI of pancreatic ductal adenocarcinoma: A pilot study to estimate the correlation with metastatic disease potential and overall survival. AJR Am J Roentgenol 2019;212(2):323-331.

Klompmaker S, van der Vliet WJ, Thoolen SJ, Ore AS, Verkoulen K, Solis-Velasco M, Canacari EG, Kruskal JB, Khwaja KO, Tseng JF, Callery MP, Kent TS, Moser AJ. Procedure-specific training for robot-assisted distal pancreatectomy. Ann Surg 2019;Mar 28 (Epub ahead of print).

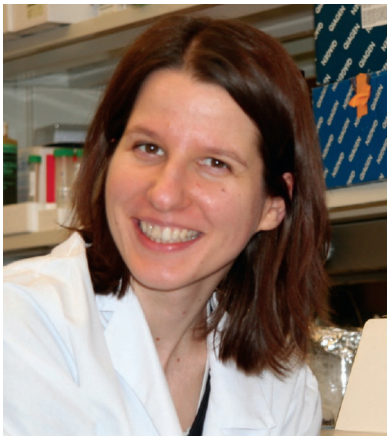
Ore AS, Klompmaker S, Stackhouse K, Solis-Velasco M, Francken M, Callery MP, Kent TS, Moser AJ. Does surgical approach affect outcomes of enucleation for benign and low-grade pancreatic tumors? An ACS-NSQIP evaluation. HPB (Oxford) 2019;May 7 (Epub ahead of print).

Schawkat K, Tabah N, Tridente D, Schlechter BL, Singer T, DeCicco C, Moser AJ, Mortele KJ. Incidental pulmonary embolism in pancreatic ductal adenocarcinoma: Impact of tumor and AJCC stages at initial staging CT. Pancreatology 2019;19(7):979-984.

Stackhouse KA, Storino A, Watkins AA, Gooding W, Callery MP, Kent TS, Sawhney MS, Moser AJ. Biliary palliation for unresectable pancreatic adenocarcinoma: Surgical bypass or self-expanding metal stent? HPB (Oxford) 2019;Sep 17 (Epub ahead of print).

Klompmaker S, de Rooij T, Koerkamp BG, Shankar A, Siebert U, Besselink MG, Moser AJ. International validation of reduced major morbidity after minimally invasive distal pancreatectomy compared with open pancreatectomy. Ann Surg 2019;Oct 17 (Epub ahead of print).

A complete list of publications begins on page 15.



Barbara Wegiel, PhD, DSc

Associate Professor of Surgery

RESEARCH GROUP

Giacomo Canesin, PhD
Tasneem Cheytan, BS
Reeham Choudhury
Eva Csizmadia, MSc
Alireza Kalbasi, PharmD, MSc

RESEARCH FOCUS

My research focuses on how the metabolites such as heme or bile pigments regulate innate inflammatory responses during organ injury and carcinogenesis. This work has implications for understanding novel targets and potential therapeutics for treatment of cancer and beyond. Working with others at BIDMC, I am developing anti-cancer molecules that target cell cycle progression and the tumor microenvironment.

Specifically, my laboratory dissects the roles of innate immune cells (i.e., myeloid cells) in stress responses. We have recently demonstrated that heme or lack of HO-1 results in an impaired DNA damage response (DDR), reduced cell proliferation, and increased cellular senescence (Figure 1, Hedlbom et al, *CDDis* 2019). Deficiency of HO-1 in residential macrophages in chimeric mice results in elevated DNA damage and senescence upon radiation-induced injury. We also found that mammalian target of rapamycin (mTOR)/S6 protein signaling is critical for heme and HO-1-regulated phenotype of macrophages. We continue studying how removing heme restores tissue equilibrium and improves immune responses.

My interest lies in regulatory mechanisms related to the heme biology and other immunometabolic genes (i.e., LDH-A) in tumor evolution and cancer therapy. The metabolic pathway of heme degradation is a critical regulator of inflammation and tumor growth.

Much of our efforts have been directed toward understanding how the enzymes involved in heme degradation (biliverdin reductase/BVR and heme oxygenase-1/HO-1) and the products (carbon monoxide, biliverdin/bilirubin, iron) control metabolism and gene regulation in both immune and cancer cells. Our recently published work using BVR conditional knockout mice describes a novel mechanism of BVR in regulating macrophage chemotaxis in response to C5a via a regulatory mechanism involving, in part, C5aR1 signaling. Conditional deletion of BVR in macrophages turns on a specific set of genes associated with chemotaxis, RANTES and IP-10. We have identified BVR as a novel regulator of C5aR *in vitro* and *in vivo* (Figure 2: Bisht, Canesin et al, *J Immunology* 2019). This work provides novel findings that explain, in part, an immunoregulatory function of BVR and the phenotype of mice with deletion of BVR in models of endotoxemia (Wegiel et al, *JBC* 2009, Wegiel et al, *PNAS* 2011).

The approaches we are currently pursuing in the laboratory include:

- The role of the heme degradation and heme scavenger pathways in modulating inflammatory responses in sterile and pathogen-induced carcinogenesis
- Metabolic control of inflammation in cancer: The role of glycolytic pathways (i.e. LDH-A) and mitochondrial function
- The role of biliverdin reductase and bile pigments in cancer and sterile inflammation-induced organ injury
- Development of small molecule anti-cancer agents that target cell cycle progression and tumor microenvironment in prostate cancer
- DNA damage, replication, and gene expression regulation by heme and secondary structures of DNA in cancer and disease
- Role of heme in endometriosis through the collaborative efforts via FERP across Harvard

ACCOMPLISHMENTS 2018-2019

- Ad-hoc reviewer of NIH (Transplant Tolerance Tumor Immunology TTT, special emphasis panels), AHA/Carrier Development Awards, and AHA/Allen Brain Health
- Promoted to Associate Professor of Surgery, Harvard Medical School
- Member of American Heart Association, American Association for Cancer Research, BIDMC Cancer Research Institute and Dana-Farber/Harvard Cancer Center (DF/HCC)
- Honorary Lecturer in Molecular Oncology, Aston University, UK

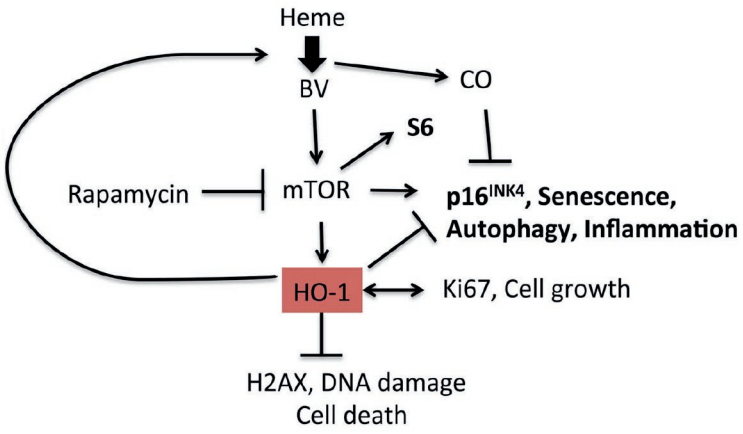
TEACHING, TRAINING, AND EDUCATION

During the last two years, I have been a supervisor for two post-doctoral fellows, one summer student, and one intern. I am involved in teaching experimental design, molecular and biochemical techniques, data acquisition and analysis, as well as manuscript and grant preparation.

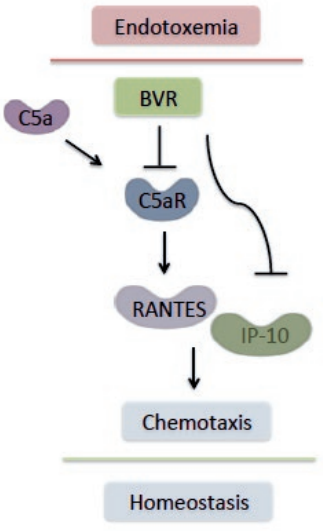
SELECTED RESEARCH SUPPORT

Role of biliverdin reductase during sterile inflammation in the liver; NIH, 2016-2020; PI: Barbara Wegiel, PhD, MSc

Fibroids and endometriosis program; BIDMC Chief Academic Office funds, 2016-2019; PI: Barbara Wegiel, PhD, MSc



▲ FIGURE 1



▲ FIGURE 2

SELECTED PUBLICATIONS

Nemeth Z, Csizmadia E, Vikstrom L, Li M, Bisht K, Feizi A, Otterbein S, Zuckerbraun B, Costa D, Pandolfi PP, Fillinger J, Döme B, Otterbein LE, Wegiel B. Alterations of tumor microenvironment by carbon monoxide impedes lung cancer growth. Oncotarget 2016;7(17):23919-32.

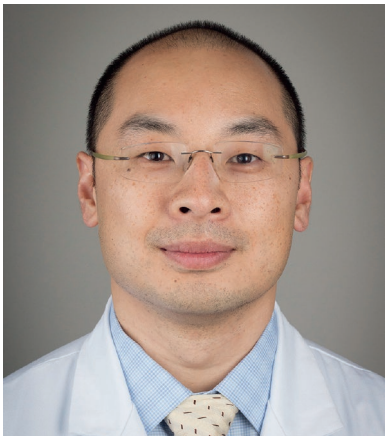
Seth P, Csizmadia E, Hedblom A, Vuerich M, Xie H, Li M, Longhi MS, Wegiel B. Deletion of lactate dehydrogenase-A in myeloid cells triggers antitumor immunity. Cancer Res 2017;77(13)3632-3643.

Hedblom A, Hejazi SM, Canesin G, Choudhury R, Hanafy KA, Csizmadia E, Persson JL, Wegiel B. Heme detoxification by heme oxygenase-1 reinstates proliferative and immune balances upon genotoxic tissue injury. Cell Death Dis 2019;10(2):72.

Bisht K, Canesin G, Cheytan T, Li M, Nemeth Z, Csizmadia E, Woodruff TM, Stec DE, Bulmer AC, Otterbein LE, Wegiel B. Deletion of biliverdin reductase A in myeloid cells promotes chemokine expression and chemotaxis in part via a complement C5a-C5aR1 pathway. J Immunol 2019;202(10):2982-2990.

Daneshmandi S, Wegiel B, Seth P. Blockade of lactate dehydrogenase-a (LDH-A) improves efficacy of anti-programmed cell death-1 (PD-1) Therapy in melanoma. Cancers (Basel) 2019;11(4).

A complete list of publications begins on page 15.



RESEARCH GROUP

Alexis Agnew, MSc
Alvaro Jose Ayala Galvis, MD
Adnan Majid, MD
Michael Mitchell, MD
Daniel Ospina, MD
Mihir Parikh, MD
Javeryah Safi, MD
Juan Pablo Uribe, MD

Alex ChunMin Chee, MD

Assistant Professor of Medicine
Director of Research, Interventional Pulmonology

RESEARCH FOCUS

My professional interests include the use of advanced bronchoscopic techniques to aid in the diagnosis and therapy of pulmonary disease. Specifically, I have an interest in novel optical techniques such as optical coherence tomography (OCT) and its application in lung cancer diagnosis and obstructive airway diseases. My previous work has involved transthoracic and endobronchial ultrasonography and I hope to add OCT to this knowledge base. My long-term goal is to contribute to the translation of novel optical imaging techniques to clinical respiratory medicine. I was fortunate to have assisted in the development of a novel OCT needle probe to be used in the assessment of lung nodules accessed by bronchoscopy. This has been submitted for a patent with Dr. Suter's group at Massachusetts General Hospital. My research on the histologic changes to the airway after bronchial thermoplasty blend well with non-invasive biopsies via optical coherence tomography and I look forward to continuing this research.

I joined the Interventional Pulmonology (IP) group at Beth Israel Deaconess Medical Center in 2017. Here I introduced airway-centered 3D printing to the IP group and facilitated its spread to the Division of Pulmonary and Critical Care, including a pilot project in customized CPAP masks for obstructive sleep apnea and neonatal ultrasound simulation. The use of 3D-printed, customized airways for teaching will accelerate skill acquisition for future trainees in pulmonary medicine. I hope to expand the use of case-derived, 3D-printed models to aid the education of physicians and patients in the future.

Interventional pulmonology is a growing field with changing opportunities and pressures on affiliated specialties. I have conducted a procedural needs survey distributed through all program directors of pulmonology and critical care programs in the United States in order to further standardize both the procedural teaching in fellowship as well as improve the coordination of procedural training between pulmonology and interventional pulmonology. We found that interventional pulmonology fellowship programs impact the volume and comfort of procedures performed by pulmonary and critical care fellows. There needs to be additional work to coordinate training and competency across overlapping training programs.

Other areas of investigation are:

- Optical coherence tomography to evaluate the effect of bronchial thermoplasty for asthma
- 3D imaging to customize CPAP mask fit to improve adherence in obstructive sleep apnea
- 3D printed airway simulation for bronchoscopy training
- Quality improvement in pleural procedures

ACCOMPLISHMENTS 2018-2019

- Appointed Director of Research, Interventional Pulmonology, BIDMC
- Appointed Chair, Fundraising Committee, World Association of Bronchology and Interventional Pulmonology
- Promoted to Assistant Professor of Medicine, Harvard Medical School

Invited Presentations

- Endoscopic management of subglottic stenosis. Society of Thoracic Surgeons annual meeting, San Diego, CA
- Disruptive innovation: Interventional respirology in airway diseases. Pneumoclub, University of Ottawa, Canada
- American management of pleural infections. Canadian Respiratory Conference, Ottawa, Canada

TEACHING, TRAINING, AND EDUCATION

As the site director of the combined Harvard BIDMC/MGH Interventional Pulmonology Fellowship Program, my goal is to improve the already renowned learning environment at BIDMC. Monthly evaluations have been standardized for rotating pulmonary and interventional pulmonary fellows, including visiting fellows in interventional pulmonology. 3D airway models are given to all fellows to improve their 3D anatomy orientation. Our fellows have gone on to careers in academic interventional pulmonology and our network has allowed us to perform multi-centered studies in pleural disease and bronchoscopy.

ABSTRACTS, POSTERS, AND EXHIBITS

Chee A, Jackson J, Pendharkhar S. Feasibility of a customized CPAP Mask for obstructive sleep apnea using 3D image capture and printing. Canadian Respiratory Conference, Vancouver, Canada, 2018

Chee A, Turkseven M, Barrett L, Majid A, Parikh M, De S. Measurement of rigid bronchoscopy intubation forces. World Congress of Bronchology and Interventional Pulmonology, Rochester, MN, 2018

Chee A, Sierra M, Parikh M, Majid A. Comparison of 3D printed stenotic airway models versus standard model for bronchoscopy training: A proof of concept. World Congress of Bronchology and Interventional Pulmonology, Rochester, MN, 2018

Alamro S, Uribe JP, Sierra M, Parikh M, Majid A, Chee A. The effect of interventional pulmonology on the training of pulmonary and critical care fellows. American Thoracic Society, Dallas, TX, 2019

SELECTED PUBLICATIONS

Tremblay A, McFadden S, Bonifazi M, Luzzi V, Kemp SV, Gasparini S, Chee A, MacEachern P, Dumoulin E, Shah PL. Endobronchial ultrasound-guided transbronchial needle aspiration with a 19-g needle device. J Bronchology Interv Pulmonol 2018;25(3):218-223.

Chee A. 3-D Printing for Medical Uses. IEEE New York Monitor 2018;65(7):11-21.

de Lima A, Holden V, Gesthalter Y, Kent MS, Parikh M, Majid A, Chee A. Treatment of persistent bronchopleural fistula with a manually modified endobronchial stent: A case report and brief literature review. J Thoracic Dis 2018;10(10):5960-5963.

Majid A, Kheir F, Sierra-Ruiz M, Ghattas C, Parikh A, Channick C, Keyes C, Chee A, Fernandez-Bussy S, Gangadharan S, Folch E. Assessment of fissure integrity in patients with intrabronchial valves for treatment of prolonged air leak. Ann Thoracic Surg 2019;107(2):407-411.

Adams DC, Miller AJ, Applegate MB, Cho JL, Hamilos DL, Chee A, Holz JA, Szabari MV, Hariri LP, Harris RS, Griffith JW, Luster AD, Medoff BD, Suter MJ. Quantitative assessment of airway remodelling and response to allergen in asthma. Respirology 2019; Epub ahead of print.

Majid A, de Lima A, Parikh M, Chee A, Fernandez-Bussy S, Kheir F. Tunneled pleural catheters for patients with chronic pleural infection and nonexpandable lung. J Bronchology Interv Pulmonol 2019;26(2): 132-136.

A complete list of publications begins on page 15.

Sidharta P. Gangadharan, MD, MHCM

Associate Professor of Surgery
Chief, Thoracic Surgery and Interventional Pulmonology

RESEARCH GROUP

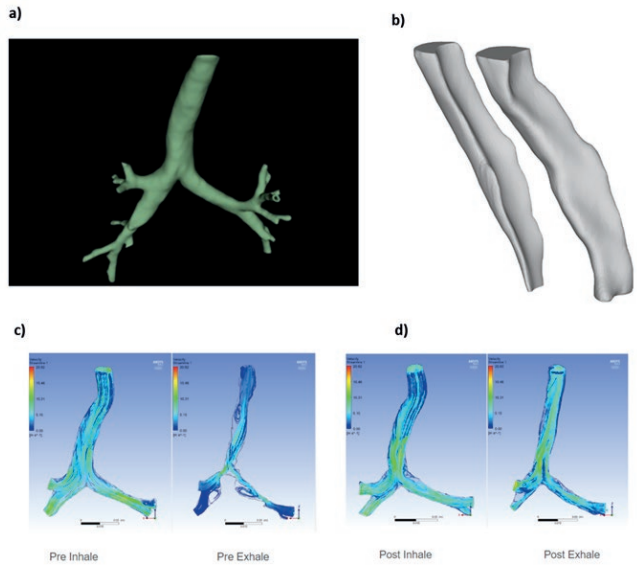
Alexis Agnew, MSc
Juan Carlos Ascanio, MD
Daniel Buitrago, MD
Oliver Chow, MD
Michael Kent, MD
Jorge Ruiz de Somocurcio, MD
Ben Scott, MD
Rani Singh, PhD
Richard Whyte, MD, MBA
Jennifer Wilson, MD
Jenny Yu, MD

RESEARCH FOCUS

I perform clinical outcomes research that spans the range of thoracic diseases, but with a particular interest in tracheobronchomalacia (TBM). To date, our department maintains the largest TBM registry in the United States, which has enabled us to develop current guidelines and analyze outcomes for medical, endoscopic, and surgical therapy. Through this analysis, we hope to delineate best care practices through refined patient selection methods and improved medical, endoscopic, and surgical techniques. In 2018, we entered into collaboration with the Draper Laboratory to develop a portable, non-invasive breath biomarker detector device that uses a differential mobility spectrometry (DMS) sensor. With this device, and combined with other technologies, we hope to provide physicians with a tool to better identify TBM breath biomarkers in the clinical setting.

We are currently analyzing data collected from our "Development of a cough & respiratory sound-based acoustic signature to diagnose severe diffuse tracheobronchomalacia" study. By recording these features, we hope to define a unique acoustic signature and eventually investigate its diagnostic utility. Preliminary analysis of a pilot study reveals that an algorithm to differentiate TBM cough from control cough has sensitivity and specificity > 95% each.

Our recent pilot study with resected tracheal specimens including TBM and different diseases exhibited unique pro-remodeling and pro-inflammatory gene expression signatures in those with TBM. This study was selected as the best abstract and we were invited to discuss our findings at the 2019 American Association for Bronchology and Interventional Pulmonology (AABIP) conference.



▲FIGURE 1: a) No tracheobronchomalacia (TBM) 3D model; b) pre- and post-tracheobronchoplasty (TBP) surgery expiration models of the TBM trachea figures-vertical angled view; c) CFD Streamline pre-TBP surgery (inhale and exhale); and d) CFD Streamline post-TBP surgery (inhale and exhale)

Over the past year, we have also collaborated with Lucy Zhang, PhD, at Rensselaer Polytechnic Institute to expand the scope of our research in airway flow simulations. This analysis applied computational fluid dynamics (CFD) in a 3-D computational model of trachea to analyze pre- and post-tracheobronchoplasty (TBP) surgery airflow characteristics. This data provided significant insights on airflow behavior and a better understanding of why and how patients are improving. In the future, we imagine this could lead to a deep understanding of the relationship between TBP and changes in airflow characteristics using new modeling skills.

I have been investigating novel methods of treating lung cancer utilizing near-infrared imaging technology. We completed "A Phase 2, Single dose, Open-Label, Exploratory Study to Investigate the Safety and Efficacy of OTL38 Injection for Intraoperative Imaging of Folate Receptor Positive Lung Nodules" clinical trial in 2019. Patients enrolled in the study were administered a single dose of OTL38, a folate analog ligand conjugated with an indole cyanine-like green dye. During their procedure as indicated by standard of care, an imaging system equipped with near-infrared technology was used to aid in malignancy detection. With the completion of the phase II study, we look forward to participating in the next phase in early 2020.

ACCOMPLISHMENTS 2018-2019

- Boston's Top Doctors, Thoracic and Cardiac Surgery; Castle Connolly and *Boston Magazine,* 2018
- Member of the editorial board for *Journal of Thoracic Disease,* 2019
- Recipient of the George W.B. Starkey Award for Excellence in Teaching by the Department of Surgery (BIDMC) for teaching of Harvard Medical School core clerkship students, 2019
- Awarded Master of Healthcare Management, Harvard T.H. Chan School of Public Health, 2019

Invited Presentations

- Excessive Dynamic Airway Collapse: State-of-the-Art. Invited speaker, Clinical Controversy Session, American College of Chest Physicians (CHEST) annual conference, San Antonio, TX
- Tracheobronchomalacia. Invited speaker, Service Line Evening Seminar Series/Pulmonary & Critical Care Medicine, BIDMC, Lahey Hospital & Medical Center, and Mount Auburn Hospital
- Tracheobronchomalacia: Diagnosis and Treatment. Grand Rounds, Department of Surgery, Boston Medical Center
- My Path to a Career in Thoracic Surgery. Invited speaker, Geisel School of Medicine at Dartmouth, Hanover, NH
- Technical Aspects of Tracheobronchoplasty for Tracheobronchomalacia. Invited operative training session, NYU Langone Medical Center, New York, NY
- Cardiothoracic Surgery in the Future: Technology Overview for Residents and Medical Students. Table instructor, esophageal anastomotic techniques, Society of Thoracic Surgeons at American College of Surgeons annual meeting, Boston, MA
- Technical Aspects of Performing Minimally-Invasive Esophagectomy. Invited speaker, Minimally Invasive and Robot-Assisted Esophagectomy course, American College of Surgeons annual meeting, Boston, MA
- Minimally-Invasive Esophagogastric Anastomotic Technique. Table instructor, Minimally Invasive and Robot-Assisted Esophagectomy course, American College of Surgeons annual meeting, Boston, MA
- STS University Course: Advanced Open Esophageal and Tracheal Procedures. Table instructor, Society of Thoracic Surgeons annual meeting, San Diego, CA
- Society of Thoracic Surgeons Residents Luncheon. Table discussant, Society of Thoracic Surgeons annual meeting, San Diego, CA
- Tracheobronchoplasty for Tracheobronchomalacia. Invited speaker, Scientific Simultaneous Breakout Session, American Association for Thoracic Surgery annual meeting, Toronto, ON
- Thoracic Trauma. Invited speaker, Criticon 2019, Raipur, Chattisgarh, India
- Tracheobronchomalacia: Evaluation and Treatment. Invited speaker, Criticon 2019, Raipur, Chattisgarh, India

SELECTED RESEARCH SUPPORT

Engineering a naturally-derived and highly adhesive surgical sealant; NIH, 2018-2022; Co-Investigator: Sidharta Gangadharan, MD, MHCM (PI: Nasim Annabi, PhD, University of California-Los Angeles)

Engineering highly elastic surgical sealants with hemostatic properties; NIH, 2018-2022; Co-Investigator: Sidharta Gangadharan, MD, MHCM (PI: Nasim Annabi, PhD, University of California-Los Angeles)

Breath analysis as a noninvasive biomarker for detection of tracheobronchomalacia (TBM); CureTBM Foundation, 2018-2020; PI: Sidharta Gangadharan, MD, MHCM

SELECTED PUBLICATIONS

Majid A, Kheir F, Alape D, Chee A, Parikh M, DeVore L, Agnew A, Gangadharan S. Combined thoracoscopic surgical stapling and endobronchial valve placement for lung volume reduction with incomplete lobar fissures: An experimental pilot animal study. J Bronchology Interv Pulmonol 2019; Aug 20 (Epub ahead of print).

Scott BB, Maxfield MW, Hamaguchi R, Wilson JL, Kent MS, Gangadharan SP. Robot-assisted thoracoscopic mediastinal parathyroidectomy: A single surgeon case series. J Laparoendosc Adv Surg Tech A 2019; Jun 12 (Epub ahead of print).

Majid A, Kheir F, Sierra-Ruiz M, Ghattas C, Parikh M, Channick C, Keyes C, Chee A, Fernandez-Bussy S, Gangadharan S, Folch E. Assessment of fissure integrity in patients with intrabronchial valves for treatment of prolonged air leak. Ann Thorac Surg 2019;107(2):407-411.

Majid A, Kheir F, Alape D, Kent M, Lembo A, Rangan VV, Carreiro M, Gangadharan SP. The prevalence of gastroesophageal reflux in patients with excessive central airway collapse. Chest 2019;155(3):540-545.

Kheir F, Fernandez-Bussy S, Gangadharan SP, Majid A. Excessive dynamic airway collapse or tracheobronchomalacia: Does it matter? Arch Bronconeumol 2019;55(2):69-70.

Bezuidenhout AF, Boiselle PM, Heidinger BH, Alape D, Buitrago DH, Majid A, Gangadharan SP, Litmanovich DE. Longitudinal follow-up of patients with tracheobronchomalacia after undergoing tracheobronchoplasty: Computed tomography findings and clinical correlation. J Thorac Imaging 2019;34(4):278-283.

A complete list of publications begins on page 15.

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.

Thoracic Surgery and Interventional Pulmonology

RESEARCH GROUP

Alexis Agnew, MSc
Alvaro Ayala, MD
Theresa Bishop, RN
Megan Carreiro, MS
Alex Chee, MD
Mary Farquhar, RN
Sebastian Fernandez-Bussy, MD
Erik Folch, MD, MSc
Fayez Kheir, MD
Mathieu Marcoux, MD
Daniel Ospina, MD
Mihir Parikh, MD
Javeryah Safi, MD
Melibea Sierra, MD
Rani Singh, PhD
Carlos Sisniega, MD
Juan Pablo Uribe, MD

** Secondary appointment*

Adnan Majid, MD

Associate Professor of Medicine
Associate Professor of Surgery*
Chief, Section of Interventional Pulmonology

RESEARCH FOCUS

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

Lung Cancer

A Prospective Evaluation of the Clinical Utility for the Ion™ Endoluminal System (PRECISE). We are evaluating the clinical utility and early performance of the Ion Endoluminal System to bronchoscopically approach and facilitate the sampling of pulmonary nodules suspicious for malignancy. Benefits of this system may include: higher yield rate than existing bronchoscopic biopsy modalities, and patient access to a minimally invasive bronchoscopic approach to the diagnosis of lung cancer.

ANET Electrosurgery Applicator Pilot Evaluation Study. This is a first in human use pilot study which aims to evaluate the preliminary safety and performance of the ANET Electrosurgery Applicator (ANET) during and after bronchoscopic ablation of a target pulmonary nodule/tumor. If shown to be safe and effective, this treatment modality may provide benefit for patients with Stage I or II hilar/central tumors and nodules who are not appropriate for surgery.

Chronic Obstructive Pulmonary Disease (COPD)

A Feasibility Study: A Safety Evaluation of the RheOx™ on Patients with Chronic Bronchitis in the United States (GALA_EFS). This is a prospective, single-arm feasibility study which will assess the safety and clinical utility of the RheOx™ in patients with chronic bronchitis. RHeOx™ is designed to ablate abnormal mucus glands of the epithelium and reduce the mucus production of the submucosal glands. Benefits to patients may include: reductions in symptoms, improvement in quality of life, and reduction in exacerbations associated with chronic bronchitis.

Multicenter, Randomized, Sham-controlled Study to Evaluate Safety and Efficacy After Treatment with the Nuvaira™ Lung Denervation System in Subjects with Chronic Obstructive Pulmonary Disease (COPD) (AIRFLOW-3). This is a multi-center, randomized, sham-controlled, double-blind, phase III clinical trial evaluating the efficacy of targeted lung denervation (TLD) in addition to optimal medical management to reduce moderate to severe exacerbations and related hospitalizations, compared with optimal medical management alone. Potential benefits of this treatment may include: reduction in respiratory events leading to hospitalizations/physician visits, and improvement in dyspnea and COPD-specific/overall quality of life.

A Sham Controlled Prospective Randomized Clinical Trial of the RejuvenAir® System for the Treatment of Moderate to Severe Chronic Obstructive Pulmonary Disease with Chronic Bronchitis (SPRAY-CB). This is a prospective, multi-center, blinded randomized sham controlled trial. The objective of this study is to demonstrate the safety and effectiveness of the Rejuvenair® System for the treatment of adult patients with a diagnosis of chronic bronchitis. Potential benefits of study participation include: reduced rate of chronic bronchitis exacerbations, reduced symptoms associated with chronic bronchitis, and improved quality of life.

Tracheobronchomalacia (TBM)

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.

Airway Stents for Excessive Dynamic Airway Collapse: A Randomized Trial. This study is a prospective, randomized clinical trial to determine the role of airway stenting and to identify patients with excessive dynamic airway collapse (EDAC) who may benefit from surgical correction or repair.

ACCOMPLISHMENTS 2018–2019

- Elected to American Association for Bronchology and Interventional Pulmonology (AABIP) Board of Directors, 2019
- Boston's Top Doctors, Castle Connolly, and *Boston Magazine,* 2019
- Ad hoc reviewer for *American Journal of Respiratory and Critical Care Medicine,* 2019
- Recipient of the Interventional Pulmonary Educator Award: In recognition for outstanding contributions to the education of interventional pulmonologists by the Association of Interventional Pulmonary Program Directors, 2018
- Multiple invited presentations, courses, and workshops internationally

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. Beginning in 2019, we grew our program to train four physicians. Over the last 19 years, 37 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

Uribe-Becerra J, Parikh M, Chee A, Kheir F, Paton A, Majid A. Tube thoracostomy with concomitant antiplatelet and/or anticoagulation therapy? ATS Conference, Dallas, TX

Ospina-Delgao D, Vidal B, Mallur P, Kheir F, De Lima A, VanderLaan PA, Gangadharan SP, Majid A. Bronchoscopic thermoablative techniques to stabilize excessive central airway collapse: An *ex-vivo* pilot study. ATS Conference, Dallas, TX

Marcoux M, Ospina-Delgado D, Chee A, Onieva-Onieva J, San Jose Estepar R, Gill R, Majid A. Custom stent planning for complex airway disease: A novel "state-of-the-art" approach. ATS Conference, Dallas, TX

Sierra-Ruiz M, Kheir F, Beattie J, Chee A, Parikh M, Majid A. Safety of percutaneous dilatation tracheostomy (PDT) with concomitant antiplatelet and anticoagulation therapy: Single center experience. ATS Conference, Dallas, TX

Sisniega C, Kheir F, Alamro S, Chee A, Parikh M, Majid A. Bleeding in patients undergoing indwelling pleural catheter insertions. ATS Conference, Dallas, TX

SELECTED PUBLICATIONS

Alape D, Singh R, Folch E, Fernandez-Bussy S, Agnew A, Majid A. Life-threatening multi-level airway stenosis due to Myhre syndrome. Am J Respir Crit Care Med 2019;Sep 20 (Epub ahead of print).

Mahajan AK, Ibrahim O, Perez R, Oberg CL, Majid A, Folch E. Electrosurgical and laser therapy tools for the treatment of malignant central airway obstructions. Chest 2019;Aug 28 (Epub ahead of print).

Majid A, Kheir F, Alape D, Chee A, Parikh M, Devore L, Agnew A, Gangadharan S. Combined thoracoscopic surgical stapling and endo-bronchial valve placement for lung volume reduction with incomplete lobar fissures: An experimental pilot animal study. J Bronchology Interv Pulmonol 2019;Aug 20 (Epub ahead of print).

Criner GJ, Delage A, Voelker K, Hogarth DK, Majid A, Zgoda M, Lazarus DR, Casal R, Benzaquen SB, Holladay RC, Wellikoff A, Calero K, Rumbak MJ, Branca PR, Abu-Hijleh M, Mallea JM, Kalhan R, Sachdeva A, Kinsey CM, Lamb CR, Reed MF, Abouzgheib WB, Kaplan PV, Marrujo GX, Johnstone DW, Gasparri MG, Meade AA, Hergott CA, Reddy C, Mularski RA, Case AH, Makani SS, Shepherd RW, Chen B, Holt GE, Martel S; EMPROVE Study Group. Improving lung function in severe heterogenous emphysema with the Spiration® Valve System (EMPROVE): A multicenter, open-label, randomized, controlled trial. Am J Respir Crit Care Med 2019;Jul 31 (Epub ahead of print).

Majid A, De Lima A, Parikh M, Chee A, Fernan-dez-Bussy S, Kheir F. Tunneled pleural catheters for patients with chronic pleural infection and nonexpandable lung. J Bronchology Interv Pulmonol 2019;26(2):132-136.

Kheir F, Majid A. Tracheobronchomalacia and excessive dynamic airway collapse: Medical and surgical treatment. Semin Respir Crit Care Med 2018;39(6):667-673.

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Mihir S. Parikh, MD

Instructor in Medicine
Director of Interventional Pulmonology, BID–Milton

RESEARCH GROUP

Jason Beattie, MD
Andres DeLima, MD
Van Holden, MD
Daniel Ospina, MD
Morgan Soffler, MD
Juan Pablo Uribe-Becerra, MD

RESEARCH FOCUS

My research aims to better understand the way we train learners in medical procedures and the metrics we use to confirm mastery of these skills. As medical training evolves from volume-based metrics to competency-based assessments, I want to find more accurate and more efficient techniques to teach medical procedures in the context of the myriad pressures facing our learners during their packed training schedules. To that end, I am conducting a number of clinical trials aimed at improving procedural education for pulmonary and critical care medicine fellows. I am also running several quality-improvement studies investigating ways to improve outcomes in commonly performed pleural procedures.

ACCOMPLISHMENTS 2018–2019

- Named Program Director of the Advanced Diagnostic Bronchoscopy Fellowship Program at BIDMC
- Invited speaker at regional medical center grand rounds (including MetroWest Medical Center, BID-Milton, and BIDMC)
- Invited speaker at CME course in Principles of Critical Care Medicine
- Multiple published manuscripts and conference presentations (see following page)

TEACHING, TRAINING, AND EDUCATION

I am one of the core training faculty for the Interventional Pulmonology Fellowship Program at BIDMC. I am Program Director of the Advanced Diagnostic Bronchoscopy Fellowship Program at BIDMC and also serve on the Program Evaluation Committee for the Combined MGH/BIDMC Pulmonary and Critical Care Medicine Fellowship Program. I direct our annual bootcamp course in bronchoscopy and pulmonary procedures attended by in-coming pulmonary and critical care medicine fellows throughout the northeastern U.S. Additionally, I teach pulmonary pathophysiology to medical students in the Harvard-MIT Health Sciences and Technology (HST) Program.

ABSTRACTS, POSTERS, AND EXHIBITS

Rivera E, Holden V, Parikh M. Characteristics of indwelling pleural catheter related infections. International Conference of the American Thoracic Society, San Diego, CA.

DeLima A, Ghattas C, Parikh M. Impact of a one-day introductory course to pulmonary and pleural procedures. International Conference of the American Thoracic Society, San Diego, CA.

Holden V, Chee A, Parikh M, Majid A. Safety and efficacy of a new fully covered self-expandable metallic airway stent. International Conference of the American Thoracic Society, San Diego, CA.

Beattie J, Uribe-Becerra, Chee A, Agnew A, Majid A, Parikh M. Pleural procedures in hepatic hydrothorax: A retrospective outcomes review. International Conference of the American Thoracic Society, Dallas, TX.

Holden V, Majid A, Chee C, Parikh M. An international survey on the use of intrapleural fibrinolytics for complicated parapneumonic effusions and empyemas. International Conference of the American Thoracic Society, Dallas, TX.

SELECTED PUBLICATIONS

Desai N, Parikh M, Lee H. The role of simulation training and competency-based education in interventional pulmonology. Semin Respir Crit Care Med 2018;39(6): 747-754.

VanderLaan P, Rangachari D, Majid A, Parikh M, Gangadharan S, Kent M, Huberman M, Kobayashi S, Costa D. Tumor biomarker testing in non-small cell lung cancer: A decade of change. Lung Cancer 2018;116:90-95.

Buitrago D, Gangadharan S, Majid A, Kent MS, Alape D, Wilson JL, Parikh M, Kim DH. Frailty characteristics predict respiratory failure in patients undergoing tracheobronchoplasty. Ann Thorac Surg 2019;06(3): 836-841.

Benn B, Parikh M, Tsau P, Seeley E, Krishna G. Using a dedicated interventional pulmonology practice decreases wait time before treatment initiation for new lung cancer diagnoses. Lung 2019;197(2): 249-255.

Majid A, Kheir M, Alape D, Chee A, Parikh M, DeVore L, Agnew A, Gangadharan S. Combined thoracoscopic surgical stapling and endobronchial valve placement for lung volume reduction with incomplete lobar fissures: An experimental pilot animal study. J Bronchology Interv Pulmonol; in press.

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Thoracic Surgery and Interventional Pulmonology

Jennifer L. Wilson, MD

Assistant Professor of Surgery

RESEARCH GROUP

Alexander Bankier, MD
Alex Chee, MD
Sidhu Gangadharan, MD, MHCM
Michael Kent, MD
Adnan Majid, MD
Mihir Parikh, MD
James Rodrigue, PhD
Gillean SteelFisher, PhD
Paul Vanderlaan, MD
Richard Whyte, MD, MBA

RESEARCH FOCUS

My research is focused largely in the following areas:

Complex Airway Disease

The high-volume program at BIDMC allows us to encounter a large number of patients with adult tracheobronchomalacia. As part of our collaboration with interventional pulmonology, we continue to build on an existing database so that we can learn more about the etiology, natural disease process with and without intervention, and surgical outcomes—and increase the recognition of this rare disease. We are currently working on developing and validating a quality of life questionnaire for adult tracheobronchomalacia so that we can better follow our patients' outcomes in the future.

Lung Cancer

I am part of several collaborative groups with Alexander Bankier, MD (Chief, Cardiothoracic Imaging Section of Radiology) and Paul Vanderlaan, MD (Director of Thoracic Pathology). Our collaborative projects have included radiology-pathology-surgical correlates of squamous cell lung cancer as well as lung cancers with specific pathologic findings such as visceral pleural invasion. In addition, we are exploring inter-observer agreement among pathologists for frozen section on lung cancer adenocarcinoma subtypes.

Lung Cancer Screening

I am a member of the Department of Public Health Lung Cancer Screening Work Group and am interested in combating lung cancer screening disparities. There are many opportunities for focus groups; pilot implementation projects; and hospital, state, and national level interventions that could help us better understand and mitigate lung cancer screening disparities.

Other Research Interests Include:

- Patient reported outcomes (PROs)
- Quality improvement and cost effectiveness
- Resident and fellow education

ACCOMPLISHMENTS 2018–2019

Invited Presentations

- Tracheobronchomalacia: Diagnosis and Treatment. Surgical Grand Rounds, Cambridge Health Alliance, Cambridge, MA
- Tracheobronchomalacia: Diagnosis and Treatment. Medicine Grand Rounds, Cambridge Health Alliance, Cambridge, MA

Invited Instructor

- Advanced open esophageal and tracheal procedures; Society of Thoracic Surgeons annual meeting, Houston, TX
- Chest tube insertion instructional video creation for BIDMC surgery residents in conjunction with the trauma surgery service
- JCTSE TSRA core curriculum presentations for BIDMC cardiothoracic residents and fellows

Other Accomplishments

- Promoted to Assistant Professor of Surgery
- Will complete the Harvard T.H. Chan Master's in Public Health–Clinical Effectiveness program in 2020
- Initiated into the Fellowship of the American College of Surgeons (FACS)

TEACHING, TRAINING, AND EDUCATION

Weekly thoracic surgery resident and fellow preoperative conference is held in order to help residents make the leap from trainee to surgeon. At this conference, residents present all upcoming cases and key points are highlighted in an open teaching environment that focuses on board preparation for the rotating residents and cardiothoracic fellows, as well as real world clinical decision making. Furthermore, having medical students, residents, and fellows in the operating room allows for continual level-appropriate teaching such as live anatomy review, basic and complex surgical techniques, and perioperative management of patients. The aim of our program is to create independent and clinically competent surgeons who recognize the importance of treating the patient and their disease.

ABSTRACTS, POSTERS, AND EXHIBITS

Chow OS, Steely AM, Senthilnathan V, Wilson JL. Late recurrence of Ewing's sarcoma presenting with lung and left atrial involvement in a postpartum patient. American Association of Thoracic Surgery meeting, Toronto, 2019 (poster presentation/Chow)

SELECTED PUBLICATIONS

Buitrago DH, Gangadharan SP, Majid A, Kent MS, Alape D, Wilson JL, Parikh MS, Kim DH. Frailty characteristics predict respiratory failure in patients undergoing tracheobronchoplasty. Ann Thorac Surg 2018;106(3):836-841.

Buitrago DH, Majid A, Alape DE, Wilson JL, Parikh M, Kent MS, Gangadharan SP. Single-center experience of tracheobronchoplasty for tracheobronchomalacia: Perioperative outcomes. Ann Thorac Surg 2018;106(3):909-915.

Scott BB, Maxfield MW, Hamaguchi R, Wilson JL, Kent MS, Gangadharan SP. Robot-assisted thoracoscopic mediastinal parathyroidectomy: A single surgeon case series. J Laparoendosc Adv Surg Tech A 2019;Jun 12.

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James R. Rodrigue, PhD

Professor

Vice Chair for Clinical Research

RESEARCH GROUP

Jasmine Austrie, BA
Matt Boger, MS
Amanda Calvo, BA
Michaela Carroll, BA
Sarah Duncan, ALB
Mario Feranil, BS
Aaron Fleishman, MPH
Lean Magrini, BS
Christopher Mistretta, RN, BSN
Claire Rosenwasser, MS
Jessica Shenkel, MA
Stephanie Ward, BA

www.RodrigueLab.com

RESEARCH FOCUS

Our research seeks to answer two central questions:

How Can We Reduce the Gap between the Number of People Who Need Organ Transplants and the Availability of Organs for Transplantation?

The number of people waiting for a lifesaving organ transplant continues to rise, far outpacing the number of potential organ donors. Together with colleagues at BIDMC, the New England Donor Services, and several other transplant programs in the United States, we are developing and evaluating novel strategies to increase rates of both living and deceased donation. These strategies address individual and systems barriers we have identified through earlier research that are associated with lower organ donation rates.

How Can We Reduce Persistent Racial and Economic Disparities in Transplantation?

Some minorities and low-income patients, relative to white patients and those with more financial resources: a) experience more kidney transplant access barriers, b) are more likely to have initiated dialysis at time of transplant referral, c) wait longer for a deceased donor transplant, d) are less likely to receive a live donor kidney transplant, e) have higher mortality rates on the waiting list, and f) have less optimal transplant outcomes. Since the proportion of patients on the kidney transplant waiting list is increasing for racial/ethnic minorities (while declining for whites), the shortage of deceased donor kidneys is likely to exacerbate these transplant disparities in the years ahead. We are conducting studies to better understand the precise cause of these disparities, to evaluate novel strategies for mitigating them, and to examine the impact of policy changes on these disparities.

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, including behavioral and medical sciences, public health, surgery, bioethics, nursing, and health services.

ACCOMPLISHMENTS 2018–2019

- Recipient of a new $1.1 million research grant from the Health Resources and Services Administration to evaluate strategies to effectively increase organ donor registrations in veterans
- Published a manuscript summarizing the development, implementation, and outcomes of the FIRST Program, a novel clinical research infrastructure platform in the BIDMC Department of Surgery
- Co-authored several manuscripts examining outcomes in living kidney donors and disparities in kidney transplantation
- Delivered invited Grand Rounds presentation on strategies to reduce racial and income disparities in access to kidney transplantation at Boston Medical Center
- Delivered invited presentation on living donation and social media at a Partners Healthcare donation and transplantation symposium in Somerville, MA and at the Ontario Renal Network in Toronto

- Delivered three invited talks on evidence-based approaches to increasing living donation, ApoL1 and living kidney donation, and psychological issues in fulminant hepatic failure at the 11th Annual Living Donation Conference in Clearwater Beach, FL
- Presented research at several regional, national, and international scientific conferences

Other Recent Accomplishments Include

- Elected as Councilor-at-Large on the Board of Directors of the American Society of Transplantation
- Selected to serve on the Living Donor Committee of the American Society of Transplant Surgeons
- Abstract reviewer for 2019 American Transplant Congress (Disparities in Outcome and Access to Healthcare)

TEACHING, TRAINING, AND EDUCATION

I continue to provide training and mentorship to surgical residents, postdoctoral fellows, and research assistants. Other activities include:

- Director of the Department of Surgery's Clinical Scholarship Program, providing first-year residents with mentored clinical research experience
- Director of the Facilitating Innovative Research & Surgical Trials (FIRST) Program in the Department of Surgery, a clinical research platform providing guidance and mentorship to faculty, fellows, and residents
- Chair of the Department of Surgery Appointment, Re-appointments, and Promotions Committee
- Implemented a new seminar series, the FIRST Program's Bi-Weekly Clinical Research Seminar, which is an interactive venue for clinical research sharing, learning, collaboration, and engagement in the department

SELECTED RESEARCH SUPPORT

Living donor wage reimbursement trial; NIH, 2017-2022; PI: James Rodrigue, PhD (Co-Investigators: Aaron Fleishman, MPH, Amy Evenson, MD, MPH, Martha Pavlakis, MD)

Comparing the effectiveness of house calls and peer mentorship to reduce racial disparities in live donor kidney transplantation; PCORI, 2017-2021; PI: James Rodrigue, PhD (Co-Investigators: Aaron Fleishman, MPH, Amy Evenson, MD, MPH, Martha Pavlakis, MD, Prabhaka Baliga, MD, Jesse Schold, PhD)

Kidney paired donation: A randomized trial to increase knowledge and reduce perceived barriers; HRSA, 2015-2019; PI: James Rodrigue, PhD (Co-Investigators: Amy Evenson, MD, MPH, Derek DuBay, MD)

Increasing VCA donation knowledge, attitudes, willingness, and designations in veterans; HRSA, 2017-2020; PI: James Rodrigue, PhD (Co-Investigators: Aaron Fleishman, MPH, Matt Boger, MS)

A randomized trial to increase donor registration and VCA donation willingness in veterans; HRSA, 2018-2021; PI: James Rodrigue, PhD (Co-Investigators: Aaron Fleishman, MPH, Matt Boger, MS)

SELECTED PUBLICATIONS

Rodrigue JR, Boger M, DuBay, D, Fleishman A. Increasing donor designation rates in adolescents: A cluster randomized trial. Am J Public Health 2019;109:1273-1279.

Tsikis S, Fleishman A, Chaikof EL, Rodrigue JR. Design and implementation of an infrastructure program to support clinical research in surgery. J Surg Res 2019; 241:264-270.

Rodrigue JR, Fleishman A, Sokas C, Schold JD, Morrissey P, Whiting J, Vella J, Kayler L, Katz D, Jones J, Kaplan B, Pavlakis M, Mandelbrot DA. Rates of living kidney donor follow-up: Findings from the KDOC Study. Transplantation 2019; 103;e209-e210.

Reese P, Allen M, Carney C, Leidy D, Levsky S, Ruchita P, Mussell A, Bermudez F, Keddem S, Thiessen C, Rodrigue JR, Emmanuel E. Outcomes for individuals turned down for living kidney donation. Clin Transplant 2018; 32:e13408.

Bui K, Kilambi V, Rodrigue JR, Mehrotra S. Patient functional status at transplant and its impact on post-transplant survival of adult deceased-donor kidney recipients. Transplantation. 2019; 103:1051-1063.

Rodrigue JR, Schold JD, Morrissey P, Whiting J, Vella J, Kayler L, Katz D, Jones J, Kaplan B, Fleishman A, Pavlakis M, Mandelbrot DA. Patterns and predictors of fatigue following living donor nephrectomy: Findings from the KDOC Study. Am J Transplant; in press.

A complete list of publications begins on page 15.

Peter Chang, MD, MPH

Assistant Professor of Surgery
Director, BIDMC Prostate Cancer Center
Director, BID-Milton Robotic Surgery Program

RESEARCH GROUP

Catrina M. Crociani, MPH
Sara Hyde
Kyle McAnally
Andrew Wagner, MD
Adrian Waisman, MD

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 are described in Dr. Wagner's report. As Director of the BIDMC Prostate Cancer Center, I will describe my research efforts to optimize quality-of-life in prostate cancer patients.

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 longlasting 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 of using EPIC-CP as part of prostate cancer care. Dr. Andrew Wagner and I recently published our results on the "real-world" use of EPIC-CP in post-surgery patients in the *Journal of Urology* (Wagner AA et al, J Urol Jan 2017). As a next step, I hope to show how using EPIC-CP can improve the practitioner workflow 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 am the 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. I recently published the results of a study showing that a subset of patients have improvement in their quality of life after prostate cancer treatment, specifically radical prostatectomy (Chang P et al, J Urol Feb 2017).

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. We published our results in the *Journal of Urology* (Berry et al, J Urol Jul 2017).

ACCOMPLISHMENTS 2018-2019

Funding from the Martin and Diane Trust Career Development Chair in Surgery helped me complete two research studies on prostate cancer quality of life, both of which resulted in primary author publications in the *Journal of Urology* in 2017.

My leadership of the PROST-QA cohort allowed securing of additional funding from the Movember Foundation to help support further prostate cancer research.

TEACHING, TRAINING, AND EDUCATION

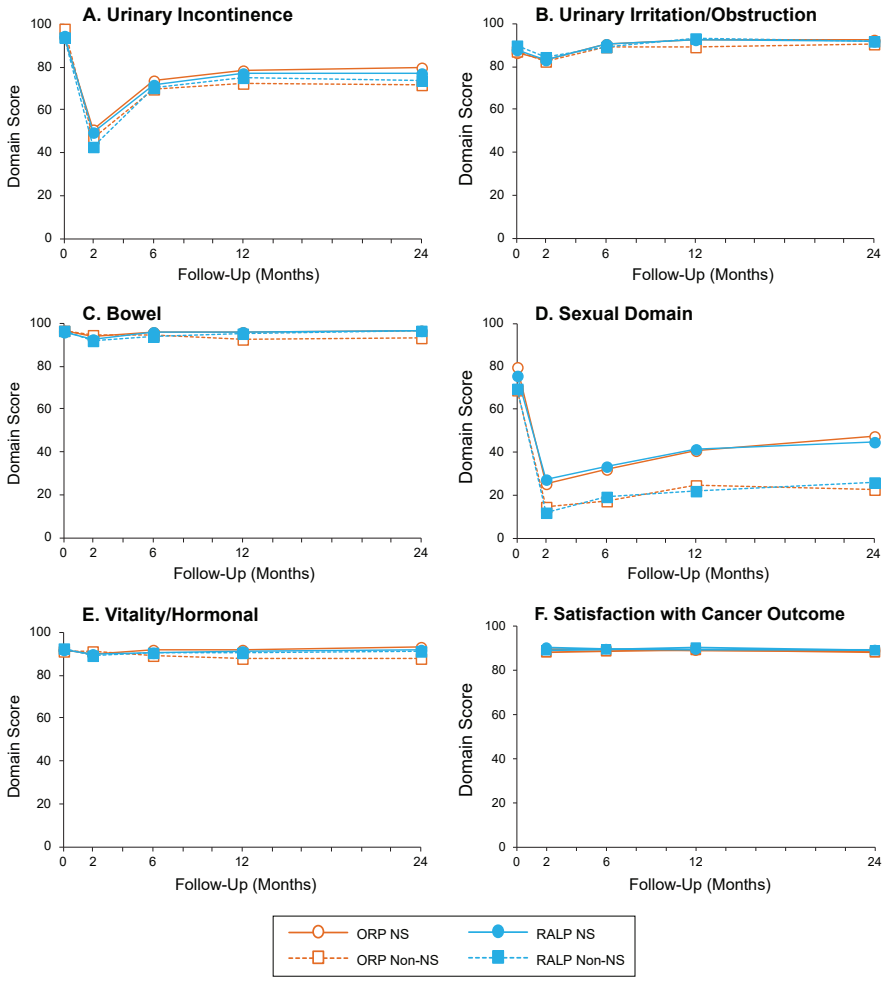
As a proud prior graduate of the Harvard Longwood Program in Urology and the BIDMC Minimally Invasive Urologic Oncology Fellowship, I now have the privilege of being the co-director of the fellowship, training the next generation of residents and last year's fellow, Marc Manganiello, MD.

I was selected to be a faculty member for the 17th Biennial Jerome P. Richie Harvard Urologic Oncology Course, a two-day CME course that takes place every other year.

SELECTED RESEARCH SUPPORT

Canary Prostate Cancer Active Surveillance Study (PASS); Canary Foundation, 2010-2018, through NIH UO1, 2019-2024; Co-investigator: Peter Chang, MD, MPH (BIDMC Site PI: Andrew Wagner, MD; PI: Daniel Lin, MD)

True Nth International; Movember Foundation, 2017-2019; PI: Peter Chang, MD, MPH



SELECTED PUBLICATIONS

Wagner AA, Cheng PJ, Carneiro A, Dovirak O, Khosla A, Taylor KN, Crociani CM, McAnally KC, Percy A, Dewey LE, Sanda MG, Chang P. Clinical use of EPIC for clinical practice (EPIC-CP) to assess patient-reported prostate cancer quality of life following robot-assisted radical prostatectomy. J Urol 2017;197(1):109-114.

Chang P, Regan MM, Ferrer M, Guedea F, Patil D, Wei JT, Hembroff LA, Michalski JM, Saigal CS, Litwin MS, Hamstra DA, Kaplan ID, Ciezki JP, Klein EA, Kibel AS, Sandler HM, Dunn RL, Crociani CM, Sanda MG, PROST-QA Consortium. Relief of urinary symptom burden after primary prostate cancer treatment. J Urol 2017;197(2): 376-384.

Danzig MR, Ghandour RA, Chang P, Wagner AA, Pierorazio PM, Allaf ME, McKiernan JM. Active surveillance is superior to radical nephrectomy and equivalent to partial nephrectomy for preserving renal function in patients with small renal masses: Results from the DISSRM registry. Urol Oncol 2017;35(3):116.

Gay HA, Sanda MG, Liu J, Wu N, Hamstra DA, Wei JT, Dunn RL, Kelin EA, Sandler HM, Saigal CS, Litwin MS, Kuban DA, Hembroff L, Regan MM, Chang P, Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment Consortium, Michalski JM. External beam radiation therapy or brachytherapy with or without short-course neoadjuvant androgen deprivation therapy: Results of a multicenter, prospective study of quality of life. Int J Radiat Oncol Biol Phys 2017;98(2):304-317.

Berry DL, Hong F, Blonquist TM, Halpenny B, Filson CP, Master VA, Sanda MG, Chang P, Chien GW, Jones RA, Krupski TL, Wolpin S, Wilson L, Hayes JH, Trinh QD, Sokoloff M, Somayaji P. Decision support with the personal patient profile-prostate: A multi-center randomized trial. J Urol 2018;199(1):89-97.

Taplin ME, Montgomery B, Xie W, Zhang Z, Bubley G, Lin D, Preston M, Trinh QD, Chang P, Wagner A, Mostaghel E, Kantoff P, Nelson P, Kibel A. Post-prostatectomy outcomes of patients with high risk prostate cancer treated with neoadjuvant androgen blockade. Prostate Cancer Prostatic Dis 2018;21(3):364-372.

◀ Comparison of quality of life outcomes after robotic and open prostatectomy

A complete list of publications begins on page 15.

Boris Gershman, MD

Assistant Professor of Surgery

RESEARCH GROUP

Peter Chang, MD, MPH
Issa Dahabreh, MD, MS, ScD
Ruslan Korets, MD
Aria Olumi, MD
Thomas Serre, PhD
Andrew Wagner, MD

RESEARCH FOCUS

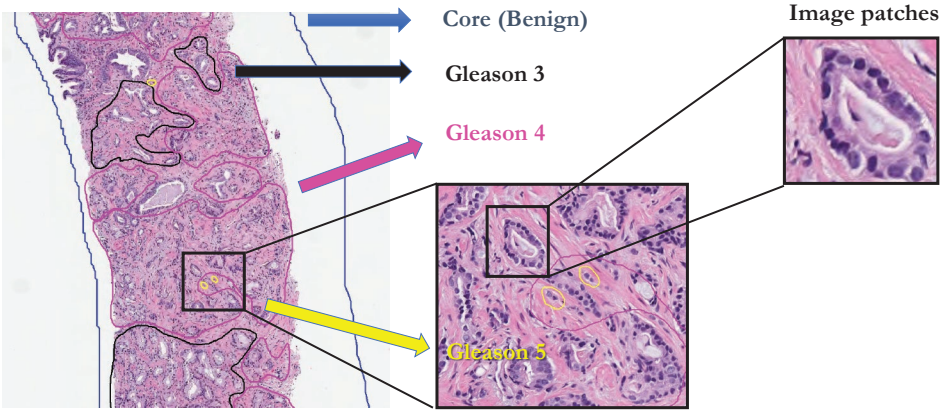
My research interests focus on investigating the comparative effectiveness of competing treatments for genitourinary malignancies and the development of deep learning methods to improve diagnosis and risk-stratification.

Using Observational Data for Comparative Effectiveness Research When Clinical Trial Evidence is Limited

Although randomized clinical trials are the preferred study design to evaluate the comparative effectiveness of interventions, there are very few trials comparing surgical treatments within genitourinary oncology, in part due to the difficulty of conducting surgical trials. To address such fundamental evidence gaps, I am interested in the application of two novel observational research methods when clinical trial evidence is limited: emulation of target clinical trials using observational datasets, and transportation of inferences from completed clinical trials to "real-world" patient populations. Together with biostatistics collaborators, we have applied the emulation framework to the study of kidney cancer. In one study, we emulated a trial of radical nephrectomy with lymph node dissection versus radical nephrectomy alone using the National Cancer Database (NCDB) to evaluate the survival benefit of lymphadenectomy. Concurrently, we are extending inferences from a completed trial of lymph node dissection in kidney cancer, EORTC 30881, to real-world target populations in the NCDB using transportability methods developed by one of my collaborators, Issa Dahabreh, MD, MS, ScD. Additional studies are ongoing to apply emulation and transportability methods to other disease settings.

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 am the 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. I recently published the results of a study showing that a subset of patients have improvement in their quality of life after prostate cancer treatment, specifically radical prostatectomy (Chang P et al, J Urol Feb 2017).



▲FIGURE 1: Classification of core biopsy specimen patches as benign versus Gleason 3 versus Gleason 4 versus Gleason 5.

Development of Deep Learning Methods to Improve Diagnosis and Risk-Stratification

Deep learning methods have emerged in recent years as a powerful approach to the classification of medical images, including radiologic images and histopathology. In a study with collaborators at Brown University (supported by NIGMS/ Advance-CTR, U54GM115677), we developed a deep learning algorithm for the histopathologic diagnosis and Gleason grading of prostate cancer core biopsy specimens. The model demonstrated 91.5% accuracy at classification of image patches

as benign versus malignant, and 85.4% accuracy at classification of image patches as benign vs. Gleason 3 vs. Gleason 4 vs. Gleason 5—performance that is similar to the interobserver variability for Gleason grading among pathologists. Additional studies are ongoing to expand applications of such deep learning algorithms.

ACCOMPLISHMENTS 2018-2019

I was invited to provide an oral presentation at the 2019 American Urological Association (AUA) Early Career Investigator Showcase. The presentation was entitled, "Emulating a Target Clinical Trial When Clinical Trial Evidence Is Limited: Examining the Role of Lymph Node Dissection in High-Risk Renal Cell Carcinoma."

In addition, I was invited to moderate a bladder cancer podium session at the 2019 American Urological Association annual meeting in Chicago, IL.

I continue to serve as a peer reviewer for multiple journals, including *Annals of Internal Medicine, Lancet, European Urology,* and *Urologic Oncology.*

I served as an invited peer reviewer for the 2019 AUA Guideline on the Diagnosis and Treatment of Early Stage Testicular Cancer.

I also served as a member on the 2019 Program Committee for the New England section of the American Urological Association annual meeting.

TEACHING, TRAINING, AND EDUCATION

I am committed to training future generations of physicians and clinician-scientists. In pursuit of this goal, I provide clinical and surgical training to urology residents and medical students through inpatient and outpatient clinical care. In addition, I enjoy opportunities to present at departmental conferences to provide didactic education in urologic oncology. Finally, I provide training in research and statistical methods through mentorship of medical students and residents in clinical research projects.

ABSTRACTS, POSTERS, AND EXHIBITS

Kott O, Linsley D, Amin A, Karagounis A, Golijanin D, Serre T, Gershman B. Automated histopathologic diagnosis and Gleason grading of prostate biopsies with machine learning. American Urological Association annual meeting, Chicago, IL (oral abstract)

Alalao O, Mueller-Leonhard C, Kim SP, Amin A, Tucci C, Pareek G, Mega A, Golijanin D, Gershman, B. Node-positive (cN+) urothelial carcinoma of the bladder treated with chemotherapy and radical cystectomy: Clinical outcomes and development of a risk prediction model. American Urological Association annual meeting, Chicago, IL (poster)

Alalao O, Mueller-Leonhard C, Kim SP, Amin A, Tucci C, Pareek G, Mega A, Golijanin D, Gershman, B. Comparative effectiveness of chemoradiation versus chemotherapy and radical cystectomy for clinically node-positive (cN+) bladder cancer. American Urological Association annual meeting, Chicago, IL (poster)

Gershman B. Emulating a target clinical trial when clinical trial evidence is limited: Examining the role of lymph node dissection in high-risk renal cell carcinoma. Early Career Investigators Showcase. American Urological Association annual meeting, Chicago, IL (oral abstract)

SELECTED PUBLICATIONS

Gershman B, Bukavina L, Chen Z, Konety B, Schumacher F, Li L, Kutikov A, Smaldone M, Abouassaly R, Kim SP. The association of robotic-assisted versus pure laparoscopic radical nephrectomy with perioperative outcomes and hospital costs. Eur Urol Focus 2019;22 Oct (Epub ahead of print).

Gershman B, Thompson RH, Boorjian SA, Lohse CM, Costello BA, Cheville JC, Leibovich BC. Radical versus partial nephrectomy for cT1 renal cell carcinoma. Eur Urol 2018;74(6):825-832.

Pereira J, Pareek G, Mueller-Leonhard C, Zheng Z, Amin A, Mega A, Tucci C, Golijanin D, Gershman B. The perioperative morbidity of transurethral resection of bladder tumor: Implications for quality improvement. Urology 2019;125:131-137.

Pelcovits A, Mueller-Leonhard C, Mega A, Amin A, Kim SP, Golijanin D, Gershman B. Outcomes of upper tract urothelial carcinoma with isolated lymph node involvement following surgical resection: Implications for multi-modal management. World J Urol; Accepted Jul 2019.

Golijanin B, Pereira J, Mueller-Leonhard C, Golijanin D, Amin A, Mega A, Boorjian SA, Thompson RH, Leibovich BC, Gershman B. The natural history of renal cell carcinoma with isolated lymph node metastases following surgical resection from 2006-2013. Urol Onc; Accepted Aug 2019.

Al-Alao O, Mueller-Leonhard C, Kim SP, Amin A, Tucci C, Kott O, Mega A, Golijanin D, Gershman B. Clinically node-positive (cN+) urothelial carcinoma of the bladder treated with chemotherapy and radical cystectomy: Clinical outcomes and development of a risk prediction model. Urol Onc; Accepted Aug 2019.

A complete list of publications begins on page 15.

RESEARCH GROUP

Peter Steinberg, MD

Ruslan Korets, MD

Assistant Professor of Surgery
Director, Urology Training

RESEARCH FOCUS

Clinical Outcomes in Surgical Treatment of Nephrolithiasis

My research focuses on kidney stone disease with an emphasis on assessing patterns of care and outcomes in patients undergoing minimally invasive treatment of nephrolithiasis. Our research team works closely with colleagues within BIDMC as well as collaborators at outside institutions. Due to the high prevalence of kidney stones and the increasing costs associated with its management, we recently examined variations in percutaneous nephrolithotomy (PCNL) cost and predictors of high- and low-cost PCNL procedures (Leow et al, *Can Urol Assoc J* 2018). Additionally, we are examining factors that affect follow-up patterns of patients presenting to the emergency room with renal colic. Our goal is to improve efficiency of care delivery for patients with nephrolithiasis by incorporating clinical variables and artificial intelligence models to identify high-risk patients who may benefit from earlier surgical intervention. We are also developing a prospective endourologic database that will examine stone characteristics of patients treated at our center.

Surgical Education

Another area of my clinical investigation focuses on evaluating learning curves for attaining calyceal access utilizing ultrasound guidance in percutaneous renal stone surgery. Incorporation of ultrasound in renal stone surgery has been shown to lower radiation exposure to patients, surgeons, and ancillary health providers when performing PCNL. I am involved in a multi-institutional study assessing adoption of these techniques in urologic training.

ACCOMPLISHMENTS 2018-2019

During the past year we started a new, independent urology residency program at BIDMC. As the Associate Director of the residency program, I oversee academic and clinical programs for training the next generation of urology residents. I also serve as the Site Director for the urology residents from the Lahey Hospital & Medical Center rotating at BIDMC as well as medical students from Harvard Medical School during advanced clinical electives.

During the most recent meeting of the New England Section of the American Urologic Association, I was invited as a panelist on a scientific session on surgical management of stone disease.

TEACHING, TRAINING, AND EDUCATION

Teaching and surgical education are important aspects of my career and practice. I have been involved in several educational initiatives utilizing technology to enhance surgical education. I have contributed to the Robotic Surgery Curriculum, which has been implemented across several of the Harvard Medical School-affiliated teaching hospitals. This curriculum incorporates robotic simulator exercises as well as one-on-one video review of performed surgeries to help familiarize residents with surgical anatomy and the procedural steps of robotic urologic procedures they will master during training.

During the past year, I served as a co-chair of a urologic forum on percutaneous renal stone surgery held in Kiev, Ukraine. Attended by more than 150 Ukrainian and Polish urologists, this three-day course consisted of lectures, semi-live surgeries, and panel discussions.

Lastly, I continue to broaden my role in surgical education by remaining involved in the BIDMC Academy of Medical Educators.

ABSTRACTS, POSTERS, AND EXHIBITS

Childs B, Davis, R, Korets R, Steinberg P. Who will follow-up? Predictors of compliance with nephrolithiasis follow-up after emergency room visits. New England Section of American Urological Association annual meeting, Providence, RI (abstract)

SELECTED PUBLICATIONS

Childs B, Manganiello M, Korets R. Novel education and simulation tools in urologic training. Curr Urol Rep 2019;20(12):81.

A complete list of publications begins on page 15.

Aria F. Olumi, MD

Beth Israel Deaconess Medical Center Professor of Surgery in the Field of Urology
Chief of Urologic Surgery

RESEARCH GROUP

Quinn Gangadharan
Christina Sharkey, BA
Pooja Unadkat, MD
Zongwei Wang, PhD
Bichen Xue, MD
Hu Zhang, MD

RESEARCH FOCUS

Over 90% of adult males develop lower urinary tract symptoms (LUTS) secondary to bladder outlet obstruction by age 80, rendering benign prostatic hyperplasia (BPH) the most common proliferative abnormality in humans. LUTS secondary to BPH negatively impact the quality of life of 210 million men globally, accounting for significant life years lost. We study the mechanisms of resistance to 5α-reductase inhibitor (5ARI), finasteride, one of the more common drugs used to manage BPH and associated LUTS.

Ongoing work in our lab has focused on steroid 5α-reductase 2 (SRD5A2, aka: 5α-reductase 2 [5AR2]), the enzyme responsible for prostatic development and growth. Our investigations have revealed that expression of SRD5A2 is variable and, in fact, 30% of men do not express SRD5A2 in prostate tissues. In previous work, we showed that somatic suppression of SRD5A2 during adulthood is dependent on epigenetic changes associated with methylation of the promoter region of the *SRD5A2* gene. Therefore, we hypothesize that absence of SRD5A2 as a result of somatic methylation is directly responsible for lack of sensitivity to 5ARI therapy in men with BPH.

ACCOMPLISHMENTS 2018-2019

- Zongwei Wang, PhD, recipient of a Research Scholar Award from American Urological Association, completed his grant support in June 2019
- Submitted R01 grant (Feb. 2019, basic science grant): Title: Methylation of SRD5A2 and sensitivity to 5α–reductase inhibitor for treatment of BPH. Grant received 29 percentile score; preparing re-submission
- Submitted R01 grant (June 2019, clinical trial grant): Title: 5-Alpha Reductase 2 as a marker of resistance to 5ARI therapy; awaiting review
- Aria F. Olumi, MD, was invited as the State-of-the-Art Speaker at New England-American Urological Association Meeting, Sept. 2019

TEACHING, TRAINING, AND EDUCATION

- Obtained ACGME approval for an independent urology residency training program: Beth Israel Deaconess/ Harvard Medical School Urology Program
  - Recruited our first two residents
  - Will participate in the urology residency match for two positions/ year
- Obtained endowment for BIDMC Minimally Invasive Fellowship Program
  - Minimally invasive fellow participates in the Harvard T. H. Chan School of Public Health Clinical Effectiveness course to enhance clinical research abilities
- Course director for online *Comprehensive Review of Urology* (Oakstone Publishing)

SELECTED RESEARCH SUPPORT

Early Detection Research Network: Prostate MRI biomarker study and reference set; NIH/NCI, 2018–2023; BIDMC is one of 11 multi-institutional national sites for patient recruitment. Site PI: Aria F. Olumi, MD

Obesity-associated inflammation mediates prostatic growth through androgenic to estrogenic switch; American Urological Association/Urology Care Foundation Research Scholar Grant, 2017-2019; PI: Zongwei Wang, PhD; Mentor: Aria F. Olumi, MD

SELECTED PUBLICATIONS

Wang Z, Olumi AF. Metformin: An anti-proliferative agent and methylation regulator in treating prostatic disease? Am J Physiol Renal Physiol 2018;314(3):F407-F411.

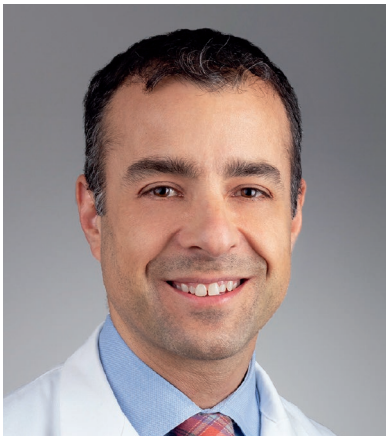
Tao Z, Zheng LD, Smith C, Luo J, Robinson A, Almeida FA, Wang Z, Olumi AF, Liu D, Cheng Z. Estradiol signaling mediates gender difference in visceral adiposity via autophagy. Cell Death Dis 2018;9(3):309.

Ingham MD, Lee RJ, MacDermed D, Olumi AF. Prostate cancer in transgender women. Urol Oncol 2018;36(12):518-525.

Burns RB, Olumi AF, Owens DK, Smetana GW. Would you recommend Prostate-Specific Antigen screening for this patient? Grand Rounds Discussion from Beth Israel Deaconess Medical Center. Ann Intern Med 2019;170(11):770-778.

Wu S, Lin SX, Lu M, Subtelny AO, Wang Z, Dahl DM, Olumi AF, Wu CL. Assessment of 5-year overall survival in bladder cancer patients with incidental prostate cancer identified at radical cystoprostatectomy. Int Urol Nephrol 2019;51(9):1527-1535.

A complete list of publications begins on page 15.



Andrew A. Wagner, MD

Associate Professor of Surgery
Director, Minimally Invasive Urologic Surgery
Director, Minimally Invasive Urologic Surgery Fellowship Program

RESEARCH GROUP

MaryAnn Chan, BS
Peter Chang, MD, MPH
Catrina Crociani, MPH
Allison Kleeman, BS
Jialin Mao, MPH
Kolo Olugbade, MD
Adrian Waisman, MD

RESEARCH FOCUS

Kidney cancer

We have prospectively collected patient-reported quality of life data after kidney surgery and using these data can now provide detailed recovery expectations for our patients. We also have defined 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 prospective analysis, the first of its kind, found patients required, on average, four weeks off of work and had the equivalent of $10,000 in lost wages during that time.

We recently published our experience using the early unclamping technique during robotic partial nephrectomy. In over 450 robotic partial nephrectomy patients our EBL was 242cc, transfusion rate was 1%, and we did not see any postoperative pseudoaneurysms or late bleeding complications. This is likely due to the specific type of renorrhaphy that we perform.

Our team is also interested in non-operative approaches to small renal masses. Together with researchers from Johns Hopkins University and Columbia University, the DISSRM trial (Delayed Intervention and Surveillance for Small Renal Masses) is a multicenter prospective study evaluating the role of surveillance and surgery of small kidney tumors over time.

Prostate cancer

We are investigating a novel method of identifying positive margins in real time during robotic prostatectomy using a non-linear microscope (NLM). Pilot data using this technology suggests NLM can evaluate prostate tissue within three minutes without the need for costly and time-consuming frozen section. We are currently designing a randomized trial to evaluate the ability of NLM to improve our rate of nerve-sparing and reduce final positive margins.

Our group is the only member of the Canary Prostate Cancer Active Surveillance Study (Canary-PASS) in the northeast. This is the largest prospective multi-center study of active surveillance for prostate cancer, with over 2,000 patients enrolled. We are evaluating biomarkers that could distinguish which patients have more aggressive prostate cancer from those with indolent disease. Recently we have looked at the timing of cancer progression, use of a four-kallikrein panel for prediction of prostate cancer progression, and evaluated a genomic index in cancer progression. This project was recently awarded an NIH UO1 grant to support research infrastructure for the next five years.

Our team has led a multi-center study that demonstrated our ability to reduce opioid pills from 30 down to five after robotic prostatectomy and from 30 to 15 after robotic partial nephrectomy. We have found postoperative day-one pain score is associated with postoperative narcotic requirements:

Correlating postop day 1 pain score to post-discharge narcotic requirements after robotic partial nephrectomy

POD1 Pain Score	Number of Patients	Median Pills Taken	Number of Patients Taking ≤ 15 Pills
0–1	22 (30%)	0	21 (95%)
2–10	51 (70%)	5	42 (82%)

Bladder cancer

Intracorporeal urinary diversion

We are the first urology team in Boston to regularly perform radical cystectomy and urinary diversion completely robotically. We are gathering prospective data with a focus on clinical outcomes, validated quality of life, our ability to train fellows during this case, and learning curve. We also recently joined the IRCC (International Radical Cystectomy Consortium) for radical cystectomy, a large (50 center) database project aimed at evaluating trends in cystectomy treatment over time.

ACCOMPLISHMENTS 2018–2019

- We published the largest known experience using the early unclamping technique for robotic partial nephrectomy
- We published the first known evaluation of societal costs after kidney surgery
- We have enrolled over 220 patients in the prospective prostate cancer active surveillance study (Canary-PASS)
- We trained our sixth Minimally Invasive Urology Fellow, Joan Delto, MD, and our fellowship, now the William C. DeWolf Fellowship in Minimally Invasive Urologic Surgery, became officially endowed by our grateful patients
- We have IRB approval to begin evaluating prostate margins in real-time using a non-linear microscope in the OR
- We published and presented on our unique experience decreasing opioid prescriptions after robotic prostatectomy and partial nephrectomy

TEACHING, TRAINING, AND EDUCATION

In addition to training our BIDMC urology residents, in July 2010 we launched a Minimally Invasive Urologic Surgery Fellowship Program. Our fellowship was recently endowed by our grateful patients and is now the William C. DeWolf Fellowship in Minimally Invasive Urologic Surgery. This fellowship is a unique training opportunity in New England, combining high-volume robotic surgery and advanced education in clinical research through the Harvard T. H. Chan School of Public Health Clinical Effectiveness Program.

SELECTED RESEARCH SUPPORT

Canary Prostate Cancer Active Surveillance Study (PASS); Canary Foundation, 2010–2018, through NIH UO1, 2019–2024; BIDMC Site PI: Andrew A. Wagner, MD

SELECTED PUBLICATIONS

Cooperberg MR, Brooks JD, Faino AV, Newcomb LF, Kearns JT, Carroll PR, Dash A, Etzioni R, Fabrizio MD, Gleave ME, Morgan TM, Nelson PS, Thompson IM, Wagner AA, Lin DW, Zheng Y. Refined analysis of prostate-specific antigen kinetics to predict prostate cancer active surveillance outcomes. Eur Urol 2018;74(2):211–17.

Chang P, Renehan P, Taylor KN, Dewey LE, McAnally KC, Hyde S, Crociani CM, Carneiro A, Beaule LT, Wagner AA. Societal costs of localized renal cancer surgery. Can J Urol 2018;25(4):9401–9406.

Cahill LC, Fujimoto JG, Giacomelli MG, Yoshitake T, Wu Y, Lin DI, Ye H, Carrasco-Zealos OM, Wagner AA, Rosen S. Comparing histologic evaluation of prostate tissue using nonlinear microscopy and paraffin H&E: A pilot study. Mod Pathol 2019;32(8):1158–1167.

Sotimehin AE, Patel HD, Alam R, Gorin MA, Johnson MH, Chang P, Wagner AA, McKiernan JM, Allaf ME, Pierorazio PM. Selecting patients with small renal masses for active surveillance: A domain based score from a prospective cohort study. J Urol 2019;201(5):886–892.

Delto JC, Chang P, Hyde S, McAnally K, Crociani C, Wagner AA. Reducing pseudo-aneurysm and urine leak after robotic partial nephrectomy: Results using the early unclamping technique. Urology 2019;132:130–135.

Stensland C, Chang P, Wagner AA. The urologist's role in the opioid epidemic. Curr Opin Urol 2019;29(4):466–468.

A complete list of publications begins on page 15.

Elliot L. Chaikof, MD, PhD

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

RESEARCH GROUP

Jiaxuan Chen, PhD
Erbin Dai, MD
Pradheep Eradi, PhD
Oki Ham, PhD
Carolyn A. Haller, PhD
Revanth Kosaraju
Liying Liu, MD
Appi Reddy Mandhapati, PhD
Torsten B. Meissner, PhD
David Miranda Nieves
Simon Park, PhD
Diane (Dayoung) Park, PhD
Rae Rokosh, PhD
Daniel Wong, MD

RESEARCH FOCUS

Our laboratory (chaikoflab.org) is focused on the discovery of new drugs and the development of tissue-engineered organs based upon the principles of chemistry, biomolecular engineering, and 3-D fabrication technologies. Ongoing research is directed at the following areas.

Drug Discovery

Identification of new drugs to inhibit inflammation and thrombosis
We are currently synthesizing compounds to block inflammatory responses that contribute to deep venous thrombosis, atherosclerosis, metabolic syndrome, inflammatory bowel disease, and cancer metastasis. A number of these drugs are designed to inhibit selectins, which play an important role in the recruitment of leukocytes to inflamed tissue, as well as nuclear receptors that modulate the immune response.

Biomaterials 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 and whose bioactive surfaces can be 'regenerated' *in situ* to extend and improve the clinical performance of blood-contacting devices, such as vascular grafts, heart valves, left ventricular devices, and implantable artificial lungs and kidneys.

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 develop bioprinting approaches, which along with new synthetic collagen and elastin analogues can be assembled with vascular wall cells derived from stem cells to engineer a living artery.

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.

ACCOMPLISHMENTS 2018-2019

Ongoing collaborations with David Liu, PhD (Broad Institute/Harvard University) have led to a new NIH-funded program directed at the design of delivery systems for *in vivo* genome editing.

Through an established collaboration with Jian Liu, PhD (Chemistry, University of North Carolina) and David Mooney, PhD (Engineering, Harvard University), we have expanded our efforts directed at identifying and harnessing biologically inspired designs to limit blood clotting on artificial surfaces.

We have recently initiated a new NIH-funded program to determine the underlying biological mechanisms, which increase the risk of venous thromboembolism among patients with cancer in collaboration with Jeffrey Zwicker, MD, PhD, and Robert Flaumenhaft, MD (Hematology, BIDMC). Likewise, we have begun a new NIH-funded research program to design a new generation of protein drugs that inhibit thrombosis without impairing hemostasis in an ongoing collaboration with Karlheinz Peter, MD, PhD (University of

Melbourne, Australia) along with a new collaboration with Karl E. Griswold, PhD, and Chris Bailey-Kellogg, PhD (Computer Science and Engineering, Dartmouth).

Additional collaborations have supported ongoing drug discovery efforts including those with Richard Cummings, PhD, Vice Chair of Translational Research in the Department of Surgery and Director, Harvard Medical School (HMS) Center for Glycoscience, and Robert Woods, PhD, Professor of Computational Chemistry, Complex Carbohydrate Research Center, University of Georgia, as well as with Lijun Sun, PhD, Associate Professor of Surgery at HMS and Director of the Center for Drug Discovery in the BIDMC Department of Surgery.

Tissue-engineering programs represent collaborations with Axel Guenther, PhD, Professor of Mechanical Engineering at the University of Toronto. The development of a new generation of infection-resistant biomaterials represents a collaboration with Joanna Aizenberg, PhD, Professor of Materials Science in the Harvard John A. Paulson School of Engineering and Applied Sciences.

- Elected Chair for Section 01 (Physical Sciences, Mathematical Sciences, Computer/ Information Sciences, Engineering Sciences) in the National Academy of Medicine
- Co-Chair, Health and Technology Interest Group (IG18), National Academy of Medicine
- Member (ex officio), Committee on Emerging, Science, Technology, and Innovation in Health and Medicine, National Academy of Medicine
- The 2019 Hunter Sweaney Lecture, Duke University
- 2019 Flance-Karl Award, American Surgical Association
- Scientific Advisory Committee, Research Institute - McGill University Health Sciences Center

TEACHING, TRAINING, AND EDUCATION

Postdoctoral fellow, Walter Wever, PhD, scientist, joined the scientific staff of Ferring Pharmaceuticals, San Diego, CA

Postdoctoral fellow, Madhukar Patel, MD, surgical resident, Massachusetts General Hospital, was accepted into a fellowship in HPB and Transplant Surgery at the University of Toronto

Postdoctoral fellow, Daniel Wong, MD, surgical resident, BIDMC, received 2019 Cummings Resident Research Award

Predoctoral fellow, Revanth Kosaraju, Harvard Medical School class of 2021, received a 2019 AHA/ASA Student Scholarship in Cardiovascular Disease

SELECTED RESEARCH SUPPORT

Biomarkers and mechanisms in cancer-associated thrombosis; NIH/NHLBI, 2018–2023; MPI: Elliot Chaikof, MD, PhD; Robert Flaumenhaft, MD, PhD; Jeffrey Zwicker, MD ($4,465,000)

The Harvard Translational Glycobiology Career Development Program: Bridging glycoscience and clinical medicine; NIH, 2018–2023; MPI: Elliot Chaikof, MD, PhD; Richard D. Cummings, PhD; Robert Sackstein, MD, PhD ($4,802,020)

Clot-targeted antithrombotics for venous thromboprophylaxis; NIH 2019–2023; PI: Elliot Chaikof, MD, PhD ($1,780,793)

Delivery technologies for *in vivo* genome editing; NIH, 2019–2022; PI: Elliot Chaikof, MD, PhD ($2,260,670)

A PSGL-1 glycopeptide mimetic for treatment of metabolic syndrome; NIH, 2016–2020; PI: Elliot Chaikof, MD, PhD ($3,700,000)

A PSGL-1 glycopeptide mimetic for treatment of venous thromboembolism; NIH, 2015–2020; PI: Elliot Chaikof, MD, PhD ($2,177,000)

Facile synthesis of glycosulfopeptides and related bioconjugates; NIH, 2015–2019; PI: Chaikof ($2,300,000)

SELECTED PUBLICATIONS

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

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 2015;35:332–40.

Kim W, Haller CA, Dai E, Wang X, Hagemeyer CE, Liu DR, Peter K, Chaikof EL. Targeted anti-thrombotic protein micelles. Angew Chem Int Ed 2015;54:1461–5.

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; 6:6387.

Patsch C, Challet-Meylan L, Thoma EC, Urich E, Heckel T, Zon LI, Chaikof EL, Gerszten RE, Graf M, Iacone R, Cowan CA. Generation of vascular endothelial and smooth muscle cells from human pluripotent stem cells. Nat Cell Biol 2015; 17(8):994–1003.

Ham HO, Qu Z, Haller CA, Dorr BM, Dai E, Kim W, Liu DR, Chaikof EL. In situ regeneration of bioactive coatings enabled by an evolved Staphylococcus aureus sortase A. Nat Commun 2016; 7:11140.

Angsana J, Chen J, Liu L, Haller CA, Chaikof EL. Efferocytosis as a regulator of macrophage chemokine receptor expression and polarization. European J Immunology 2016; 46:1592–1599.

Chen J, Howell C, Haller CA, Patel MS, Ayala P, Moravec KA, Dai E, Liying L, Sotiri I, Aizenberg M, Aizenberg J, Chaikof EL. An immobilized liquid interface prevents device associated bacterial infection in vivo. Biomaterials 2017; 113:80–92.

Hanjaya-Putra D, Haller C, Wang X, Dai E, Lim B, Liu L, Jaminet P, Yao J, Searle A, Bonnard T, Hagemeyer CE, Peter K, Chaikof EL. Platelet-targeted dual pathway antithrombotic inhibits thrombosis with preserved hemostasis. JCI Insight 2018;3(15). pii: 99329.

Chen J, Haller CA, Jernigan FE, Koerner SK, Wong DJ, Wang Y, Cheong JE, Kosaraju R, Kwan J, Park DD, De La Rosa RC, Premji AM, Liu L, Park E, Moss AC, Emili A, Bhasin M, Sun L, Chaikof EL. Modulation of lymphocyte mediated tissue repair by rational design of heterocyclic aryl hydrocarbon receptor agonists. Sci Adv 2020;6;3,eaay8230.

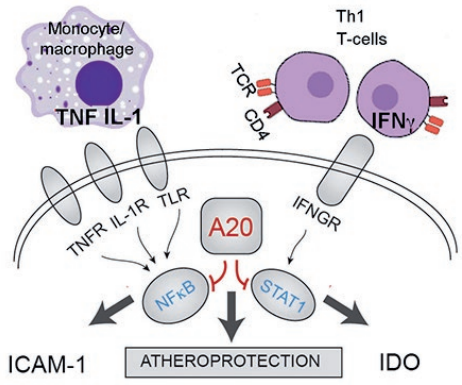
A complete list of publications begins on page 15.

Christiane J. Ferran, MD, PhD

Lewis Thomas Professor of Surgery

RESEARCH GROUP

Cleide Angolano, PhD
Mauricio Contreras, MD
John Gigioli, MD
Ravirasmi Jasti, BS
Philip LoGerfo, MS
Erin McIntosh, MD
Nyah Patel, student



▲FIGURE 1: The atheroprotective umbrella of A20

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, i.e. the "molecular basis of health"
- Identifying the culprits that hinder "return to homeostasis," and thus result in pathology
- Validating signature molecules in animal models of human disease for potential clinical translation as diagnostic, prognostic, and most importantly, therapeutic tools

This line of research was triggered by our seminal discovery that up-regulation of the ubiquitin-modulatory protein A20, AKA, TNFAIP3 or the anti-apoptotic Bcl members, A1, Bcl-2 and Bcl-xL in endothelial cells in response to inflammatory stimuli, serves a general "protective" function by shutting down inflammation through inhibition of the transcription factor NF-κB (JBC 1996;271:18068). Subsequent studies confirmed A20 as one of humans' most potent and ubiquitous physiologic anti-inflammatory molecules. A20 not only goes to the NF-κB heart of inflammation, but also beyond to control Interferonγ and α/β signaling, and modulate cell survival and proliferation, with return to homeostasis as the ultimate goal. We established the therapeutic benefits of A20-based therapies in a number of animal models of human diseases that share inflammation as a central pathogenic component, focusing on the three fields listed below.

Vascular Diseases

Our data qualifies A20 as a potent "atheroprotective" and "modulator of angiogenesis" molecule, as evidenced in numerous animal models of disease:

- neointimal hyperplasia post-balloon angioplasty
- transplant arteriosclerosis, the main cause of failure of vascularized allografts
- accelerated atherosclerosis of diabetes
- vein graft and prosthetic arterial graft failure
- proliferative retinopathies, and blinding eye disease

Liver Regeneration and Repair

We have also extensively documented 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 90% 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 50% lethality. These data have important clinical implications. 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 lately discovered that A20 regulates lipid metabolism in a way that improves fatty liver disease in a mouse model of human non-alcoholic fatty liver disease.

Current pre-translational studies in pigs using clinically safe viral vectors to specifically induce A20 expression in the liver are very promising and prelude clinical implementation in transplantation and xenotransplantation.

Treatment of Diabetes

Islet transplantation: 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.

Insulin alternatives: Recently, we discovered a novel anti-diabetic function

of A20, whereby a single injection of a hepatotropic A20 gene therapy vector restored glycemic control in a mouse model of type I diabetes. Remarkably, this effect was long-lasting and insulin independent. We are characterizing the molecular basis of this novel function of A20, and exploring its potential use as an anti-diabetic therapy. We are encouraged by the fact that this project was selected as a finalist (12/176) at the MassBio Science 2 Startup 2019 competition, and generated interest from venture capital and biotech firms.

ACCOMPLISHMENTS 2018-2019

Administrative

- Elected member and docket member: Harvard Medical School Faculty Council
- Member: Committee for Senior Appointment, BIDMC
- Member: Promotion and Reappointment Committee, Department of Surgery, BIDMC
- Member: Search Committee for Scientific Director of the Transplant Center, MGH, HMS
- Member: Search Committee for Chief of Transplant Surgery, BIDMC, HMS
- Member: Search Committee for Chief Academic Officer, Beth Israel Lahey Health, HMS
- Member: Executive Committee, Center for Vascular Biology Research, BIDMC

Scientific Review Boards

- Reviewer: NIH SBIR/STTR CVRS (10) Small Business: Cardiovascular Sciences Activities SEP study section
- Reviewer: NIH Surgery Anesthesia Traumatology study section
- Reviewer: Fund for Scientific Research-FNRS, Brussels, Belgium
- Reviewer: Swiss National Science Foundation, Zurich, Switzerland

Invited Presentations and Visiting Professorships

A20 and Vascular Homeodynamics: A Tale of Discovery and Translation. Molecular Cardiology Research Institute, Tufts University School of Medicine, Boston, MA

Novel Technologies Fueling Medical Revolutions. Plenary lecture, Les Printemps de la Faculté annual meeting, Saint Joseph University School of Medicine, Beirut, Lebanon

Molecular Insights into Macrovascular and Microvascular Complications of Diabetes. Les Printemps de la Faculté annual meeting, Saint Joseph University School of Medicine, Beirut, Lebanon

A20 and Vascular Homeodynamics: A Translational Story. Whitaker Cardiovascular Institute Visiting Professorship and Seminar Series, Boston University School of Medicine, Boston, MA

Xenotransplantation: Prospects for Large-Scale Diabetes Cell Therapy. Invited Session Chair, 79th Scientific Meeting, American Diabetes Association, San Francisco, CA

Awards

Christiane Ferran, MD, PhD, selected as finalist for a pitch presentation at the MassBio Science to Start up (S2S) 2019 competition for work related to A20 as a novel gene therapy for the treatment of diabetes and its complications

Erin McIntosh, MD, recipient of the best data club award at the Center for Vascular Biology Research (CVBR) for her work on small molecule inhibitors of atherosclerotic disease

Patents

Novel therapies to achieve glycemic control. International publication of docket number WIPO PCT WO2018/035121 A1. Inventors: Christiane Ferran MD, PhD, Cleide da Silva, PhD, Alessandra Mele, MD

TEACHING, TRAINING, AND EDUCATION

For the past 22 years I have been training postdoctoral research fellows, surgical residents, undergraduate, graduate, and medical students, and research associates who rotate in my laboratory. I also mentor junior faculty in the Department of Surgery and the CVBR. Reflecting my commitment to teaching/mentoring, I serve on three NIH-funded T32, one K12, and one T35 training grants as:

- Co-director, Longwood-Harvard T32 in vascular surgery (Director: Frank LoGerfo, MD, BIDMC)
- Faculty mentor, renal T32 (Director: Martin Pollak, MD, BIDMC)
- Faculty mentor, transplantation biology T32 (Director: Joren Madsen, MD, MGH)
- Faculty mentor, vascular surgery T35 (Directors: Frank LoGerfo, MD, Leena Pradhan-Nabzdyk, PhD, MBA, BIDMC)
- Faculty, translational glycobiology K12 program (Director: Robert Sackstein, MD, BWH)

SELECTED PUBLICATIONS

Huynh C, Shih TY, Mammoo A, Samant A, Pathan SG, Nelson DW, Ferran C, Mooney DJ, LoGerfo FW, Pradhan-Nabdzyk L. Delivery of targeted gene therapies using a hybrid cryogel-coated prosthetic vascular graft. PeerJ 2019;7:e7377.

Essayagh S, Choi LY, Scali ST, Moll HP, Fisher MD, Csizmadia E, Studer P, Fischer MD, Siracuse JJ, Lee A, Kaczmarek E, McIntosh E, LoGerfo P, Revuelta Cervantes J, LoGerfo P, Clermont A, Angolano C, Ferran C. A20 modulates angiogenic VEGF signaling in retinal endothelial cells to protect from proliferative retinopathies. ATVB 2019; manuscript under revision.

A complete list of publications begins on page 15.

SELECTED RESEARCH SUPPORT

Novel therapies to achieve glycemic control; Juvenile Diabetes Research Foundation, 2016-2020; PI: Christiane Ferran, MD, PhD (Co-investigator: Cleide da Silva, PhD)

Bioengineering of vein graft to resist intimal hyperplasia; NIH, 2018-2021. PI: Christiane Ferran MD, PhD (Co-investigator: Mauricio Contreras, MD)

Mechanisms of prosthetic arterial graft failure; NIH, 1987-2021; Multi-PIs: Christiane Ferran MD, PhD; Frank LoGerfo, MD, David Mooney, PhD

Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery; NIH, 2007-2023; Multi-PIs: Christiane Ferran, MD, PhD, Frank LoGerfo, MD, and Manoj Bhasin, PhD

RESEARCH GROUP

Mauricio Contreras, MD
Winston Crumb, BS
Jennifer Li, MD
Patric Liang, MD
Navneet Momi, PhD
Akshi Thakkar, MS

Frank W. LoGerfo, MD

William McDermott Distinguished Professor of Surgery

Leena Pradhan-Nabzdyk, PhD, MBA

Assistant Professor of Surgery

RESEARCH FOCUS

Our group has been extensively involved in different areas of vascular biology, diabetes, and neuropeptide research: 1) evaluating mechanisms responsible for development of intimal hyperplasia (IH) in vein grafts and prosthetic grafts; and 2) developing novel techniques to prevent IH in both vein grafts and prosthetic grafts using bioengineering methodologies.

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. Our 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).

ACCOMPLISHMENTS 2018-2019

Based on our previous work, the LoGerfo-Pradhan-Nabzdyk 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 led to manuscripts.

In collaboration with Dr. Christiane Ferran and Dr. Manoj Bhasin of BIDMC, we conducted single cell genomics in a canine model of vein graft IH. This work, which is currently ongoing, will be first such single cell genomics study in the field. Additionally, based on these preliminary results, our group successfully renewed its R01 funding for this project. The results have been presented at various international and national meetings by postdoctoral fellow, Navneet Momi.

The prosthetic IH project, being conducted in collaboration with Dr. Christiane Ferran and Dr. David Mooney (Harvard School of Engineering), is focused on developing Click-Hydrogels that can be coated on clinically used prosthetic grafts as dacron to deliver siRNA at the anastomotic site. The results from this project have been presented at international and national meetings by postdoctoral fellows Cindy Huynh and Patric Liang.

Through NIH R21 funding, Dr. Pradhan-Nabzdyk, in close collaboration with Dr. Lijun Sun of BIDMC, has discovered several small molecule inhibitors of the pro-inflammatory cytokine, IL-18. IL-18 is implicated in many chronic conditions including ulcerative colitis, cardiovascular disease, psoriasis, and various cancers. In addition to testing the efficacy of these inhibitors in vascular-disease models, Drs. Pradhan-Nabzdyk and Sun are collaborating with colleagues in the BIDMC divisions of gastroenterology and colon and rectal surgery to test the efficacy in patient samples of ulcerative colitis. The data from these experiments are extremely promising. A provisional patent application has been filed for these molecules.

TEACHING, TRAINING, AND EDUCATION

We have mentored several students and postdocs in the lab. Additionally, Drs. LoGerfo, Pradhan-Nabzdyk, and Ferran are the Co-program Directors of the NIH T-32 Harvard-Longwood Research Training Program in Vascular Surgery. This two- or three-year research training program is the oldest such program in vascular surgery in the country. Currently there are 10 trainees (eight surgical residents and two PhD postdoctoral fellows) mentored in different labs in the Longwood Medical Area. Trainees from around the country apply to this program and thus far 82 trainees have graduated from the program. This grant was successfully renewed for years 26-30.

In addition, Drs. LoGerfo and Pradhan-Nabzdyk co-direct the NIH T-35 program, the Harvard-Longwood Short-Term Research Training Program in Vascular Surgery. Now in its seventh year, this 10- to 12-week summer program trains medical students in vascular surgery research. Medical students from across the country apply to this program and conduct research in various labs in the Longwood Medical Area. To date, 43 students have graduated from this program.

ABSTRACTS, POSTERS, AND EXHIBITS

Liang P, Mooney D, Pradhan-Nabzdyk L, LoGerfo F. Perivascular gene targeted therapy using biodegradable CLICK-Gelatin hydrogels. American College of Surgeons Clinical Congress 2019; San Francisco, CA

Momi N, Liang P, Bhasin S, LoGerfo FW, Ferran C, Pradhan-Nabzdyk L, Bhasin M. Vein graft failure: Single cell genomics. Academic Surgical Conference, Houston TX

Momi N, Bhasin S, Liang P, LoGerfo FW, Ferran C, Bhasin M, Pradhan-Nabzdyk L. Vein graft failure and single cell genomics. 8th Annual Harvard Surgery Research Day, Boston, MA

Momi N, Bhasin M, Bhasin S, Liang P, LoGerfo FW, Ferran C, Crumb W, Contreras MA, Pradhan-Nabzdyk L. Vein graft failure: Single cell genomics and real-time energetics. Center for Vascular Biology Research 15th annual retreat, Boston, MA

Momi N, Bhasin M, Bhasin S, Liang P, LoGerfo FW, Ferran C, Crumb W, Contreras MA, Pradhan-Nabzdyk L. Vein graft failure: Single cell genomics and real-time energetics. (submitted), 16th Academic Surgical Congress, Orlando, FL

SELECTED RESEARCH SUPPORT

Mechanisms of prosthetic arterial graft failure; NIH, 1987-2021; PIs: Frank W. LoGerfo, MD, Christiane Ferran, MD, PhD, David Mooney, PhD; Co-Investigator: Leena Pradhan-Nabzdyk, PhD, MBA

Genetic engineering of vein bypass grafts in vascular and cardiovascular surgery; NIH, 2008-2021; PIs: Frank W. LoGerfo, MD, Christiane Ferran, MD, PhD, Manoj Bhasin, PhD; Co-Investigator: Leena Pradhan-Nabzdyk, PhD, MBA

Harvard-Longwood Research Training Program in Vascular Surgery; NIH, 1993-2024; PI: Frank W. LoGerfo, MD; Executive Committee: Leena Pradhan-Nabzdyk, PhD, MBA

Harvard-Longwood Short-Term Research Training Program in Vascular Surgery; NIH, 2013-2023 (formerly William J. von Liebig Summer Research in Vascular Surgery Program, 2000-2012); Program Co-Directors: Frank W. LoGerfo, MD, Leena Pradhan-Nabzdyk, PhD, MBA

SELECTED PUBLICATIONS

Huynh C, Shih TY, Mammoo A, Samant A, Pathan S, Nelson DW, Ferran C, Mooney D, LoGerfo F, Pradhan-Nabzdyk L. Delivery of targeted gene therapies using a hybrid cryogel-coated prosthetic vascular graft. PeerJ 2019;20;7:e7377.

Nabzdyk CS, Pradhan-Nabzdyk L, LoGerfo FW. RNAi therapy to the wall of arteries and veins: Anatomical, physiologic, and pharmacological considerations. J Transl Med 2017;28;15(1):164.

Shean KE, Soden PA, Schermerhorn ML, Zettervall SL, Deery SE, Darling JD, Hamdan A, LoGerfo FW. Lifelong limb preservation: A patient-centered description of lower extremity arterial reconstruction outcomes. J Vasc Surg 2017;66(4):1117-1122.

Bodewes T, Johnson J, Hyunh C, Muralidharan S, Contreras M, LoGerfo FW, Pradhan-Nabzdyk L. Intraluminal delivery of thrombospondin-2 siRNA inhibits the vascular response to injury in a rat carotid balloon angioplasty model. FASEB J 2017;31(1):109-11.

Mammoo A, Bencheriff SA, Nabzdyk C, Shih TY, Huynh C, Mooney DJ, LoGerfo FW, Pradhan-Nabzdyk L. Heparin containing cryogels as surfaces for local cardiovascular drug delivery. Polymers; in preparation.

A complete list of publications begins on page 15.

Marc L. Schermerhorn, MD

George H.A. Clowes, Jr. Professor of Surgery
Chief, Division of Vascular and Endovascular Surgery

RESEARCH GROUP

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Chun Li, MD
Jennifer Li, MD
Patric Liang, MD
Jinny Lu, MD
Thomas F.X. O'Donnell, MD
Priya Patel, MD
Alexander Pothof, MD
Katie E. Shean, MD
Peter A. Soden, MD
Nicholas J. Swerdlow, MD
Klaas Ultee, MD, PhD
Rens Varkevisser, MD
Jacqueline Wade, MD
Winona Wu, MD
Cecilia Yao, MD
Sara L. Zettervall, MD

RESEARCH FOCUS

My clinical research group has an active interest in vascular surgery outcomes research on a local and national level. As emerging technologies evolve the way we practice medicine, 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 aneurysms, carotid disease, and lower extremity arterial disease, in order to help guide patient selection for each type of procedure. We utilize a wide range of observational, registry, and administrative data from real-world settings to better understand the impact of vascular treatments on disease processes.

Our experience at BIDMC, boasting the world's largest series of distal bypass and tibial angioplasty procedures, provided rich data from which we have published on the effectiveness of primary endovascular therapy for critical limb-threatening ischemia and the benefits of statin dose intensities. We have used our institutional experience with novel imaging systems to show reduced radiation exposure and contrast dose for patients and providers. Joining other institutions in the region and nationally, we are an active participant in the Vascular Study Group of New England (VSGNE) and the Vascular Quality Initiative (VQI). These large databases provide detailed procedural and patient-related information from which we have investigated regional differences in patient selection, treatment, and outcomes of abdominal aortic aneurysms (AAA), carotid artery stenosis, and peripheral arterial disease (PAD), among other vascular diseases. We have developed and published work on risk-prediction models that can be used in real-world settings to guide physicians in counseling a patient on his/her individual risk of surgery. Through the VQI as well as other databases such as the National Surgical Quality Improvement Project (NSQIP), we shed light on disparities in presentation, treatment selection, and outcomes across genders and racial groups.

In addition, administrative data such as the Nationwide Inpatient Sample (NIS), a 20% sampling of all inpatient admissions, and the State Ambulatory Surgery Databases (SASD), a database of all ambulatory surgical encounters by 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 partnered with the Centers for Medicaid and Medicare Services (CMS) to obtain Medicare data for the study of open versus endovascular AAA management, including a comparison of different endovascular stent grafts for AAA repair. 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 datasets against the backdrop of our busy clinical practice has allowed our group to produce tangible improvements in the management of vascular disease by translating clinical issues into tangible research questions.

▲Members of Dr. Schermerhorn's laboratory at SVS 2019 (from left): Patric Liang, MD, Livia de Guerre, MD, Winona Wu, MD, Mark Wyers, MD, Kirsten Dansey, MD, Nicholas Swerdlow, MD, Jinny Lu, MD, Marc Schermerhorn, MD, and Chun Li, MD.

ACCOMPLISHMENTS 2018-2019

With more than 53 peer-reviewed publications and more than 47 presentations* at national and regional society meetings and international symposia in the last two years, my research group has continued to make significant contributions to vascular surgery in the area of comparative-effectiveness research. This rich clinical activity has facilitated our participation in multi-center clinical trials in the areas of endovascular abdominal aortic aneurysm repair, best treatment for critical limb-threatening ischemia, 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 from which participants have published novel insights on the management of vascular diseases. The success of the VSGNE has provided a model for quality-improvement efforts nationally through the formation of the VQI, a cooperative of 18 regional quality groups in the U.S. and Canada, and 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 many peer-reviewed publications

** Vascular Annual Meeting for the Society for Vascular Surgery (14 presentations in 2018 and 10 presentations in 2019), and the Society for Clinical Vascular Surgery, Vascular Annual Symposium (16 presentations in 2018 and 7 presentations in 2019)*

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 past 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 ninth year of existence. In addition, we have developed research collaborations with Toronto, Rotterdam, Amsterdam, and Milan. All research fellows receive formal instruction in research methods and statistics through the Harvard T.H. Chan School of Public Health, and have gone on to present our work at national meetings in vascular surgery.

SELECTED RESEARCH SUPPORT

Carotid revascularization and medical management for asymptomatic carotid stenosis trial (CREST-2); NINDS, 2016-2019; PI: Marc L. Schermerhorn, MD

Randomized, multicenter, controlled trial to compare best endovascular versus best surgical therapy in patients with critical limb ischemia (BEST-CLI); NHLBI, 2014-2019, Co-PI: Marc L. Schermerhorn, MD (PI: Allen D. Hamdan, MD)

Harvard/Longwood Training Grant in Vascular Surgery; NIH, 1993-2024; Co-Investigator: Marc L. Schermerhorn, MD (PI: Frank LoGerfo, MD)

SELECTED PUBLICATIONS

Swerdlow NJ, Wu WW, Schermerhorn ML. Open and endovascular management of aortic aneurysms. Circ Res 2019; Feb 15; 124(4):647-661.

O'Donnell TFX, Li C, Swerdlow NJ, Liang P, Pothof AB, Patel VI, Giles KA, Malas MB, Schermerhorn ML. The weekend effect in AAA Repair. Ann Surg 2019; Jun;269(6): 1170-1175.

Schermerhorn ML, Liang P, Dakour-Aridi H, Kashyap VS, Wang GJ, Nolan BW, Cronenwett JL, Eldrup-Jorgensen J, Malas MB. In-hospital outcomes of transcarotid artery revascularization and carotid endarterectomy in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg 2019; Jun 18 (Epub ahead of print).

Darling JD, O'Donnell TFX, Deery SE, Norman AV, Vu GH, Guzman RJ, Wyers MC, Hamdan AD, Schermerhorn ML. Outcomes after first-time lower extremity revascularization for chronic limb-threatening ischemia in insulin-dependent diabetic patients. J Vasc Surg 2018; Nov;68(5): 1455-1464.e1.

Liang P, O'Donnell TFX, Swerdlow NJ, Li C, Lee A, Wyers MC, Hamdan AD, Schermerhorn ML. Preoperative risk score for access site failure in ultrasound-guided percutaneous aortic procedures. J Vasc Surg 2019; Mar 6 (Epub ahead of print).

O'Donnell TFX, Wade JE, Liang P, Li C, Swerdlow NJ, DeMartino RR, Malas MB, Landon BE, Schermerhorn ML. Endovascular aneurysm repair in patients over 75 is associated with excellent 5-year survival, which suggests benefit from expanded screening into this cohort. J Vasc Surg. 2019 Mar;69(3):728-737.

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