

Beth Israel Deaconess
Medical Center



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Roberta and Stephen R. Weiner Department of Surgery

Surgery Research Report



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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 2020 issue of our Surgery Research Report highlights research that spans from bench to bedside. Our robust research platform has more than \$21 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*, *Lancet*, *Science*, and *Nature*, among others. In addition, they participate in leading medical and scientific organizations, many in leadership roles.

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 exceptional clinical training in surgery and novel educational opportunities that promote innovation in identifying and solving our most pressing clinical problems.

The individuals whose research is highlighted in this report represent the very best of our department and 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

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 and surgical outcomes 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 FY20, 34 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, clinical coordinators, and biostatisticians 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 411 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 FY20, 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 Benjamin C. James, MD, MS, Director of Resident Research.



Richard D. Cummings, PhD, Vice Chair, Basic and Translational Research

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, Vice Chair, Clinical Research

Dr. Rodrigue, Professor at Harvard Medical School, oversees the FIRST (Facilitating Innovative Research and Surgical Trials) Program and the Faculty Clinician-Investigator Mentorship Program. He also serves as Director of the Clinical Scholarship Program, a structured faculty-mentored clinical research experience for all first-year general surgery residents. In addition, he also serves as Chair of the Academic Promotions Committee in the Department of Surgery.



Benjamin C. James, MD, MS, Director, Resident Research

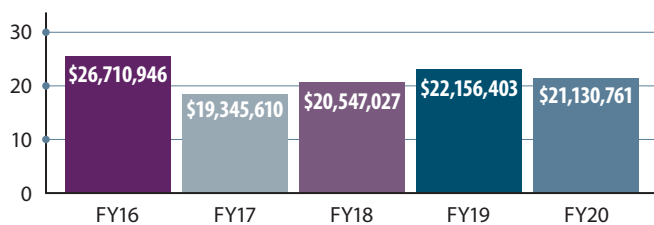
Dr. James is an Assistant Professor of Surgery at Harvard Medical School, Section Chief of Endocrine Surgery in the Division of Surgical Oncology at BIDMC, and Associate Surgery Clerkship Director in the Department of Surgery. In his role as Director of Resident Research, Dr. James oversees resident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

Research Infrastructure

In FY20, research in the Department of Surgery occupied 24,957 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. Space for clinical research is located in the Deaconess and Sherman buildings. The overall dollar density for research space in FY20 was not calculated due to the COVID-19-related research shutdown in 2020.

Research Funding

Investigators in the Department of Surgery hold numerous federal awards from the National Institutes of Health including 13 R01 grants, 5 R01 subcontracts, and numerous NIH R03, R21, R39, R43/R44, RF1, U01, DP3, P30, P41, UG3, and U39 grants. There are also four other large federal research project grants: from the Department of Defense (U.S. Army), Defense Advanced Research Projects Agency, the Patient-Centered Outcomes Research Institute, and DHHS Health Resources and Service Administration. Surgery investigators also hold numerous grants from non-profit agencies and industry.



Total research funding in FY20 was more than \$21 million (*Figure 1*), which is approximately the same level of funding awarded in FY19. Grant awards showed a broad distribution among divisions within the Department of Surgery (*Table 1*).

FIGURE 1: Total (federal and non-federal) research dollars awarded per year during fiscal years (FY) 2016-2020.

TABLE 1. Number of T32, T35, F32, and K training grants or investigator-initiated research awards and total amount of research funding in FY20, by division.

DIVISION	T32, T35, F32, AND K TRAINING AWARDS	INVESTIGATOR-INITIATED RESEARCH AWARDS	TOTAL AMOUNT OF FUNDING
Acute Care Surgery, Trauma, and Surgical Critical Care		12	\$4,246,546
Cardiac Surgery		1	\$218,600
General Surgery	3	8	\$992,566
Interdisciplinary Surgery		17	\$2,438,158
Neurosurgery		6	\$302,256
Plastic and Reconstructive Surgery		2	\$187,515
Podiatric Surgery		5	\$1,522,767
Surgical Oncology		6	\$1,458,502
Thoracic Surgery and Interventional Pulmonology		12	\$406,566
Transplant Surgery		5	\$2,148,440
Urologic Surgery		5	\$893,625
Vascular and Endovascular Surgery	3	33	\$6,313,045

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). 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 FY20, recipients of these training awards were Jordan Broekhuis, MD, Gabrielle Dombek, MD, Lumeng Jenny Yu, MD, and Anirudh Penumaka, MD, MSc.

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 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 R. 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. In 2020, Harvard Medical School recognized the Clinical Scholarship Program with its annual Program Award for a Culture of Excellence in Mentoring.

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.

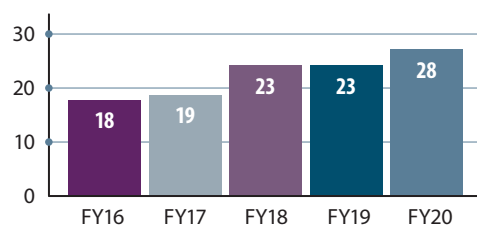
Residents' Research Rotation

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. In the last two years, residents on their research electives have produced more than 200 publications and presented their work at more than 100 national meetings.

It is also possible for residents to seek advanced degrees in public health, business administration, education, or public policy. We recognize the importance of developing the next generation of surgeon-scientists and are supportive of residents who wish to pursue an advanced professional degree 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 2: 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 Aaron Fleishman, MPH, Associate Director and Associate in Surgery at Harvard Medical School, 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.

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 FY20 was Funda Meric-Bernstam, MD. Dr. Meric-Bernstam is Chair, Department of Investigational Cancer Therapeutics; Medical Director, Department of Khalifa Institute for Personalized Cancer Therapy; Nellie B. Connally Chair in Breast Cancer, Department of Investigational Cancer Therapeutics; and Professor, Department of Breast Surgical Oncology, Division of Surgery, at the University of Texas MD Anderson Cancer Center in Houston.

Events during Dr. Meric-Bernstam'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 faculty of the Department of Surgery identified four basic science and five clinical research abstracts for oral presentation. As listed below, one in each category was chosen as a winner by faculty in collaboration with Dr. Meric-Bernstam:

Basic Science

Quynh Chu, MD (*Winner, Basic Science*)

"Double-Loaded Paclitaxel Nanoparticles for the Treatment of Aggressive Breast Cancer"

Mentor: Yolonda Colson, MD, PhD

Gabrielle E. Dombek, MD

"Expression of Tn Antigen in Tumors and Translational Margins of Colorectal Cancer"

Mentor: Richard D. Cummings, PhD

Stephanie Lazow, MD

"Fetal Bone Marrow Gene Delivery via Transamniotic Stem Cell Therapy"

Mentor: Dario Fauza, MD, PhD

L. Jenny Yu, MD

"The Effect of Anticoagulation on Pulmonary Function and Endothelial Cell Survival"

Mentor: Mark Puder, MD, PhD

Clinical Research

Santiago Gomez-Paz, MD (*Winner, Clinical Research*)

"Women Smokers with Chronic Hypertension Have a Seven-Fold Increased Risk for Having an Intracranial Aneurysm: A New Target Population for Screening"

Mentor: Ajith J. Thomas, MD

Livia de Guerre, MD

"EVAR for Large Abdominal Aortic Aneurysms is Associated with Higher Late Reinterventions, Ruptures and Mortality"

Mentor: Marc L. Schermerhorn, MD

Rashi Jhunjhunwala, MD, MA

"Data Visualization for Surgical Informed Consent to Communicate Personalized Risks and Patient Preferences"

Mentor: Gabriel Brat, MD, MPH, MSc, and Nils Gehlenborg, PhD

M. Juanita Rodriguez, MD

"Treatment Burden following Standard of Care Open vs. Robotic D2-Gastrectomy plus Neoadjuvant Chemotherapy (NAC) for Locally-advanced Gastric Cancer (LAGC)"

Mentor: A. James Moser, MD, MA

Mark A. Kashtan, MD, MPH

"Influence of Stapler Use on Perioperative Efficiency, Cost and Outcomes in Appendicitis in Children: A Multicenter Severity-Adjusted Cohort Study"

Mentor: Shawn Rangel, MD, MSCE

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 24, 2019

Lee M. Kaplan, MD, PhD

Obesity, Metabolism & Nutrition Institute, Massachusetts General Hospital

"Precision Medicine and Surgery for Obesity"

November 7, 2019

Mark W. Grinstaff, PhD

Biomedical Engineering, Chemistry, Materials Science, and Medicine, Boston University

"Clinically Informed Biomaterials: Chemistry and Engineering"

December 19, 2019

Elizabeth A. Mittendorf, MD, PhD

Department of Surgery, Brigham and Women's Hospital, Dana-Farber/Brigham and Women's Cancer Center

"Immunotherapy for Breast Cancer: Contributions of a Surgeon Scientist"

January 16, 2020

Korkut Uygun, PhD

Organ Reengineering Lab and Center for Engineering in Medicine, Massachusetts General Hospital

"Extending the Limits of Organ Preservation"

February 20, 2020

Jerrold R. Turner, MD, PhD

Pathology and Medicine, Brigham and Women's Hospital

"Therapeutic Targeting of Tight Junctions in Intestinal Diseases"

Due to the COVID-19 epidemic, seminars for March–May 2020 were rescheduled. We started virtual seminars in June 2020 with the following speakers:

June 11, 2020

Jose Gomez-Marquez

Little Devices Lab, Institute for Medical Engineering and Science, Massachusetts Institute of Technology

"A Dunkirk Moment in Medical Technology: What DIY Can Teach Us about Transparent Technologies for Health"

September 17, 2020

Brain M. Wolpin, MD, MPH

Pancreatic Tumor Center, Dana-Farber Cancer Institute; Medical Oncology, Brigham and Women's Hospital
"Personalized Detection and Treatment of Pancreatic Cancer"

FIRST Program Seminars

The FIRST Program also hosts seminars throughout the academic year:

September 10, 2019

Jennifer Tseng, MD, MPH

James Utley Professor and Chair, Department of Surgery, Boston University
Surgeon-in-Chief, Boston Medical Center
"Strengths and Weaknesses of Claims and Registry Data for Surgical Outcomes Research"

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"

September 24, 2019

Boris Gershman, MD

Division of Urologic Surgery, Beth Israel Deaconess Medical Center
Assistant Professor of Surgery, Harvard Medical School
"Deep Learning for the Analysis of Prostate Cancer Histopathology Specimens"

October 8, 2019

Jordan Strom, MD, MSc

Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center
Instructor in Medicine, Harvard Medical School
"Imprecision Medicine: Sharpening the Knife"

October 22, 2019

Miguel Hernan, MD, DPH

Kolokotronis Professor of Biostatistics and Epidemiology, Harvard T. H. Chan School of Public Health
"How Do We Know What Works? Causal Inference from Observational Data"

November 12, 2019

James G. Naples, MD

Division of Otolaryngology, Beth Israel Deaconess Medical Center
Instructor in Otolaryngology
"Ear Research: A Big Picture Approach to a Small Organ"

November 26, 2019

Anna Merport Modest, PhD, MPH

Staff Scientist, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center
Instructor in Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School
"In Vitro Fertilization and Placental Disorders: Addressing the Association with Multiple Studies"

December 10, 2019

Griffin Weber, MD

Director, Beth Israel Deaconess Medical Center Biomedical Research Informatics Core
Associate Professor of Medicine and Biomedical Informatics, Harvard Medical School
"Clinical Query 2 (CQ2): An Online Tool for Accessing BIDMC's Clinical Data Warehouse for Research"

January 14, 2020

John Torous, MD

Director of Digital Psychiatry, Beth Israel Deaconess Medical Center
Instructor of Psychiatry, Harvard Medical School
"Early Career Research Pathways in Digital Health: Focusing on Smartphone Apps for Mental Health"

February 11, 2020

Dasha Kazei, MD

Research Fellow, Division of Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center
"BIDMC Plastic Surgery Research Update"

National and International Impact

Faculty members in the Department of Surgery have national and international impact through their research published in many high-impact journals, such as *New England Journal of Medicine*, *Nature Medicine*, *Lancet*, *Science*, *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, are the recipients of notable honors, and serve as editors or on editorial boards of national and international journals (see page 13).

Leadership Positions and Notable Honors

Jeffrey Arle, MD, PhD

Member of Epilepsy Foundation of New England Patient Advisory Board

Jorge G. Arroyo, MD, MPH

President of New England Ophthalmologic Society

Gabriel Brat, MD, MPH, MSc

Recipient of 2019-2020 Innovation Grant from the BIDMC Center for Healthcare Delivery Science

Mark P. Callery, MD

Awarded, Fellowship ad hominem by Royal College of Surgeons of Edinburgh

President of Society for Surgery of the Alimentary Tract (SSAT)

David Caradonna, MD, DMD

Elected to Harvard Medical School/Harvard School of Dental Medicine Faculty Council, representing Otolaryngology

Appointed Associate Program Director, Otolaryngology/Head and Neck Surgery Residency at BIDMC/Harvard Medical School

Elliot L. Chaikof, MD, PhD

Chair, Section 1 (one of 12 standing committees), 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

Member, National Materials and Manufacturing Board, Roundtable on Biomedical Engineering Materials and Applications, National Academies of Science, Engineering, and Medicine

Member, Association of American Physicians

Richard D. Cummings, PhD

Drug (crizanlizumab, brand name Adakveo) developed by Selexys Pharmaceuticals, which was co-founded by Dr. Cummings, receives FDA approval for treatment of vaso-occlusive crises in patients with sickle cell disease

Distinguished Alumnus Award, University of Montevallo

Thanh Dinh, DPM

President-Elect of American College of Foot & Ankle Surgeons

Devin E. Eckhoff, MD

Elected as Councilor-at-Large, Board of Directors, American Society of Transplant Surgeons

Amy Evenson, MD, MPH

Co-Chair of American Society of Transplant Surgeons Curriculum Committee

Christiane J. Ferran, MD, PhD

Recipient of \$1M Blavatnik Therapeutics Challenge Award from Harvard Medical School

John M. Giurini, DPM

Obtained five-year reaccreditation for the BIDMC Podiatric Medicine and Surgery Residency Program from the Council on Podiatric Medical Education of the American Podiatric Medical Association

Susan J. Hagen, PhD

Executive Committee, Harvard Digestive Diseases Center

Advisory Board, International GI section, International Union of Basic and Clinical Pharmacology

Scharukh Jalisi, MD

Obtained ACGME approval for the Otolaryngology/Head and Neck Surgery Residency at BIDMC/Harvard Medical School

Benjamin C. James, MD, MS

Elected to Membership Committee, Association for Academic Surgery
Research Committee, American Association of Endocrine Surgeons

Ted A. James, MD, MS

Member of Research Committee, American Society of Breast Surgeons
Member of Physician Well-Being Task Force, American Society of Clinical Oncology
Member of Missions Outcomes Committee, American Cancer Society
Member of Quality Committee, Society of Surgical Oncology

Daniel B. Jones, MD, MS

Received Award of Honour: T.E. Udwadia Oration, Indian Association of Gastrointestinal Endoscopic Surgeons
Trustee-at-Large and member of International Committee, Society for Surgery of the Alimentary Tract
Elected to Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Global Affairs Committee, Leadership Development Committee, Robot Committee, and Nominating Committee

Tara S. Kent, MD, MS

Keynote speaker, 14th World Congress of the International Hepato-Pancreato-Biliary Association
Elected Vice Chair (2021) and Chair (2023) for Americas Hepato-Pancreato-Biliary Association Program

Bernard T. Lee, MD, MBA, MPH

Recipient of 2020 A. Clifford Barger Excellence in Mentoring Award at Harvard Medical School
President-Elect of Plastic Surgery Foundation
Board of Directors of American Board of Plastic Surgery

Frank LoGerfo, MD

Named "All Star Doctor" by the American Diabetes Association-New England

A. James Moser, MD

Chair of Project Survival Joint Steering Committee

James G. Naples, MD

Member of Education Committee, Otology & Neurotology/American Neurotology Society
Member of History and Archives Committee, American Academy of Ophthalmology

Aria F. Olumi, MD

Recipient of 2020 Society for Basic Urologic Research Distinguished Service Award
Member of Planning Committee, American Urological Association/Johns Hopkins Bladder Cancer Symposium
Member of Planning Committee, American Urological Association Stone Lab Symposium

Mihir S. Parikh, MD

Recipient of Rabkin Fellowship for 2020-2021
Member of Critical Care Program Committee, American Thoracic Society

Alia Qureshi, MD, MSc

Chair of Leadership and Professional Development Task Force, Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

James R. Rodrigue, PhD

Board of Directors, American Society of Transplantation
Appointed to Inclusion, Diversity, and Equity Task Force, American Society of Transplantation

Barry I. Rosenblum, DPM

Board of Directors, American College of Foot & Ankle Surgeons
Member of Research Committee, American College of Foot & Ankle Surgeons

Lars Stangenberg, MD, PhD

Member of Executive and Research Advisory Committee, Society for Vascular Surgery Vascular Quality Initiative

Recipient of 2020 Young Urologist of the Year Award by the American Urological Association

Elected Chair of Women in Neurosurgery

President of Western Thoracic Surgical Association

Appointed Director of MIT Center for Precision Cancer Medicine
Member, Association of American Physicians
Recipient of Margaret MacVicar Faculty Fellowship Award from MIT

1. Per-Olof Hasselgren, Author. *Thyroid Cancer & Thyroid Nodules in 30 Minutes: A Guide to Symptoms, Diagnosis, Surgery, and Disease Management*. i30 Media, 2020.
2. Jeffrey Arle, Editor. *The Neuromodulation Casebook*. Elsevier, Academic Press, 2020.
3. Aria Olumi, Editor. *Comprehensive Review of Urology*, Oakstone Publishing.
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I run the Surgical Informatics Lab, a collaboration between the Department of Bioinformatics at Harvard Medical School and the BIDMC Department of Surgery. My lab is interested in developing and delivering informatics tools to improve surgical care. The research spans three main domains:

- development of surgeon-oriented machine learning prediction algorithms
- leveraging computer vision in the operating room, and
- surgeon- and patient-focused interfaces to deliver these tools

In these domains, we have published extensively on developing better models for post-surgery opioid use, optimizing surgical timing for patients receiving chronic medical care, operative performance analysis and temporal analytics, and better understanding trauma outcomes.

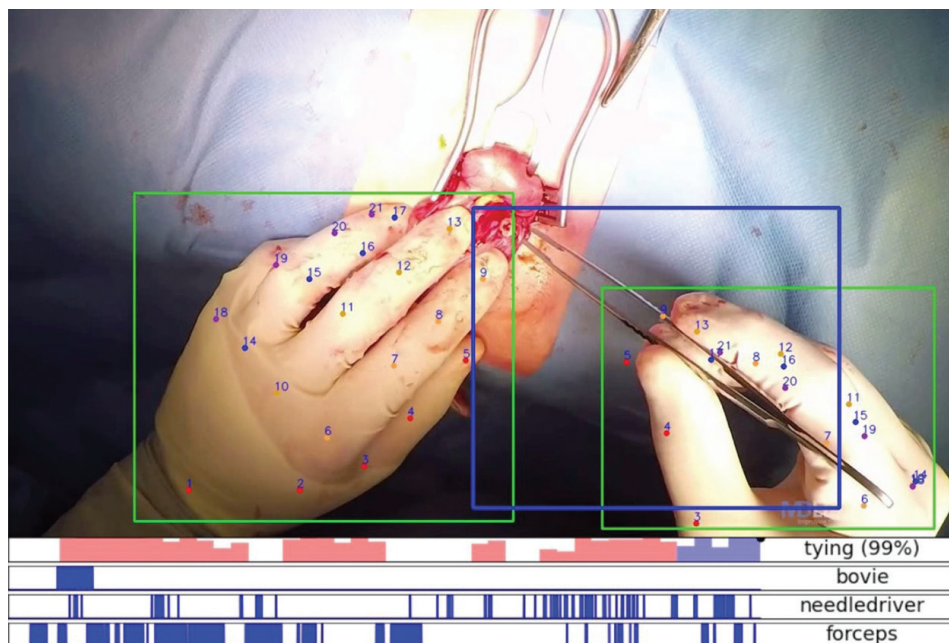
I am also the clinical lead for the 4CE Consortium. Founded in March 2020, this consortium of 342 hospitals across eight countries is using novel federated methods to perform international comparisons to better understand COVID-19 and uncover nuances in care associated with differential outcomes.

RESEARCH GROUP

Brandon Booth, BA
Jevin Clark, BA
Nils Gehlenborg, PhD*
Christopher Kennedy, PhD
Jayson Marwaha, MD
Nathan Palmer, PhD*
Jasmine Pantan, BA
Serena Yeung, PhD*
William Yuan, PhD
Yilun Zhang, BS

*Collaborators

► With collaborators at Stanford, our lab has recently developed automated video analysis tools that track surgeon hand and finger movements, tools, and surgical behaviors. These real-time tools enable creation of surgical signatures, evaluation of surgical skill, and are a first step toward understanding the contribution of individual surgeon behaviors to the outcomes of patients.



ACCOMPLISHMENTS 2019-2020

- Clinical lead of the 4CE International COVID Research Consortium
- Awarded an Blavatnik Pilot Grant for Digital Health Innovation
- Gave multiple national and international presentations on novel work to develop federated international COVID analytics platform
- Recipient of 2019-2020 Innovation Grant from BIDMC Center for Healthcare Delivery Science for the BIDMC@Home app to track opioid use and digital phenotypes of pain in surgical patients

TEACHING, TRAINING, AND EDUCATION

I am the Associate Director of BMI 741, the "Health Information and Technology: From Ideation to Implementation" course at Harvard Medical School. This class applies health information technology and digital health to solve health care problems, teaching the skills to identify health care needs and pain points, design technology-based solutions (new solution, optimize existing system, or purchase vendor solution), and lead successful implementations.

I also coordinate fellow research projects and the journal club within the Division of Acute Care Surgery, Trauma, and Surgical Critical Care. As a busy trauma intensivist, I am involved in the ICU journal club and regularly give lectures to residents and medical students.

SELECTED RESEARCH SUPPORT

Post-Surgical Opioid and Point-of-Care Surgical Decision-Making Tools. Blavatnik Innovation Grant, 2019-2021; PI: Gabriel Brat, MD, MPH, MSc

Evaluation of Post-Surgical Opioid Use in the Elderly. NIH R56, 2019-2021; Co-I: Gabriel Brat, MD, MPH, MSc

Surgical Surveillance Innovation Grant. Philanthropy, 2019-2022; PI: Gabriel Brat, MD, MPH, MSc

SELECTED PUBLICATIONS

Brat GA, Hersey S, Chhabra K, Gupta A, Scott J. Protecting surgical teams during the COVID-19 outbreak: A narrative review and clinical considerations. *Ann Surg* 2020; in press.

Brat GA, Weber GM, Gehlenborg N, 4CE Consortium, Cai T, Kohane IS. International electronic health record-derived COVID-19 clinical course profiles: The 4CE consortium. *NPJ Digit Med* 2020;19;3:109.

Robinson KA, Thiels CA, Stokes S, Duncan S, Feranil M, Fleishman A, Cook CH, Nathanson LA, Huang LC, Habermann EB, Brat GA. Comparing clinician consensus recommendations to patient-reported opioid use across multiple hospital systems. *Ann Surg* 2020; in press.

Klann JG, Weber GM, Estiri H, 4 CE Consortium, Brat GA, Murphy SN. Validation of an internationally derived patient severity phenotype to support COVID-19 analytics from electronic health record data. *J Am Med Inform Assoc* 2021;Feb 10 (Epub ahead of print).

Weber GM, Hong C, Palmer NP, 4 CE Consortium, Cai T, Brat GA. International comparisons of harmonized laboratory value trajectories to predict severe COVID-19: Leveraging the 4CE Collaborative across 342 hospitals and 6 countries: A retrospective cohort study. *Preprint. medRxiv* 2021; Feb 5.

Robinson KA, Carroll M, Ward SB, Osman S, Chhabra KR, Arinze N, Amedi A, Kaafarani H, Smink DS, Kent TS, Aner MM, Brat G. Implementing and evaluating a multihospital standardized opioid curriculum for surgical providers. *J Surg Educ* 2020;77(3):621-626.

Bicket MC, Brat GA, Hutfless S, Wu CL, Nesbit SA, Alexander GC. Optimizing opioid prescribing and pain treatment for surgery: Review and conceptual framework. *Am J Health Syst Pharm* 2019;76(18):1403-1412.



RESEARCH GROUP

Kiyoshi Itagaki, PhD
Hyo In Kim, PhD
Jimbong Park, PhD

RESEARCH FOCUS

Our major research focus is clinical inflammation biology and the mechanisms and management of infection after injury and surgery. Our lab is especially interested in the role of “Danger” molecules (aka, “damage-associated molecular patterns,” “DAMPs,” “alarmins”) in inflammation and is a world leader in investigating the role of intracellular DAMPs derived from mitochondria. Our original work on this subject (*Nature*, March 4, 2010) has been widely cited as a groundbreaking conceptual advance in sepsis and inflammation research. This single paper has been cited more than 3,000 times. Important known mitochondrial DAMPs include mitochondrial DNA, formyl peptides, mitochondrial lipids, ATP, and heme. Our work shows that mitochondrial formyl peptides are potent DAMPs that circulate in plasma after injury. They activate innate immune cells while causing suppression of cell-surface chemoreceptors for leuko-attractants like chemokines and leukotrienes. Thus mtDAMPs 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 showed mtDNA is also a potent activator of neutrophil (PMN) extracellular traps (“NETs”) and TLR-9 activation also results in suppression of chemotaxis. Thus it plays a critical role in sepsis after injury.

Mitochondrial formyl peptides (mtFPs) are potent chemoattractants that activate immune responses to injury like phagocytic wound debridement. Thus they also help initiate healing. Conversely, mtFPs compete for the immune system’s “attention” after major injury. We showed that innate responses to FPs released by injury render the host susceptible to pneumonia by suppressing immune surveillance of the lung. We also showed that only 5/13 native mitochondrial FPs are active at the FP receptors. We have developed antagonists for human and mouse FP receptors (FPRs) and used these tools for therapeutic intervention. We used knockout mice to show post-traumatic pneumonia results from FPR-1 engagement and reversed post-traumatic pneumonia using designer FPR-1 inhibitors (*Critical Care Med*, 2020).

Our current work centers on balancing the need for inflammation after injury and the susceptibility to infection that inflammation incurs. Molecular aspects of these problems we study (that participants can become expert in) include cell signaling, chemokine biology, cellular calcium signaling, chemotaxis, regulation of permeability, neutrophil NET formation, and microparticle signaling. Our collaborations include studies as diverse as sepsis in injured warfighters and plasma mediator phenotypes in COVID-19. Current collaborations within BIDMC include work with my longtime colleague Kiyoshi Itagaki, PhD, and the laboratories of Leo Otterbein, PhD, Simon Robson, MD, PhD, and Michael Yaffe, MD, PhD.

For the last four years we have been funded by the Department of Defense to perform a “focused program award” addressing the role of DAMPs in creating susceptibility to infection in wounded warfighters. The labs in this multi-PI grant have grouped together as the Harvard-Longwood Consortium for Translational Biology, or “HALO” group. This program uses computational biology to address the role of DAMPs in changes in cellular and humoral immune phenotypes (“endotypes”) over time and determine how these are permissive of health care-acquired pneumonia.

Our currently evolving programs center on: 1) using machine learning and multiplexed plasma mediator phenotyping to distinguish inflammatory syndromes like sepsis, SIRS, and viral illnesses, thus allowing outcomes prediction and directed interventions, and 2) the creation of immunologically active wound dressings that will suppress infection for use in military applications.

ACCOMPLISHMENTS 2019-2020

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

Visiting Professorships and Invited Presentations

- Mechanisms and Management of Inflammation in Trauma and Shock. Keynote address, 43rd International Congress on Military Medicine; Basel, Switzerland
- The Differential Roles of DAMPs and PAMPs in Mononuclear Cell Chemoattraction of Neutrophils. 9th International DAMPs and Alarmin Symposium; Okayama, Japan
- Sterile and Infective Danger Signaling in Surgery. Visiting Professor, Ryder Trauma Center, University of Miami
- 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
- Monocyte Exocytosis of Mitochondrial DAMPs in Sepsis Suppresses Neutrophil Chemotaxis. Virtual presentation, 79th Annual Meeting of the American Association for the Surgery of Trauma

TEACHING, TRAINING, AND EDUCATION

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

HBI-002 to Treat Traumatic Injury. NIH, 2017-2019; Collaborator: Carl J. Hauser, MD (PI: Stephen Gomperts, MD, PhD; Academic Site PI: Leo Otterbein, PhD)

SELECTED PUBLICATIONS

Hauser CJ, Otterbein LE: Danger signals from mitochondrial DAMPs in trauma and post-injury sepsis. *Eur J Trauma Emerg Surg* 2018;44:317-324.

Brown CV, Alam HB, Brasel KJ, Hauser CJ, deMoya M, Martin M, Moore EE, Rowell S, Vercruysse G, Inaba K. Western Trauma Association Critical Decisions in Trauma: Management of renal trauma. *J Trauma Acute Care Surg* 2019; 85;5, 1021-1025.

Martin MJ, Brown CVR, Shatz DV, Alam H, Brasel K, Hauser CJ, de Moya M, Moore EE, Vercruysse G, Inaba K. Evaluation and management of abdominal gunshot wounds: A Western Trauma Association critical decisions algorithm. *J Trauma Acute Care Surg* 2019;87(5):1220-1227.

Itagaki K, Kaczmarek E, Kwon WY, Chen L, Vlkova B, Zhang Q, Riça I, Yaffe MB, Gong WH, Wang JM, Gao J, 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. *Crit Care Med* 2020;48(2):e123-e132.

Cahill LA, Joughin BA, Kwon W-Y, Itagaki K, Kirk CH, Shapiro NI, Otterbein LE, Yaffe MB, Lederer JA, Hauser CJ. Multiplexed plasma immune mediator signatures can differentiate sepsis from non-infective SIRS. (American Surgical Association podium paper.) *Ann Surg* 2020;272(4):604-610.

Konecna B, Park J, Kwon W-Y, Vlkova B, Zhang Q, Huang W, Kim HI, Yaffe B, Otterbein LE, Itagaki K, Hauser CJ. Monocyte exocytosis of mitochondrial DAMPs in sepsis suppresses neutrophil chemotaxis. (American Association for the Surgery of Trauma podium paper.) *J Trauma Acute Care Surg* 2020;Oct 5 (Epub ahead of print).

Zhang Q, Kwon WY, Vlková B, Riça I, Kaczmarek E, Jung F, Douglas G, Otterbein LE, Hauser CJ, Itagaki K. Direct airway instillation of neutrophils overcomes chemotactic deficits induced by injury. *Shock* 2020;Nov 11 (Epub ahead of print).



RESEARCH GROUP

Carl J. Hauser, MD
Hyo In Kim, PhD
Barbora Konečná, PhD
Jinbong Park, PhD
Wei Huang, PhD

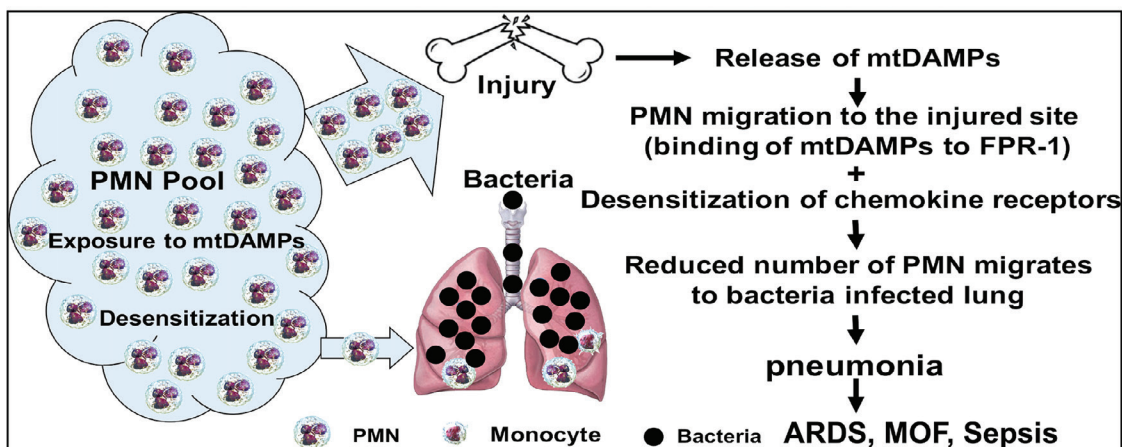
RESEARCH FOCUS

We are 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 from damaged tissues/cells after injury, causing dysfunction of neutrophils upon interaction of formyl peptides contained in mitochondria via formyl peptide receptor 1 (FPR1). Neutrophils will migrate to the injury sites following mitochondrial formyl peptides to protect the body from bacterial infections or to clean up debris. However, this process causes internalization of chemokine receptors on neutrophils so that neutrophils cannot respond to the help signals from bacteria-infected lungs. This will lead to the development of nosocomial pneumonia, ARDS, and sepsis.

We developed two methods that may prevent seriously injured people from developing nosocomial pneumonia. These are: 1) Reduce the number of neutrophils that encounter mitochondrial formyl peptides by FPR1 antagonist 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.

The application of FPR1 antagonist and exogenous neutrophils showed promising effects using mouse injury/lung bacterial infection models. Before we move on to primates and humans, we want to try these methods with pigs, which are the best animal models in which to study infectious diseases because they have immune responses that are very similar to humans.

► mtDAMPs released after injury induce nosocomial pneumonia



ACCOMPLISHMENTS 2019-2020

- I submitted three R21 grant applications in June 2020. One was a COVID-19 emergency request type of grant application, which was not scored but received very encouraging critiques as the reviewers were interested in my approach.
- I was invited to give a talk at the 6th International Symposium at Wide River Institute of Immunology (WRII), Seoul National University College of Medicine, in October 2019. The title was Mitochondrial DAMPs and Nosocomial Pneumonia.
- Beginning in March 2020 our productivity was greatly impacted due to COVID-19 and the need to work from home or during limited lab hours. Despite this, I was able to write grants and papers and tried to maintain our lab work by communicating remotely with my fellows. Some fellows had to depart to their home countries to avoid lockdowns, further affecting our productivity.

TEACHING, TRAINING, AND EDUCATION

Despite the impact of COVID-19, I was able to engage in frequent online conversations about our experiments with members of the lab. Although we could not meet face-to-face, we communicated efficiently to ensure the advancement of our research projects.

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 Focused Program Award, 2016-2021; Co-Investigator: Kiyoshi Itagaki, PhD (PI: Carl J. Hauser, MD)

SELECTED PUBLICATIONS

Cahill LA, Joughin BA, Kwon WY, Itagaki K, Kirk CH, Shapiro NI, Otterbein LE, Yaffe MB, Lederer JA, Hauser CJ. Multiplexed plasma immune mediator signatures can differentiate sepsis from noninfective SIRS: American Surgical Association 2020 Annual Meeting. *Ann Surg* 2020;272(4):604-610.

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. Formyl peptide receptor-1 blockade prevents receptor regulation by mitochondrial danger-associated molecular patterns and preserves neutrophil function after trauma. *Critical Care Med* 2020;48(2):e123-132.

Konečná B, Park J, Kwon W-Y, Vlkova B, Zhang Q, Huang W, In Kim H, Yaffe MB, Otterbein LE, Itagaki K, Hauser CJ. Monocyte exocytosis of mitochondrial DAMPs in sepsis suppresses neutrophil chemotaxis. *J Trauma Acute Care Surg* 2021;1;90(1):46-5.

Zhang Q, Kwon WY, Vlková B, Riça I, Kaczmarek E, Jung F, Douglas G, Otterbein LE, Hauser CJ, Itagaki K. Direct airway instillation of neutrophils overcomes chemotactic deficits induced by injury. *Shock* 2020;Nov 11 (Epub ahead of print).



Wolfgang G. Junger, PhD

Professor of Surgery

RESEARCH GROUP

Dilan Aytan

Carola Ledderose, PhD

Yong Shen

Christian Slubowski, PhD

Koichiro Sueyoshi, MD, PhD

RESEARCH FOCUS

Immune cells release adenosine triphosphate (ATP) that induces autocrine signaling mechanisms needed for cell function. In healthy individuals, these autocrine signaling mechanisms coordinate chemotaxis, pathogen recognition, immune cell interactions, antigen processing, and immune cell proliferation. ATP release and the subsequent autocrine feedback mechanisms triggered by ATP are therefore prerequisites for a successful host immune response. We have elucidated a complex system of ATP and adenosine receptors—collectively termed purinergic receptors—that regulate these immune cellular responses.

We found that purinergic receptors fine-tune localized calcium influx and downstream signaling pathways that trigger cell activation, organize cytoskeletal rearrangements, and coordinate processes needed for functional cell responses. We further found that these mechanisms are impaired under pathological conditions. Traumatic injuries, cardiopulmonary arrest, and bacterial and viral infections all cause large amounts of ATP to be released from inflamed tissues and damaged cells. The resulting excess amount of extracellular ATP in critically ill patients interferes with the autocrine purinergic signaling mechanisms needed for immune cell functions. As a result, immune dysfunction in these patients causes sepsis, host organ damage, and multiple organ failure syndrome, which are major causes of death in critically ill patients. The focus of our laboratory has been to define the cellular and molecular mechanisms that lead to these complications.

Our most recent work has shown that metabolic pathways regulate cellular ATP release. We found that mitochondria produce the ATP that cells release in order to fuel their autocrine purinergic signaling mechanisms. We could show that mitochondrial ATP production, intracellular translocation of mitochondria, localized ATP release, and selective stimulation of purinergic receptors on the cell surface represent complex signaling networks that regulate neutrophils, T lymphocytes, and monocytes. Our current focus is on the question of how mitochondrial defects and dysregulated ATP signaling impact immune responses in vulnerable populations. Our long-term goal is to identify therapeutic strategies to restore purinergic signaling and effective immune defenses in critically ill patients, particularly in pediatric and older patients who are disproportionately impacted by bacterial and viral infections.

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 2019-2020

- 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 Carola Ledderose, PhD
- Thesis advisor of medical students from the Paracelsus Medical University, Salzburg, Austria
- Thesis advisor of master students from the Fachhochschule Technikum, Vienna, Austria
- Advisor of Harvard undergraduate students

SELECTED RESEARCH SUPPORT

Metabolic and Purinergic Immune Regulation. R35, NIH/NIGMS, 2020-2025; PI: Wolfgang Junger, PhD

Role of Purinergic Signaling in Pediatric Multi-Organ Failure. R01, NIH/NICHD, 2019-2024; PI: Wolfgang Junger, PhD

Harvard Trauma Inflammation Training Program. T32, NIH/NIGMS, 2013-2018; PI: Wolfgang Junger, PhD

Autocrine Regulation of Neutrophil Chemotaxis. R01, NIH/NIGMS, 2009-2019; PI: Wolfgang Junger, PhD

Regulation of T Cell Signaling in Trauma. R01, NIH/NIGMS, 2013-2018; PI: Wolfgang Junger, PhD

SELECTED PUBLICATIONS

Zhong EH, Ledderose C, De Andrade Mello P, Enjyoji K, Lunderberg JM, Junger WG, Robson SC. Structural and functional characterization of engineered bifunctional fusion proteins of CD39 and CD73 ectonucleotidases. *Am J Physiol Cell Physiol* 2021;320(1):C15-C29.

Ledderose C, Junger WG. Mitochondria synergize with P2 receptors to regulate human T cell function. *Front Immunol* 2020;11:549889.

Badimon A, Strasburger HJ, Ayata P, Chen X, Nair A, Ikegami A, Hwang P, Chan AT, Graves SM, Uweru JO, Ledderose C, Kutlu MG, Wheeler MA, Kahan A, Ishikawa M, Wang YC, Loh YE, Jiang JX, Surmeier DJ, Robson SC, Junger WG, Sebra R, Calipari ES, Kenny PJ, Eyo UB, Colonna M, Quintana FJ, Wake H, Gradinaru V, Schaefer A. Negative feedback control of neuronal activity by microglia. *Nature* 2020;586(7829):417-423.

Ledderose C, Bromberger S, Slubowski CJ, Sueyoshi K, Aytan D, Shen Y, Junger WG. The purinergic receptor P2Y11 choreographs the polarization, mitochondrial metabolism, and migration of T lymphocytes. *Sci Signal* 2020;13(651):eaba3300.

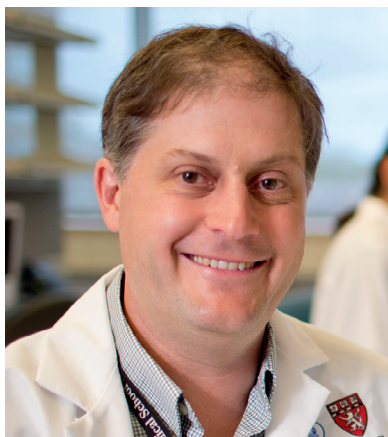
Ledderose C, Bromberger S, Slubowski CJ, Sueyoshi K, Junger WG. Frontline Science: P2Y11 receptors support T cell activation by directing mitochondrial trafficking to the immune synapse. *J Leukoc Biol* 2020;Jun 12 (Epub ahead of print).

Bai A, Moss A, Rothweiler S, Longhi MS, Wu Y, Junger WG, Robson SC. Author Correction: NADH oxidase-dependent CD39 expression by CD8⁺ T cells modulates interferon gamma responses via generation of adenosine. *Nat Commun* 2020;11(1):3036. *Erratum for: Nat Commun* 2015;6:8819.

Novak T, Hall MW, McDonald DR, Newhams MM, Mistry AJ, Panoskaltis-Mortari A, Mourani PM, Loftis LL, Weiss SL, Tarquinio KM, Markovitz B, Hartman ME, Schwarz A, Junger WG, Randolph AG; PALISI Pediatric Intensive Care Influenza (PICFLU) Network Investigators. RIG-I and TLR4 responses and adverse outcomes in pediatric influenza-related critical illness. *J Allergy Clin Immunol* 2020;145(6):1673-1680.

Ualiyeva S, Hallen N, Kanaoka Y, Ledderose C, Matsumoto I, Junger WG, Barrett NA, Bankova LG. Airway brush cells generate cysteinyl leukotrienes through the ATP sensor P2Y2. *Sci Immunol* 2020;5(43):eaax7224.

A complete list of publications begins on page 15.



RESEARCH GROUP

Louis Chu, MD
Eva Csizmadia, MS
Julius Ekert, BS
David Gallo, BS
Ghee Lee, MS
Alexa Schaufler, BS
Shazhad Shaefi, MD
Sidharth Shankar, BS
Rosalba Siracusa, PhD
Rodrigo Souza, PhD
Vanessa Voltarelli, PhD

RESEARCH FOCUS

Inhaled carbon monoxide (CO) is in numerous FDA phase trials, based in large part from the research 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 genes are intimately involved in the stress response and function in large part by generating CO and bilirubin as endogenous bioactive products. We expanded our research program to include collaborative projects on cancer, neurology, GI 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 to alleviate human suffering.

Role of Heme in Trauma and Infection

As Co-Director of a Department of Defense focused research award (\$10M), I and my team continue our efforts to identify and characterize deliverables to benefit injured warfighters. We are defining how heme influences recovery from trauma and subsequent susceptibility to bacterial infection. This research involves studies with Drs. Carl Hauser, Daniel Talmor, Simon Robson, and Michael Yaffe of BIDMC and Jim Lederer of BWH. 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 (\$250K) to evaluate a novel orally delivered CO solution that can be rapidly consumed for effective CO delivery. As part of a collaborative project funded by a multi-PI R01 with Boston University (\$350K), we are studying how noncoding RNA (lncRNA) influences macrophage signaling.

Neuroprotection against Concussion with HO-1

Funded by the National Football League (\$2.5M), we are studying the effects of CO to reduce the sequelae of mild repetitive concussion in mice as a model of mild repetitive traumatic brain injury (mTBI). We maintain an active collaboration with Patrick Fuller, PhD (BIDMC, Neurology) in the study of brain injury, where we find that glia-expressed HO-1 are critical in resolution of injury and impact neurotransmission. Inhaled CO enhances recovery, reduces inflammation and cell death, and improves cognitive function. We are studying the effects of mTBI on arousal and behavior as it relates to athletes who experience multiple concussions. This work is funded with a multi-institutional program grant (\$18M) to evaluate the effects of CO to alleviate brain injury. Over the next four years we will study the mechanisms of action and the role of HO-1/CO to limit injury and promote recovery. Exciting preliminary data in mice demonstrate the remarkable role of HO-1 in brain homeostasis.

Oral Carbon Monoxide Liquid and Anthracyclin Cardiotoxicity

We are funded with an NIH SBIR grant (\$300K) to study an innovative oral CO solution in a mouse model of doxorubicin cardiotoxicity in collaboration with Hillhurst Biopharmaceuticals. These studies complement and expand on those we have reported on with inhaled CO, which protects against acute and chronic cardiac injury. The oral formulation is simple and is being applied to multiple model systems, including TBI and trauma. Proof of principle has been demonstrated and human testing begins in 2021.

Oral Carbon Monoxide Liquid and Experimental Colitis

We are funded with an NIH SBIR grant (\$300K) to study the innovative oral CO solution in models of colitis in mice, in collaboration with Hillhurst Biopharmaceuticals. These studies complement and expand on those we have reported on with inhaled CO, which protects against inflammation of the GI system.

HO-1 in Cancer

In collaboration with and funded (\$350K) by a company in Cambridge 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 and HO-1/HO-2 regulated knockouts, 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 inflammatory bowel disease, but the challenge is to define novel methods to deliver CO. Through a multi-PI project with Georgia State University, we were funded with an R01 to use medicinal chemistry technology to develop new classes of molecules to influence the host tissue response and the microbiome toward one promoting GI health.

Relationship Between the Microbiome, Glycome, and Tissue Damage

It is 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 Drs. Richard Cummings and Carl Hauser of BIDMC to integrate glycobiological changes that occur in response to injury, comparing human and murine samples.

HO-1 and Exercise Metabolism

Rodrigo Souza, PhD, was awarded an American Heart Association Career Development Award (\$225K) to study how 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 2019-2020

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.

- 11th International Conference on Heme Oxygenases. Invited presentation, University of California
- Military Health System Research Symposium. Invited presentation, Orlando, FL
- Chair, BIDMC Institutional Animal Care and Use Committee
- BIDMC Site Miner, CIMIT; BIDMC representative, B-BIC, Technology Assessment and Development Group
- 17th consecutive year as NIH study section member for K01, K08, K02, K99, R25, and loan repayment, grant applications
- Grant reviewer: Wellcome Trust, UK Medical Research Council, New Zealand Research Foundation, Polish National Science Center, Pasteur Institute
- Director, Postgraduate Research Program, Department of Surgery

TEACHING, TRAINING, AND EDUCATION

I continue to participate in the training of graduate students, postdoctoral 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 mentor a K08 awardee (Shahad 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 expertise in entrepreneurial start-up ventures for innovative technologies and liaison with the Technology Ventures Office (TVO). I advise on grant submissions, commercialization of ideas, interactions with the TVO, 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 Experimental Colitis. NIH, 2020-2022; PI: Leo Otterbein, PhD

Immunomodulatory Effects of Bilirubin are Mediated through the Aryl Hydrocarbon Receptor, O₂ and Purinergic Pathways. NIH, 2017-2022; Co-Investigator: Leo Otterbein, PhD

Heme Oxygenase-1 and Tumor Growth. Agios Pharmaceuticals, 2017-2022; PI: Leo Otterbein, PhD

HBI-002 to Treat Anthracycline Cardiotoxicity. 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; PI: Leo Otterbein, PhD

Examining Carbon Monoxide to Treat Inflammatory Conditions Using Experimental Colitis Models. NIH R01, 2019-2024; PI: Leo Otterbein, PhD

lncRNA Regulates Lung Inflammation. NIH, 2019-2024; Co-Investigator: Leo Otterbein, PhD

SELECTED PUBLICATIONS

Cahill LA, Guo F, Nguyen J, Zhang F, Seshadri A, Keegan J, Hauser CJ, Otterbein LE, Robson S, Shaefi S, Yaffe MB, Lederer JA. Circulating factors in trauma plasma activate specific human immune cell subsets. *Injury* 2020;51(4):819-829.

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Zhang Q, Kwon WY, Vlková B, Riça I, Kaczmarek E, Park J, Kim HI, Konecna B, Jung F, Douglas G, Otterbein LE, Hauser CJ, Itagaki K. Direct airway instillation of neutrophils overcomes chemotactic deficits induced by injury. *Shock* 2020;Nov 11 (Epub ahead of print).

Tift MS, Alves de Souza RW, Weber J, Heinrich EC, Villafuerte FC, Malhotra A, Otterbein LE, Simonson TS. Adaptive potential of the heme oxygenase/carbon monoxide pathway during hypoxia. *Front Physiol* 2020;11:886.

Otterbein LE. Conquering radicals with a sense of humor. *Cell Chem Biol* 2019;26(10):1335-1337.

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* 2020;48(2):e123-e132.

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A complete list of publications begins on page 15.



Michael B. Yaffe, MD, PhD

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

RESEARCH FOCUS

The goal of our research is to understand how cells respond to stress and injury 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 long-standing 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 cell stress and DNA damage, for example, play critical roles in tumor development and progression. Targeting these pathways increases the ability of DNA-damaging chemotherapy, radiation, and immunotherapy to cure cancer. Our research is directed 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 stress and injury signaling pathways and the DNA damage response can be 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/injury 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, particularly in ovarian cancer. Finally, we discovered that inhibitors of

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

Tatiana Netterfield

Jesse Patterson, PhD

Ingred Goretti Rica, PhD

Samantha Rosenberg

Xueyang Yu, PhD

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

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 PIK1 inhibition in patients with progressive castrate-resistant prostate cancer.

Signaling Pathways and Networks That Control Inflammation, Blood Clotting, and Immune Function in Trauma, Cancer, and COVID-19

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, and this is partly recapitulated in COVID-19. The molecular basis for these effects is poorly understood but involves dysregulation of key signaling pathways in neutrophils and macrophages that control tissue damage, clot lysis, and inflammation. We have found that signaling through the p38-MK2 pathway is crucial for cytokine control and innate immune function, in part by modulating the phenotypic switch between pro-inflammatory macrophages and neutrophils and immunosuppressive macrophages and neutrophils. Our work has led to an ongoing clinical trial for ovarian cancer in collaboration with Dr. Brahm Segal at Roswell Park Cancer Center, and a multicenter clinical trial using tissue plasminogen activator for critically ill patients with COVID-19 ARDS.

ACCOMPLISHMENTS 2019-2020

- 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
- Elected to the Association of American Physicians
- Recipient of Margaret MacVicar Faculty Fellowship Award from MIT

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.

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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.

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Lim DC, Joukov V, Rettenmaier TJ, Kumagi A, Dunphy WG, Wells JA, Yaffe MB. Redox priming promotes Aurora A activation during mitosis. *Sci Signal* 2020;13(641):eabb6707.

Barrett CD, Kong, YW, Yaffe, MB. Influence of tranexamic acid on inflammatory signaling in trauma. *Semin Thromb Hemost* 2020;46:183-188.

Moore HB, Barrett CD, Moore EE, McIntyre RC, Moore PK, Talmor DS, Moore FA, Yaffe MB. Is there a role for tissue plasminogen activator (TPA) as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome (ARDS)? *J Acute Trauma Care Surg* 2020;88:713-714.



Daniel B. Jones, MD, MS

Professor of Surgery

Vice Chair, Surgery (Technology and Innovation)

Chief, Bariatric and Minimally Invasive Surgery

Co-Director, Carl J. Shapiro Simulation and Skills Center

RESEARCH GROUP

Souheil Adra, MD
Barbara Ainsley
Leigh-Ann Berk, NP
Dale Bond, MD
Morgan Bresnick, MD
Caroline Cao, PhD
Jaime Cudmore
Suvranu De, PhD
Jody Dushay, MD
Rahul Gupta, MD
Cullen Jackson, PHD
Mojdeh Kappus, MD
Evgeniya Larionova, NP
Kietaro Nakamoto, MD
Bao Nasri, MD, PhD
Elizabeth Nemolyaeva
Brian O'Gara, MD, MPH
Jaisa Olasky, MD
Ganesh Sankaranarayanan, PhD
Mandeep Sawhney, MD, MPH
Steven Schwaitzberg, MD
Linda Trainor, RN
Hung Truong, MD, MS
Christina Wee, MD, MPH



▲ Virtual mock OR

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. OR team training with simulation advanced patient safety.

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 developed and validated virtual reality (VR) simulators for laparoscopic hernia repair, LapBand, NOTES cholecystectomy, and FLS tasks. The current aim is to develop the Virtual OR Team Experience (VORTex) and within VR operating room avatars respond to crisis (fire, hemorrhage).

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 2019-2020

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

Invited Presentations

- Gastric Bypass: How to Avoid Complications. 27th Annual Congress of the European Association for Endoscopic Surgery (EAES); Sevilla, Spain
- Sparks, OR Fires, & Fiascos: Why the FUSE Program? Halsted Surgical Society; Charleston, NC
- Bariatric Surgery: Primum Non Nocere. Hawaii Bariatric Society; Honolulu, HI
- Unintended Consequences of Denying Patients Bariatric Surgery. ASMBS Connecticut Bariatric Chapter, CT
- Restarting Surgery in the COVID Era. Robotic Surgery Collaboration (RSC); online presentation

- OR Team Training Using Simulation: Hope or Hype? Association for Surgical Education (ASE) Virtual Meeting; online presentation
- Leak after Gastric Bypass: Timing is Everything. SAGES Virtual Meeting; online presentation
- Promoting Diversity in Your Department. Women's Leadership in Surgery Conference; online presentation

Recognition and Awards

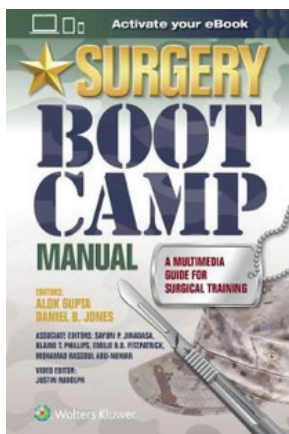
- 2020 BIDMC Department of Surgery Mentoring Award, Nominee
- Best Doctors in America; Top Doctors, *Boston Magazine*; America's Top Surgeons

Editorial Roles

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

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
- ASBMS Essentials: Multidisciplinary curriculum for management of bariatric surgery patient
- SAGES MASTERS program: Curriculum for deliberate learning after fellowship
- Course Director: BIDMC Surgery Grand Rounds, weekly CME lecture series



- ▲ **Surgery Boot Camp Manual: A Multimedia Guide for Surgical Training.** Wolters Kluwer, Philadelphia, PA, 2019; Alok Gupta, Daniel B. Jones, Editors.

SELECTED RESEARCH SUPPORT

Physically Realistic Virtual Surgery. NIH, 2011-2024; PI: Suvranu De, PhD; Co-PI: Daniel Jones, MD, MS

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 a Virtual Endoluminal Surgery Simulator (VESS) for the Treatment of Colorectal Cancer. NIH, 2016 -2021; PI: Suvranu De, PhD; Co-PI: Daniel Jones, MD, MS

Comparison of Postoperative Opioid Requirements among Patients Undergoing Laparoscopic Sleeve Gastrectomy Before and After Implementation of a ERAS Protocol. BIDMC Department of Surgery, 2019-2020; PI: Leigh-Ann Berk, NP; Co-I: Daniel Jones, MD, MS

Virtual Reality and Pain Management in the PACU for Bariatric Surgery. BIDMC Department of Anesthesiology, 2020-2021; PI: Brian O'Gara, MD, MPH; Co-I: Daniel Jones, MD, MS

Development and Validation of a Virtual Reality Robotic Simulation Training Program Using the Da Vinci Simnow Platform. SAGES, 2020-2021; PI: Keitaro Nakamoto, MD; Co-I: Souheil Adra, MD, Daniel Jones, MD, MS

SELECTED PUBLICATIONS

Stefanidis D, Schultz L, Bostian S, Sylla P, Pauli E, Oleynikov D, Kurian M, Khaitan L, Cripps M, Bachman S, Alseidi A, Brunt M, Asbun A, Jones DB. SAGES Masters Program: Determining the seminal articles for each pathway. *Surg Endosc* 2020;(34):1465-1481.

Qi D, Ryason A, Milef N, Alfred S, Abu-Nuwar R, Kappus M, De S, Jones DB. Virtual reality operating room with AI guidance: Design and validation of fire scenario. *Surg Endosc* 2020; in press.

Kappus M, Phillips B, Zenquis N, Larinova E, Cudmore J, Jones DB. Unintended consequences for patients denied bariatric surgery: A 12-year follow-up. *SOARD* 2020; 16(10):1458-1462.

Jones DB, Abu-Nuwar MR, Ku C, Berk L, Trainor L, Jones SB. Less pain and earlier discharge after implementation of a multidisciplinary enhanced recovery after surgery (ERAS) protocol for laparoscopic sleeve gastrectomy. *Surg Endosc* 2020; in press.

Abu-Nuwar MR, Adra S, Jones DB. Acute surgery for bariatric complications. In: Lim R (ed), *Multidisciplinary Approaches to Common Surgical Problems*. Springer, 2019; 3-15.

Sankaranarayanan G, Odlozil C, Wells KO, Leeds SG, Chauhan S, Fleshman JW, Jones DB, De S. Training with cognitive load improves performance under similar conditions in a real surgical task. *Am J Surg* 2020; in press.

Kappus M, Jones DB. Staplers, cartridges and energy devices. In: Gagner M, Ramos A, Palermo M, Noel P, Nocca D. *The Perfect Sleeve Gastrectomy: A Clinical Guide to Evaluation, Treatment and Techniques*. Springer, 2020;109-123.

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:

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 2019-2020

Several studies are in progress; those 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

O’Gara BP, Mueller A, Gasangwa DVI, Patxot M, Shaeji S, Khabbaz K, Banner-Goodspeed V, Pascal-Leone A, Marcantonio ER, Subramaniam B. Prevention of early postoperative decline: A randomized, controlled feasibility trial of perioperative cognitive training. *Anesth Analg* 2020;130(3):586-595.

Van Mieghem NM, Popma JJ, Deeb GM, Yakubov SJ, Serruys PW, Windecker S, Søndergaard L, Mumtaz M, Gada H, Chetcuti S, Kleiman NS, Kodali S, George I, Teefy P, Kiaii B, Oh JK, Kappetein AP, Chang Y, Mugglin AS, Reardon MJ; SURTAVI Trial Investigators; Clinical Trial. Complete 2-year results confirm Bayesian analysis of the SURTAVI trial. *JACC Cardiovasc Interv* 2020;13(3):323-331.

Mufarrih SH, Qureshi NQ, Khabbaz KR, Mahmood F, Sharkey A. Curious case of mitral and tricuspid regurgitation. *J Cardiothorac Vasc Anesth* 2020;Sep 15:S1053-0770(20)31008-9.

Fatima H, Matyal R, Mahmood F, Baribeau Y, Khabbaz KR. Ischemic mitral regurgitation: To fix or not to fix. *J Cardiothorac Vasc Anesth* 2020;34(9):2532-2535.

Fatima H, Mahmood F, Sehgal S, Belani K, Sharkey A, Chaudhary O, Baribeau Y, Matyal R, Khabbaz KR. Artificial intelligence for dynamic echocardiographic tricuspid valve analysis: A new tool in echocardiography. *J Cardiothorac Vasc Anesth* 2020;34(10):2703-2706.

Liu S, Bose R, Ahmed A, Maslow A, Feng Y, Sharkey A, Baribeau Y, Mahmood F, Matyal R, Khabbaz K. Artificial intelligence-based assessment of indices of right ventricular function. *J Cardiothorac Vasc Anesth* 2020;34(10):2698-2702.



Evangelos Messaris, MD, PhD

Associate Professor of Surgery
Chief, Colon and Rectal Surgery

Thomas Cataldo, MD

Assistant Professor of Surgery

Kristen Crowell, MD

Assistant Professor of Surgery

Anne Fabrizio, MD

Instructor in Surgery



RESEARCH GROUP

Benjamin Allar, MD
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Israel Gaytan, MD
Ana Sofia Ore, MD
Jonathan Pastrana Del Valle, MD

Raje Praachi, MD
Eve Roth, MD
Claire Sokas, MD
Alessandra Storino, MD
Jacqueline Wade, MD
Ashlyn Whitlock, 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 NSQIP or NCDB.

Our 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 ileocelectomy
- 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 2019-2020

- *Boston Magazine* Top Doctors: Dr. Thomas Cataldo
- Curriculum Director for Reviewer's Guild for the journal *Diseases of the Colon and Rectum*: Dr. Evangelos Messaris
- John L. Rowbotham Teaching Award, Department of Surgery: Dr. Thomas Cataldo

TEACHING, TRAINING, AND EDUCATION

The entire division is invested in education:

- Second 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 examiners for BIDMC and New England Society of Colon and Rectal Surgeons

ABSTRACTS, POSTERS, AND EXHIBITS

Fakler M, Wong DJ, Sokas CM, Ore AS, Fleishman A, Fabrizio AC, Cataldo TE, Messaris E. Elderly, Functionally Dependent Patients Undergoing Laparoscopic Rectopexy for Rectal Prolapse Do Not Have Increased Morbidity Relative to Patients Undergoing Perineal Repairs. ACS 2020 (Virtual)

Robinson K, Duncan SG, Messaris E, Brat G. Anorectal Disease and Post-Discharge Consumption of Opioids. ACS 2020 (Virtual)

Wong DJ, Sokas CM, Fakler M, Fleishman A, Cataldo TE, Fabrizio AC, Feuerstein JD, Messaris E. Increased Morbidity for the Elderly in IBD Surgery is Context Dependent. ACS 2020 (Virtual)

Storino A, Wong D, Ore A, Fuentes IA, Fabrizio A, Cataldo TE, Messaris E. Recurrence and Survival of Localized Neuroendocrine Tumors of the Rectum: Single Center Experience. ASCRS 2020 (Virtual)

Wong D, Kosaraju R, Serifis N, Fabrizio A, Cataldo TE, Feuerstein J, Messaris E. Dose-Intensified Infliximab Rescue Therapy for Acute Ulcerative Colitis: Does It Decrease the Need for Colectomy? ASCRS 2020 (Virtual)

Dombek GE, Matsumoto Y, Fleishman A, Glickman J, Poylin VY, Cataldo TE, Messaris E, Cummings RD. Expression of TN Antigen in Tumors and Transitional Margins of Colorectal Cancer. ASCRS 2020 (Virtual)

Ore A, Storino A, Fabrizio A, Cataldo TE, Messaris E. Cultural Diversity and Limited English Proficiency: Evaluation of Post-Surgical Outcomes after Elective Colectomy. ASCRS 2020 (Virtual)

SELECTED PUBLICATIONS

Hamid HK, Emile SH, Saber AA, Ruiz-Tovar J, Minas V, Cataldo TE. Laparoscopic-guided transversus abdominis plane block for postoperative pain management in minimally invasive surgery: Systematic review and meta-analysis. *J Am Coll Surg* 2020;231(3):376-386.

Feuerstein JD, Curran T, Alvares D, Alosilla M, Lerner A, Cataldo T, Falchuk KR, Poylin V. Surgery for ulcerative colitis in geriatric patients is safe with similar risk to younger patients. *Eur J Gastroenterol Hepatol* 2019;31(11):1356-1360.

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* 2020;34(7):3011-3019.

Cataneo J, Mowschenson P, Cataldo TE, Poylin VY. Rectal eversion: Safe and effective way to achieve low transaction in minimally invasive ileal pouch-anal anastomosis surgery, short- and long-term outcomes. *Surg Endosc* 2020;34(3):1290-1293.

Kulaylat AN, Kulaylat AS, Schaefer EW, Mirkin K, Tinsley A, Williams E, Koltun WA, Hollenbeak CS, Messaris E. The impact of preoperative anti-TNF α therapy on postoperative outcomes following ileocelectomy in Crohn's disease. *J Gastrointest Surg* 2020; in press.

Eisenstein S, Holubar SD, Hilbert N, Bordeianou L, Crawford LA, Hall B, Hull T, Hyman N, Keenan M, Kunitake H, Lee EC, Lewis WD, Maron D, Messaris E, Miller R, Mutch M, Ortenzi G, Ramamoorthy S, Smith R, Steinhagen RM, Wexner SD. The ACS National Surgical Quality Improvement Program-Inflammatory Bowel Disease Collaborative: Design, implementation, and validation of a disease-specific module. *Inflamm Bowel Dis* 2019;25(11):1731-1739.



Jordan Bohnen, MD, MBA

Minimally Invasive Surgeon

Member of the Faculty of Surgery

RESEARCH FOCUS

I am passionate about health systems improvement and enjoy exploring novel ways to optimize healthcare delivery. Over the last several years, my research has drawn on a variety of data sources including outcomes databases (e.g., NSQIP), surgical video data, high-fidelity simulation, and smartphones to investigate topics across the fields of delivery science, outcomes research, surgical education, mobile technology, and artificial intelligence.

Recent collaborations include:

- Design and implementation of a smartphone-based application (SIMPLTM) to measure surgical trainee autonomy and improve operative performance feedback (<https://www.procedurallearning.org/>)
- Analysis of intraoperative safety factors using a clinically-trained artificial intelligence platform (OR Black Box®) (<https://www.surgicalsafety.com/>)
- Detailed investigation of intraoperative adverse events (i.e., outcomes, costs, emotional toll)
- Development of a Second Victim Peer-Support Program for surgeons after complications
- Validation of a novel scoring system to predict outcomes after emergency surgery
- Creation of a high-fidelity surgical simulator with beating-heart technology (<https://www.nytimes.com/video/science/100000004027097/hollywood-in-the-operating-room.html>)
- Design of a case-based curriculum to improve surgical trainees' leadership skills
- Development of an Enhanced Recovery After Surgery (ERAS) Program for foregut surgery

I look forward to developing innovative research collaborations across the BIDMC and extended Harvard Medical School community in the areas of surgical safety, educational quality improvement, and systems redesign.

ACCOMPLISHMENTS 2019-2020

- Invited podium presentation: Trainee Autonomy in Minimally Invasive General Surgery in the United States: Establishing a National Benchmark. Association of Program Directors in Surgery Annual Meeting (virtual)
- Invited participant: Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Video Annotation Conference, Houston, TX
- Developed and led a multidisciplinary case-based foregut conference with participation from General Surgery, Thoracic Surgery, and Gastroenterology
- *Annals of Surgery*, ad hoc reviewer
- *Journal of Surgical Education*, ad hoc reviewer

TEACHING, TRAINING, AND EDUCATION

I am actively engaged in teaching surgical residents and medical students in the operating room, on the wards, and through surgical didactics sessions. In addition, I led several laparoscopic skills training sessions for surgical trainees and participated in both informal and formal assessments of trainees' minimally invasive skills.

SELECTED RESEARCH SUPPORT

Using Learning Curves to Redefine Training Requirements in General Surgery. Edward J. Stemmler, MD, Medical Education Research Fund of the National Board of Medical Examiners, 2018-2020 (\$150,000); Co-investigator: Jordan Bohnen, MD, MBA; PI: Brian C. George, MD

SELECTED PUBLICATIONS

Meyerson SL, Odell DD, Zwischenberger JB, Schuller M, Williams RG, Bohnen JD, Dunnington GL, Torbeck L, Mullen JT, Mandell SP, Choti MA, Foley E, Are C, Auyang E, Chipman J, Choi J, Meier AH, Smink DS, Terhune KP, Wise PE, Soper N, Lillemoe K, Fryer JP, George BC; Procedural Learning and Safety Collaborative. The effect of gender on operative autonomy in general surgery residents. *Surgery* 2019;166(5):738-743.

Chen JX, Kozin E, Bohnen J, George B, Deschler DG, Emerick K, Gray ST. Assessments of otolaryngology resident operative experiences using mobile technology: A pilot study. *Otolaryngol Head Neck Surg* 2019;161(6):939-945.

El Hechi M, Bohnen JD, Westfal M, Han K, Cauley C, Wright C, Schulz J, Mort E, Ferris T, Lillemoe KD, Kaafarani HM. Design and impact of a novel surgery-specific second victim peer-support program. *J Am Coll Surg* 2020;230(6):926-933.

Scully RE, Deal SB, Clark MJ, Yang K, Wnuk G, Smink DS, Fryer JP, Bohnen JD, Teitelbaum EN, Meyerson SL, Meier AH, Gauger PG, Reddy RM, Kendrick DE, Stern M, Hughes DT, Chipman JG, Patel JA, Alseidi A, George BC. Concordance between expert and nonexpert ratings of condensed video-based trainee operative performance assessment. *J Surg Educ* 2020;77(3):627-634.

Bohnen JD, Meireles OR. Masters program flexible endoscopy pathway: Balloon dilation. Nau P, Pauli EM, Sandler BJ, Trus TL (Editors.) *The SAGES Manual of Flexible Endoscopy*, Springer, 2019.

George BC, Bohnen JD, Schuller MC, Fryer JP. Using smartphones for trainee performance assessment: A SIMPL case study. *Surgery* 2020;167(6):903-906.

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 FOCUS

Gastric Cancer Projects

One 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.

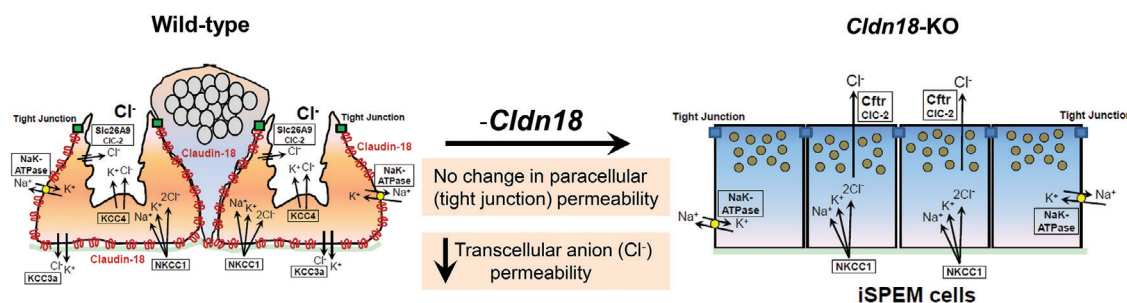
Although the stomach expresses a specific subset of claudin molecules, which are proteins that confer barrier properties to epithelial cells at the tight junction, one particular claudin is highly expressed in stomach, claudin-18 (*CLDN18*). Claudin-18 is a cation-selective tight junction protein that is transcriptionally down-regulated in *H. pylori* infection in mice as well as in human patients with gastric cancer. Because claudin-18 (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 demonstrated that claudin-18 is most highly expressed as a basolateral membrane protein and functions as a potent tumor suppressor in the stomach; knockout of *Cldn18* promotes gastric cancer development (Gastroenterology, 2018).

In the past year, using Ussing chambers to study paracellular flux across the mucosa in *ex vivo* stomach, we showed that no paracellular permeability defects occur in *CLDN18* knockout mice (Figure 1). These unexpected results suggested that cancer pathogenesis in the absence of *Cldn18* does not occur because increased mucosal permeability promotes inflammation, mucosa damage, and cancer development. We are now investigating signaling pathways regulated by *Cldn18* that affect cancer development in our *Cldn18* knockout and conditional knockout mouse models.

Metabolism Projects

A second project in the lab involves a close collaboration with David Cohen, MD, PhD, Chief of Gastroenterology and Hepatology at Weill Cornell Medical College in New York and Eric Ortlund, PhD, Professor of Biochemistry at Emory University, to study the role of thioesterase superfamily member 1 (Them1) in hepatic steatosis/NAFLD. We became involved with this project due to our expertise in microscopy. In the past year, we used near super-resolution confocal microscopy and CLEM (Figure 2), bioinformatic, genetic, and metabolic techniques, which required the combined expertise of the three labs, to demonstrate that Them1 *in vivo* and *in vitro* forms novel biomolecular condensates (we call "puncta") that represent the functionally active form of Them1. Upon stimulation, the Them1-containing puncta disperse via phosphorylation of specific serine residues at the amino terminus. Using LSMS, we demonstrated the position of serine phosphorylation events and showed the role each plays in regulating Them1 function. We are currently working to understand mechanisms that regulate the phase transition required to form puncta and looking at the role Them1 plays in regulating transcriptional events that occur after stimulation. In its diffuse state, Them1 transits to the nucleus, where we believe it is involved in the transcription of metabolic proteins that regulate fatty acid metabolism.

▼ FIGURE 1: Published in *Cellular and Molecular Gastroenterology and Hepatology* by Tyler Caron, DVM (a previous postdoctoral fellow in the lab) et al, *Cldn18*-loss does not affect barrier function but results in changes in ion transport characteristics of the stomach.



Individual Accomplishments

- The most important accomplishment was that both of our main research grants were renewed in FY20. Our Them1 project renewal was refunded and the HDDC Center grant was refunded. Both grant applications received an outstanding score in peer review.
- Susan Hagen, PhD, continued work on the editorial board of *Tissue Barriers*.
- Susan Hagen, PhD, was asked to join the review group for *Current Opinion in Gastroenterology* and to write yearly updates on GI Mucosal Protection.
- Susan Hagen, PhD, was the COVID-19 floor manager for Dana 8. For this, with assistance from Barbara Ainsley, she ensured shut-down and return to work guidelines were met during the COVID-19 pandemic.
- Yue Li, PhD, finished his Them1/metabolism paper and submitted it to bioRxiv. The work was reviewed by *Nature Communications* and is currently under revision.
- Yue Li, PhD, was promoted from a Postdoctoral Fellow to a Research Associate at Harvard Medical School.
- Mahnoor Baqai, MD, was accepted to the Surgical Residency program at Johns Hopkins School of Medicine.

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

The BIDMC resident's course in Comparative Physiology and the GI Fellows course entitled "Origins and Frontiers of Hepatobiliary and Gastrointestinal Physiology" at Mount Desert Island Biological Laboratory were cancelled this year due to the COVID-19 pandemic.

RSI Program

The Research Science Institute (RSI) summer research program was cancelled this year so no students worked in the lab for the summer due to the COVID-19 pandemic.

SELECTED RESEARCH SUPPORT

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

Them1-Mediated Metabolic Regulation and Pathogenic Role in NAFLD. NIH, 2020-2024; 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, P30 Research Center grant, 2020-2025; PI and Director, Microscopy and Histopathology Core B: Susan J. Hagen, PhD (Grant PI: Wayne Lencer, MD)

Research Training in Alimentary Tract Surgery. NIH, 2016-2021; Academic Mentor, Susan J. Hagen, PhD (PI: Richard A. Hodin, MD)

SELECTED PUBLICATIONS

Gastric Cancer Project

Hagen SJ. Do ulcers heal structurally and functionally? *Dig Dis Sci* 2020;65(1):3-5.

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;99(12):1887-1905.

Caron TJ, Scott KE, Sinha N, Muthupalani S, Baqai M, Ang LH, Li Y, Turner JR, Fox JG, Hagen SJ. Claudin-18 loss alters transcellular chloride flux but not tight junction ion selectivity in gastric epithelial cells. *Cell Mol Gastroenterol Hepatol* 2020; in press.

Metabolism Project

Li Y, Imai N, Goyal S, Nicholls HT, Krisko TI, Baqai M, Ang LH, Tillman MC, Ortlund EA, Cohen DE, Hagen SJ. Thioesterase superfamily member 1 undergoes stimulus-coupled reorganization to regulate metabolism. *bioRxiv* 2020. MS ID: 954818.

Tillman MC, Imai N, Li Y, Khadka M, Okafor CD, Juneja P, Adhiyaman A, Hagen SJ, Cohen DE, Ortlund EA. Allosteric regulation of thioesterase superfamily member 1 by lipid sensor domain binding fatty acids and lysophosphatidylcholine. *Proc Natl Acad Sci USA* 2020;117(36):22080-9.

Wang CH, Lundh M, Fu A, Kriszt R, Huang TL, Lynes MD, Leiria LO, Shamsi F, Darcy J, Greenwood BP, Narain NR, Tolstikov V, Smith KL, Emanuelli B, Chang YT, Hagen SJ, Danial NN, Kiebish MA, Tseng YH. CRISPR-engineered human brown-like adipocytes prevent diet-induced obesity and ameliorate metabolic syndrome in mice. *Sci Transl Med* 2020;12(558):eaaz8664

A complete list of publications begins on page 15.

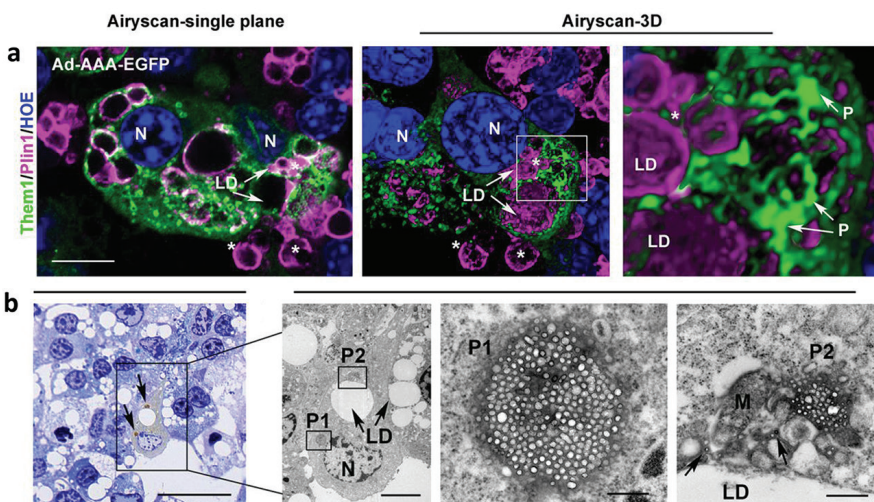


FIGURE 2: Images of puncta in cultured brown adipose cells transduced with the Them1 mutant S15-S18-S25D (AAA) whereby all cells contain puncta (P). In A, puncta are labeled with EGFP (green), lipid droplets with perilipin1 in magenta, and the nucleus with Hoechst in blue. In B, cells were transduced with AAA-APEX2 and stained by conventional histochemical techniques so that puncta are brown (arrows or P1, P2, P3). Puncta were typically localized near lipid droplets LD. The images are from Li et al, 2020.



Tara S. Kent, MD, MS

Associate Professor of Surgery

Vice Chair for Education

Program Director, General Surgery Residency

RESEARCH FOCUS

Research in Pancreaticobiliary Surgery (Dr. Kent, Dr. Callery)

Our group's work focuses on patient-centered outcomes research in pancreaticobiliary surgery. A large prospective database has been developed and maintained from a robust clinical practice, providing the substrate for our outcomes investigations. In addition, we have utilized national large databases of pancreas cancer patients/outcomes.

Areas of emphasis are factors associated with patient-centered decision making and care, as well as care transitions, 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 investigating 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 preferred language and time to definitive treatment. We are 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 Americas Hepato-Pancreato-Biliary Association (AHPBA) and International Hepato-Pancreato-Biliary Association (IHPBA) networks.

Surgical Education Research (Dr. Kent)

Our surgical education research effort includes the study of factors influencing resident acquisition of knowledge and skills, as well as development of novel curricula. Recently, we have been studying potential sources of bias in the residency application process. We are also involved in an NIH-funded multi-center study of the impact of a surgical resident curriculum on cultural dexterity. In addition, I am providing technical assistance via a USAID grant to help restructure surgical residency in Vietnam.

RESEARCH GROUP

Mark P. Callery, MD

William V. McDermott Professor
of Surgery

Chief, General Surgery

Chair, Surgery Leadership Council

Benjamin Allar, MD

Donna Alvino, MD

Manuel Castillo-Angeles, MD, MPH

John Polanco, MD

Alessandra Storino, MD, MS

ACCOMPLISHMENTS 2019-2020

- Morgan-Zinsser Fellow of the Harvard Medical School Academy of Medical Educators (Dr. Kent)
- Selected as Americas Hepato-Pancreato-Biliary Association (AHPBA) Program Vice-Chair for 2021 and Program Chair for 2023 (Dr. Kent)
- Member, local Organizing Committee, International Hepato-Pancreato-Biliary Association (IHPBA) 2022 World Congress (Dr. Kent)
- Appointed as the William V. McDermott Professor of Surgery at Harvard Medical School (Dr. Callery)
- President of the Society for Surgery of the Alimentary Tract (SSAT), 2019-2021 (Dr. Callery)

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 eight preliminary trainees
- As Vice Chair for Education (since 2014), I oversee the department's educational programs at the student, resident, and fellow levels
- I was invited to participate in the Harvard Medical School Academy of Medical Educators Fellowship

SELECTED RESEARCH SUPPORT

The Provider Awareness and Cultural Dexterity Toolkit for Surgeons Trial. NIH R01, 2018-2022; Co-Investigator: Tara S. 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 S. Kent, MD, MS (PI: Lisa Cosimi, MD)

SELECTED PUBLICATIONS

Casciani F, Trudeau MT, Asbun HJ, Ball CG, Bassi C, Behrman SW, Berger AC, Bloomston MP, Callery MP, Christein JD, Falconi M, Fernandez-Del Castillo C, Dillhoff ME, Dickson EJ, Dixon E, Fisher WE, House MG, Hughes SJ, Kent TS, Malleo G, Partelli S, Salem RR, Stauffer JA, Wolfgang CL, Zureikat AH, Vollmer CM Jr; Pancreas Fistula Study Group. Surgeon experience contributes to improved outcomes in pancreatoduodenectomies at high risk for fistula development. *Surgery* 2020;Dec 29 (Epub ahead of print).

Lee GJ, Ortega G, Reidy E, Atkinson RB, Pichardo MS, Reich AJ, Ladin K, Chun MBJ, Demko C, Barreiro-Rosado JA, Udyavar NR, Kent TS, Green AR, Haider AH, Smink DS. A qualitative analysis of surgical faculty and surgical resident perceptions of potential barriers to implementing a novel surgical education curriculum. *J Surg Educ* 2020;S1931-7204.

Moekotte AL, van Roessel S, Malleo G, Rajak R, Ecker BL, Fontana M, Han HS, Rabie M, Roberts KJ, Khalil K, White SA, Robinson S, Halimi A, Zantonello L, Fusai GK, Gradinaru G, Alseidi A, Bonds M, Dreyer S, Jamieson NB, Mowbray N, Al-Sarireh B, Mavroeidis VK, Soonawalla Z, Napoli N, Boggi U, Kent TS, Fisher WE, Tang CN, Bolm L, House MG, Dillhoff ME, Behrman SW, Nakamura M, Ball CG, Berger AC, Christein JD, Zureikat AH, Salem RR, Vollmer CM, Salvia R, Besselink MG, Abu Hilal M; International Study Group on Ampullary Cancer (ISGACA) Collaborators, Aljarrah R, Barrows C, Cagigas MN, Lai ECH, Wellner U, Aversa J, Dickson PV, Ohtsuka T, Dixon E, Zheng R, Kowalski S, Freedman-Weiss M. Development and external validation of a prediction model for survival in patients with resected ampullary adenocarcinoma. *Eur J Surg Oncol* 2020;46:1717-1726.

Trudeau MT, Casciani F, Ecker BL, Maggino L, Seykora TF, Puri P, McMillan MT, Miller B, Pratt WB, Asbun HJ, Ball CG, Bassi C, Behrman SW, Berger AC, Bloomston MP, Callery MP, Castillo CF, Christein JD, Dillhoff ME, Dickson EJ, Dixon E, Fisher WE, House MG, Hughes SJ, Kent TS, Malleo G, Salem RR, Wolfgang CL, Zureikat AH, Vollmer CM; on behalf of the Pancreas Fistula Study Group. The fistula risk score catalog: Toward precision medicine for pancreatic fistula after pancreatoduodenectomy. *Ann Surg* 2020;Jun 11 (Epub ahead of print).

Kent TS, Freischlag J, Minter R, Hawn M, Al-Refaie W, James BC, Eskander M, Chu D. Overcoming a hostile work and learning environment in academic surgery-tools for change at every level. *J Surg Res* 2020;252:281-284.

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* 2020;77:61-68.

Fligor SC, Wang S, Allar BG, Tsikis ST, Ore AS, Whitlock AE, Calvillo-Ortiz R, Arndt KR, Gangadharan SP, Callery MP. Gastrointestinal malignancies and the COVID-19 pandemic: Evidence-based triage to surgery. *J Gastrointest Surg* 2020;24(10):2357-2373.

Fong ZV, Qadan M, McKinney R Jr, Griggs CL, Shah PC, Buyske J, Sachdeva AK, Callery MP, Altieri MS. Practical implications of novel coronavirus COVID-19 on hospital operations, board certification, and medical education in surgery in the USA. *J Gastrointest Surg* 2020;24(6):1232-1236.

A complete list of publications begins on page 15.



RESEARCH GROUP

Benjamin Blum, PhD candidate
 Michaela Carroll
 Richard D. Cummings, PhD
 Sarah Duncan
 Andrew Emili, PhD
 Ryan Hekman
 Pingzhao Hu, PhD
 Matthew Lawton
 Sylvain Lehoux, PhD
 Qian Liu
 Jarrod Moore, MD, PhD candidate
 Douglas Pleskow, MD
 Mandeep Sawhney, MD

RESEARCH FOCUS

My research interests include basic science and the pathophysiology of Barrett's esophagus (BE). I am currently focusing on the application of global phosphor profiling to discover signaling proteins/pathways involved in the progression of BE. My past research in the area of molecular biology and genomics laid the seeds for such a project as this. My interest in esophageal and gastric biology fuels my desire to study the fundamental biology of foregut disease, namely BE and gastric cancer using high-throughput technologies such as mass spectrometry as a powerful proteomic tool to interrogate protein machinery in aberrant molecular processes.

Currently, I am principal investigator of an IRB approved, pilot study of BE with multi-institutional, international collaborative involvement. BE results from chronic acid reflux and inflammation to the squamous esophageal epithelium lining the esophagus and induces metaplastic changes in cellular architecture that can lead to esophageal cancer (EAC). The majority of patients undergoing endoscopy for BE tolerate the burden of unnecessary, frequent invasive endoscopy and biopsy for surveillance and concern about progression to near fatal EAC.

Efforts to reduce this burden have been hindered by the lack of knowledge of the molecular mechanisms that underly progression as well as the lack of effective diagnostics that can decipher those patients who will progress to EAC from those who will not. Of note, fewer than 1% of patients will progress to the near fatal EAC. The challenge is how to distinguish patients who will benefit from invasive surveillance from those who will not.

Our research has set out to interrogate endoscopic biopsy specimens from living patients with and without (controls) BE, and analyze these biopsy specimens using state-of-the-art mass spectrometry analysis to see if there are detectable differences at the molecular level in patients who have BE versus those who do not.

Our central hypothesis is that patients with BE who progress to EAC do so via molecular changes that are triggered in the setting of chronic acid reflux. If one can identify the molecular mechanisms

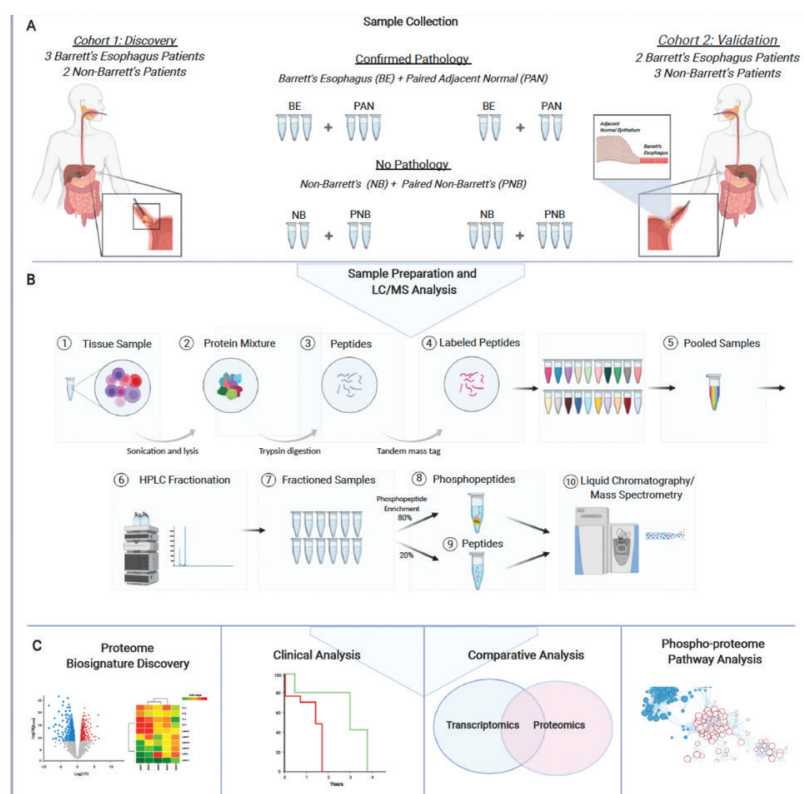


FIGURE 1: Depictions of the process of (A) sample collection and categorization (BE=Barrett's Esophagus, PAN=paired adjacent normal, PNB=paired non-Barrett's, NB=non-Barrett's) from two cohorts; (B) 26 sample preparation pipeline for LC/MS analysis from biopsy to mass spectrometry analysis; and (C) biosignature discovery from data obtained in B (left); clinical data on the survivability of esophageal cancer patients with proteomic signatures of BE (middle left); pathway level comparative analysis between independent transcriptomic datasets of BE tissue with neighboring unaffected tissue and the matched samples of our study (middle right); and phospho-proteome pathway analysis of study samples (right).

that underpin these cellular changes, the potential exists for intervention with targeted therapeutics. The goal of this work is to compare and contrast biopsied normal esophageal epithelium to that of Barrett's pathology using quantitative phosphor-proteomic profiling for measuring signalling perturbations when comparing Barrett's epithelium to normal and dysplastic esophageal epithelium.

Our aim is to examine the networks and interactions of clinically relevant signalling proteins disrupted during the progression of BE to gain insight into the molecular mechanisms that drive its progression. Global phosphor-proteomic profiling offers a powerful means for interrogating critical cancer cell systems on a holistic, cellular scale.

In our pilot study, we identified 7,018 proteins and 8,420 phosphosites in the discovery cohort, revealing hundreds of statistically significant ($p < 0.05$, moderated t-test) differences in protein and phospho-site abundance between BE and matched normal esophageal epithelium. We further identified a proteomic signature that classified samples on disease status. To take this one step further, we used projection analysis of the discovery signature against EAC tumor profiles and have found it to be strongly predictive of survival outcomes. Lastly, subsequent comparative analysis with published BE transcriptomic profiles provided independent evidence in support of these results. We have just submitted this work for peer review.

ACCOMPLISHMENTS 2019-2020

- I have continued to serve an active role in the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). I was invited to serve as Chair of the Leadership and Professional Development Task Force of SAGES for 2020-2021. From 2017 to 2020, I served as Co-Chair of the SAGES Committee on Diversity and Inclusion.
- In 2020, I was appointed as a Site Reviewer for the American College of Surgeons High-Risk GI Group, Esophageal section.
- In addition, in 2020 I served as Co-Chair of the CineMed Women's Leadership in Surgery Conference in September, a virtual two-day conference for trainees and junior faculty aspiring to leadership roles in surgery. In addition to moderating several panels, I spoke on "Overcoming Unexpected Clinical Outcomes and Complications."
- From its inception in 2018 until mid-2020, I served as Chair of the Department of Surgery's Committee on Diversity, Equity, and Inclusion.

Invited Presentations

- The Art and Science of Fundoplication: Devil's in the Details; SAGES Annual Meeting, 2019
- Barrett's Esophagus: Biomarkers—Are We There Yet? SAGES Annual Meeting, 2020
- The Great Foregut Debate: Experts Debate; Manometry is Miserable—It Can be Done Selectively. SAGES Annual Meeting, 2020
- Revisional Foregut Surgery and Pre-operative Preparation. SAGES Annual Meeting, 2020
- How to Set Up a Foregut Center: The Academic Perspective. SAGES Annual Meeting, 2020

TEACHING, TRAINING, AND EDUCATION

My educational responsibilities focus on teaching surgical residents and Harvard Medical School students at all levels. I teach residents in the operating room, in informal/formal oral exam sessions, and on the wards. I also participate in the Harvard Medical School curriculum by teaching anatomy sessions in the winter semester and I am a tutor for second- and third-year Harvard Medical School students.

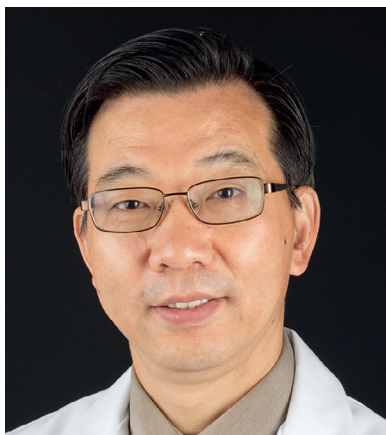
SELECTED PUBLICATIONS

Sandhu C, Qureshi A, Emili A. Panomics for precision medicine. *Trends Mol Med* 2018;24(1):85-101.

Qureshi AP, Stachler MD, Haque O, Odze RD. Biomarkers for Barrett's esophagus: A contemporary review. *Expert Rev Mol Diagn* 2018;18(11):939-946.

Telem DA, Qureshi AP, Edwards M, Jones DB; WRS Task Force. *Surg Endosc* 2018;32(10):4105-4110.

Al-Mansour MR, Caycedo-Marulanda A, Davis BR, Alawashez A, Docimo S, Qureshi A, Tsuda S. SAGES TAVAC safety and efficacy analysis confocal laser endocicroscopy. *Surg Endosc* 2020; May 13 (Epub ahead of print).



Jin-Rong Zhou, PhD

Associate Professor of Surgery

Director, Nutrition/Metabolism Laboratory

RESEARCH GROUP

Hamid Abdolmaleky, MD
Suthakar Ganapathy, PhD
Juan Li, PhD
Kehuan Lin
Xin Pan
Xiaohui Sun, MD, PhD
Sheng Yin, PhD

RESEARCH FOCUS

The long-term goal of my research is to define efficacious and safe nutritional and bioactive regimens for the prevention and therapy of cancer and other metabolic disorders. My laboratory has focused on evaluating the effects of bioactive natural compounds on inhibition of growth and progression of certain types of cancer, blood glucose management, alleviation of chronic kidney disease, promotion of gut health, prevention of osteoporosis, improvement of cognition, inhibition of UV-induced skin damage, and investigating the mechanisms of action of bioactive components. In the past year, my laboratory has focused on the following projects.

Synergistic Combinations of Tanshinones against Cancer Progression

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. We also found that the CT and T1 combination had synergistic effect against prostate cancer in part via downregulation of aurora kinases and c-Myc. Our animal studies further verified that the T1 and CT combination inhibited prostate cancer progression in a synergistical manner.

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

We have studied the effects of oligo-lactic acid product (LAP) and a fermented soybean product (ImmuBalance, IMB) on chronic kidney disease and associated cognitive impairment *in vivo*. LAP or IMB delayed the progression of adenine-induced chronic kidney injury in mice by inhibiting inflammation and reducing kidney toxicity via modulation of inflammation biomarkers in blood and kidney samples and alteration of gut microbiota, and could significantly improve cognition. We are investigating the underlying mechanisms of action of these bioactive components on improving cognition.

Effects of Bioactive Components on Control of Hyperglycemia and Associated Cognitive Decline

In this project, we evaluated the effects of novel dietary ingredients, nostoc and its

fiber fraction, 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 in part via increasing pancreatic beta-cell proliferation.

Effects of Epimedium Components on Osteoporosis Prevention

In this project, we evaluated the effects of an epimedium flavonoids extract (EFE) and the major component, icariin, on bone metabolism. *In vitro* studies indicated that EFE and icariin could stimulate osteoblast differentiation, but inhibit osteoclast differentiation. The animal study showed that EFE and icariin reduced osteoporosis. We are in the process of studying underlying mechanisms of action.

Effects of Acai Components on Prevention of UV-Induced Skin Damage

In this project, we evaluated the effect of acai components on UV-induced skin damage. *In vitro* studies showed that acai bioactive components inhibited the UV-induced keratinocyte apoptosis and ROS production associated with modulation of oxidative stress and skin damage-related biomarkers. We are conducting an animal study to confirm the efficacy of acai bioactive components in protecting the UV-induced skin damage and to elucidate the underlying mechanisms of action.

ACCOMPLISHMENTS 2019-2020

Grant Review Activities

- Review panel, General Research Fund, Research Grant Council, Hong Kong, 2020
- Review panel, Faculty Development Scheme, Research Grant Council, Hong Kong, 2020
- Special Emphasis Panel, Cancer Drug Development and Therapeutics, ZRG1 OTC-T (10), NCI/NIH, 2020
- Review panel, Function and Efficacy of Nutrients Review Panel of National Institute of Food and Agriculture (NIFA), U.S. Department of Agriculture (USDA), 2019, 2020

Editorial Roles

- Editorial board member: *Clinical Medicine: Endocrinology and Diabetes*; *Digital Chinese Medicine*; *Hepatobiliary Surgery and Nutrition*; *Journal of Disease and Global Health*; *Journal of Personalized Medicine*; *Precision Medical Sciences*; *Single Cell Biology*
- Associate Editor: *Integrative Oncology and Rehabilitation*
- Field Editor: *Functional Foods in Health & Disease*
- Editor-in-Chief: *Nutrition and Metabolic Insights* (2012-present)

Invited Presentations

- Overview of Evidence-Based Platforms for Research and Development of Nutraceuticals. Kunming Institute of Botany; Kunming, China
- The Role of Nutrition in the Prevention and Management of Cancer. Cross-Cutting Innovation Summit 2020, Chinese Association for Science & Technology in Greater Boston; Boston, MA,
- Nutrition and COVID-19: Dietary and Nutritional Guidelines during the COVID-19 Pandemic. Online presentation; North America Chinese Society for Nutrition (NACSN)

Other

- Vice Chair, First Board of Specialty Committee of Breast Diseases, World Federation of Chinese Medicine Societies, 2019
- Organizing Committee member; 23rd World Conference on Food and Nutrition Science, Tokyo, Japan, 2019
- President-Elect, North America Chinese Society for Nutrition (NACSN), 2020
- President, Chinese Association for Science and Technology-Greater Boston Chapter, 2020
- Board of Directors, Nanjing University of Chinese Medicine, Nanjing, China, 2020

TEACHING, TRAINING, AND EDUCATION

I have been training one postdoctoral fellow, two sponsored research fellows, and one undergraduate student on a daily

basis for the past year. In addition, I supervised a high school senior on a daily basis during the summer of 2020.

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., China, 2018-2020; PI: Jin-Rong Zhou, PhD

Evaluation of Anti-Oxidative Activities of Acai Preparations. Vitamin World (China) Limited, China, 2018-2021; PI: Jin-Rong Zhou, PhD

SELECTED PUBLICATIONS

Zhao Z, Shi A, Wang Q, Zhou J. High oleic acid peanut oil and extra virgin olive oil supplementation attenuate metabolic syndrome in rats by modulating the gut microbiota. *Nutrients* 2019;11:3005.

Kamarudin MNA, Sarker MMR, Zhou J-R, Parhar I. Metformin in colorectal cancer: Molecular mechanism, preclinical and clinical aspects. *J Exp Clin Cancer Res* 2019;38:491.

Wu H, You L, Li Y, Zhao Z, Shi G, Chen Z, Wang Z, Li X, Du S, Ye W, Gao X, Duan J, Cheng Y, Tao W, Bian J, Zhou J-R, Zhu Q, Yang Y. Loss of a negative feedback loop between IRF8 and AR promotes prostate cancer growth and enzalutamide resistance. *Cancer Research* 2020;80(13):2927-39.

He L-X, Abdolmaleky HM, Yin S, Wang Y, Zhou J-R. Dietary fermented soy extract and oligo-lactic acid alleviate chronic kidney disease in mice via inhibition of inflammation and modulation of gut microbiota. *Nutrients* 2020;12:2376.

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

Scientific Advisor, BIDMC Glycomics Core

RESEARCH FOCUS

A key quest of my research has been to understand the factors regulating cellular interactions and cell signaling in immunology, cancer and development, with an emphasis on the structure and function of glycoconjugates. This has led to major discoveries in molecular mechanisms of leukocyte trafficking in inflammation and homing, and the roles of glycoproteins in autoimmunity, neurobiology, and infectious diseases, as well as fundamental genetic regulation of protein glycosylation in normal biological processes and disease states. We also develop technologies to explore 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 associated with the National Center for Functional Glycomics, headquartered in our lab. In addition, my lab has been instrumental as a training site for educating researchers in the field of glycoscience.

My laboratory has established the identities and specificities of many glycosyltransferases that regulate protein glycosylation and glycan-binding proteins, including novel antibodies to glycan antigens. 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, including glycan microarrays from natural tissues. We also use a novel sea lamprey system for developing unique antibodies that target glycan structures found on glycoconjugates or specific cells and tissues. These antibodies, termed VLRs, are instrumental in our work to define the human glycome. We are also developing semi-synthetic methods for making glycoconjugates and for isolating, characterizing, and derivatizing glycans, which are revolutionary and growing at a rapid pace.

I currently hold 32 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 web-based tools 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 and in understanding and characterizing the human glycome.

RESEARCH GROUP

Rajindra Aryal, PhD
 Kelly Baker, BS
 Jordan Broekhuis, MD
 Gabrielle E. Dombek, MD
 Jane Cheng, MD
 Sandra Cummings, BS
 Sonia Donskaya, BS
 Deniz Eris, PhD
 Chao Gao, PhD
 Jamie Heimburg-Molinaro, PhD
 Nan Jia, PhD
 Sylvain Lehoux, PhD
 Yasuyuki Matsumoto, PhD
 Tanya McKittrick, PhD
 Alyssa McQuillan, BS
 Robert Mealer, MD, PhD
 Akul Mehta, PhD
 Nandini Mondal, PhD
 Maxence Noel, PhD
 Kristine Ring
 Steven Siegel, MD, PhD
 Kathrin Stavenhagen, PhD
 Cecilia Voelcker, MS
 Mohui Wei, PhD
 Junwei Zeng, PhD

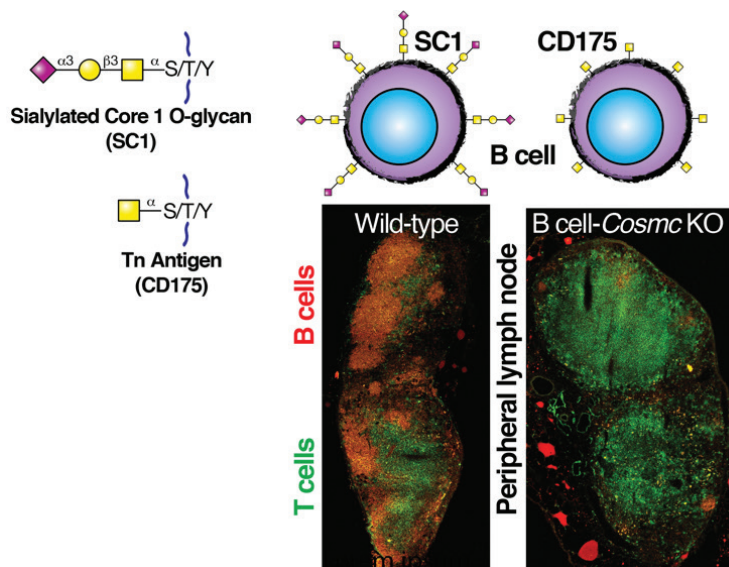


FIGURE 1: Lymphocyte homing to lymph nodes requires sialylated core 1 O-glycans (SC1) on surface glycoproteins, regulated by the *Cosmc* gene. Image shows murine B and T cells in lymph nodes in wild type versus B cell *Cosmc*-null animals. Loss of B cell *Cosmc* function leads to expression of CD175 and loss of B cell homing.

ACCOMPLISHMENTS 2019-2020

- Director, National Center for Functional Glycomics (NCFG), 2015–Present
- Scientific Director, Feihe Nutrition Laboratory, 2018–Present
- Editorial Board of *Nature Scientific Reports*, 2019–Present
- Editorial Board of *Biomolecules*, 2018–Present
- Editorial Board of *Molecular and Cellular Proteomics*, 2011–Present
- Editorial Board of *Glycobiology*, 1996–Present
- IGO Award 2019 from the International Glycoconjugate Organization (IGO) for exceptional contributions to the field of glycobiology, Milan, Italy 2019
- Co-Organizer and Co-Director of the Human Glycome Project, 2018–Present
- Director, Harvard Medical School Center for Glycoscience, 2017–Present
- Symposium at Boston University School of Medicine; Boston, MA
- Organizer and Session Chair, Satellite Symposium-Tools in Glycoscience, Society for Glycobiology Annual Meeting; Phoenix, AZ
- Invited Lecture, Symposium on “Spinoza Award Meets Glyco-Science and its Medical Implications,” Amsterdam University Medical Center, Amsterdam
- Invited Speaker, Albert Einstein College of Medicine; New York, NY
- Keynote Speaker, 11th Annual SBP Rare Disease Day Symposium; San Diego, CA
- Co-Organizer and Speaker, GlycoT 2020, 12th International Symposium on Glycosyltransferases; Boston, MA
- Invited Speaker, 2020 New England Glycochemistry Meeting; Boston, MA
- Invited Speaker and Participant, National Cancer Institute-Sponsored Workshop on “Glycans, Microbes & Cancer”
- Invited Lecture, Department of Translational Dental Medicine, Henry M. Goldman School of Dental Medicine at Boston University; Boston, MA

Invited Presentations

- Medical Grand Rounds, BIDMC, Harvard Medical School; Boston, MA

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,” which includes regular seminars with the supported fellows.

I have participated in training numerous BIDMC and HMS MD Research Fellows. Dr. Katie Stackhouse trained in my group for several years working on glycan expression in pancreatic cancer before moving on to a position at the Cleveland Clinic. Dr. Gabrielle Dombek, Dr. Jane Cheng, and Dr. Jordan Broekhuis are current fellows in my group working on colon cancer, breast cancer,

pancreatic cancer, thyroid cancer, and the involvement of glycans in disease. Dr. Robbie Mealer, who is an Instructor in Psychiatry at MGH and Harvard Medical School, and Staff Psychiatrist at McLean Hospital, is also training in our laboratory, studying brain glycosylation and the role in diseases such as schizophrenia. Dr. Steven Siegel is a K12 fellow working in our lab through a collaboration with Boston Children's Hospital. He is exploring the intestinal glycome and its interactions with the microbiome. I also train postdoctoral fellows in multiple research areas. Additionally, our centers offer training to investigators outside of our laboratory in order to teach glycobiology techniques and fundamentals to other laboratories throughout Harvard Medical School and the Boston area.

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

Protein-Glycan Interaction Resource at the National Center for Functional Glycomics, National and Regional Resource Center. NIH/NIGMS, 2020–2025; PI: Richard D. Cummings, PhD

Human Milk Glycan and Immunity Research. Abbott Laboratories, 2015–2020; PI: Richard D. Cummings, PhD

Integrating Microbial Glycan Arrays with Genomic Sequences to Study Host Microbe Interactions. NIH/NCI, 2019–2021; Co-PI: Richard D. Cummings, PhD

SELECTED PUBLICATIONS

Zeng J, Eljalby M, Aryal RP, Lehoux S, Stavenhagen K, Kudelka MR, Wang Y, Wang J, Ju T, von Andrian UH, Cummings RD. *Cosmc* controls B cell homing. *Nat Commun* 2020;11(1):3990.

Mehta AY, Veeraiah RKH, Dutta S, Goth CK, Hanes MS, Gao C, Stavenhagen K, Kardish R, Matsumoto Y, Heimbürg-Molinaro J, Boyce M, Pohl NLB, Cummings RD. Parallel Glyco-SPOT synthesis of glycopeptide libraries. *Cell Chem Biol* 2020;27(9):1207-1219.e9.

Luetscher RND, McKittrick TR, Gao C, Mehta AY, McQuillan AM, Kardish R, Boligan KF, Song X, Lu L, Heimbürg-Molinaro J, von Gunten S, Alter G, Cummings RD. Unique repertoire of anti-carbohydrate antibodies in individual human serum. *Sci Rep* 2020;10(1):15436.

Cervoni GE, Cheng JJ, Stackhouse KA, Heimbürg-Molinaro J, Cummings RD. O-glycan recognition and function in mice and human cancers. *Biochem J* 2020;477(8):1541-1564.

Jia N, Byrd-Leotis L, Matsumoto Y, Gao C, Wein AN, Lobby JL, Kohlmeier JE, Steinhauer DA, Cummings RD. The human lung glycome reveals novel glycan ligands for influenza A Virus. *Sci Rep* 2020;24;10(1):5320.

McKittrick TR, Goth CK, Rosenberg CS, Nakahara H, Heimbürg-Molinaro J, McQuillan AM, Falco R, Rivers NJ, Herrin BR, Cooper MD, Cummings RD. Development of smart anti-glycan reagents using immunized lampreys. *Commun Biol* 2020;3(1):91.



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 (collaborator: Dr. J. Ashot Kozak, Wright State University), as well as the arylhydrocarbon receptor (AhR) and the PSGL-1 mimetics (collaborator: Dr. Elliot Chaikof, BIDMC).

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*. Our current focus is to optimize the kinetics of the channel-blocker interactions, which might provide insights for defining their mechanism of action and generating improved pharmacological tool molecules.

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 (published in *Science Advances*).

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 we have recently shown inhibit tumor growth in multiple mouse models, including prostate, lung, and colon cancer.

ACCOMPLISHMENTS 2019-2020

One of our anticancer projects entered into a licensing option agreement with an emerging biotech company, which might lead to its clinical development as a first-in-class anticancer drug for patients who do not respond to existing anticancer therapies.

I reviewed a grant proposal for the Auckland Medical Research Foundation (New Zealand).

I served as a reviewer for journals including the *European Journal of Medicinal Chemistry* and *Journal of Clinical Pharmacology*.

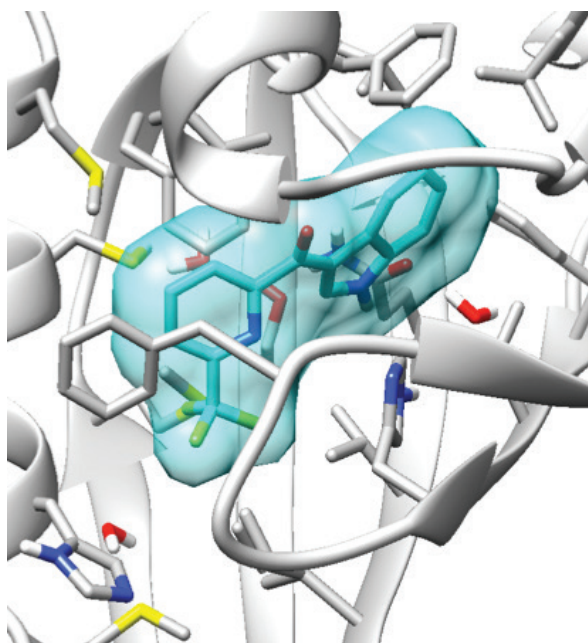
TEACHING, TRAINING, AND EDUCATION

I am committed to the training of next-generation scientists who are passionate about translational biomedical research. In the spring of 2020, I offered a virtual ten-lecture educational series in drug discovery and drug development to research fellows. 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 these talented fellows and motivated to transform the center to become a platform of excellence for training and biomedical innovation.

SELECTED RESEARCH SUPPORT

A PSGL-1 Glycopeptide Mimetic for Treatment of Metabolic Syndrome. NIH, 2016-2020; Co-Investigator: Lijun Sun, PhD (PI: Elliot Chaikof, MD, PhD)

Selectin Inhibitors for Prevention of Cancer-Associated Venous Thromboembolism. Blavatnik Therapeutics Challenge Award/HMS, 2020-2022; Co-PI: Lijun Sun, PhD (PI: Elliot Chaikof, MD, PhD)



◀ **FIGURE 1:** Molecular simulation reveals the binding interactions of the arylhydrocarbon receptor (AHR) and a novel selective AHR modulator.

SELECTED PUBLICATIONS

Tellechea A, Bai S, Dangwal S, Theocharidis 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* 2020;140(4):901-11.

Chen J, Haller CA, Jernigan FE, Koerner SK, Wong DJ, Wang Y, Cheong JE, Kosaraju R, Kwan J, Park DD, Thomas B, Bhasin S, De La Rosa RC, Premji AM, Li 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. *Science Advances* 2020;6:eaay8230.

Sun L. Advances in the discovery and development of selective heme-displacing IDO1 inhibitors. *Expert Opin Drug Discov* 2020;15(10):1223-1232.



Jeffrey Arle, MD, PhD

Associate Professor of Neurosurgery

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.

Normally, our work would have been presented at several national and international meetings. This expectation was, of course, quite severely constricted by the COVID-19 pandemic and instead, I gave several webinars or moderated virtual meetings that would have been held in Orlando, Miami, Barcelona, Montreal, and Mumbai.

In recent efforts, we have further developed and refined our hypothesis on how high-frequency and other waveforms in 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. In addition, we have taken on a new project examining more theoretical aspects of neural modeling, and also analysis of health care diagnosis and treatment with an eye toward how artificial intelligence methods might contribute to advancing the field.

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.

ACCOMPLISHMENTS 2019-2020

Organizational and Academic Work

- Continued as Co-chair of the Research and Scientific Policy Committee for the International Neuromodulation Society
- Appointed board member in Artificial Intelligence in IOM for the International Society of Intraoperative Neurophysiology
- Continued as a member of the North American Neuromodulation Society Policy and Advocacy Committee
- Continued as a member of the Epilepsy Foundation of New England Patient Advisory Board
- Continued as Associate Editor of *Neurosurgery* for the Stereotactic and Functional section and selected as an Associate Editor for the Pain section
- Appointed Section Editor for the Brain Section of *Neuromodulation*
- Became a member of the Institute of Neuromodulation and the Neuromodulation Foundation

Invited Presentations and Meetings

- Troubleshooting and Assessment in Spinal Cord Stimulation. International Neuromodulation Society meeting
- Moderator, Section on SCS, International Neuromodulation Society meeting
- Mechanisms of Action and Waveforms in SCS. International Neuromodulation Society meeting
- Effects of Neuromodulation on Glia, North American Neuromodulation Society meeting
- Moderator, Glia and their Role in Neuropathic Pain. North American Neuromodulation Society meeting
- VariLift as a Better Solution for Non-Contiguous and Adjacent Segment Anterior Cervical Fusion. Wenzel Spine Webinar
- Robustness in Neural Circuitry-Relationship to Neural Modeling, IEEE meeting

SELECTED RESEARCH SUPPORT

The Sydney Family Foundation, 2005-present

Abbott Labs, Inc.

CRPS, Pty

SELECTED PUBLICATIONS

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 Med* 2020;21(7):1415-1420.

Deer TR, Grider JS, Lamer TS, Pope JE, Falowski S, Hunter CW, Provenzano DA, Slavin KV, Russo M, Carayannopoulos A, Shah JM, Harned ME, Hagedorn JM, Bolash RB, Arle JE, Kapural L, Amirdelfan K, Jain S, Liem L, Carlson JD, Malinowski MN, Bendel M, Yang A, Aiyer R, Valimahomed A, Antony A, Craig J, Fishman MA, Al-Kaisy AA, Christelis N, Rosenquist RW, Levy RM, Mekhail N. A systematic literature review of spine neurostimulation therapies for the treatment of pain. *Pain Med* 2020;21(7):1421-1432.

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.

Schlesinger S, Krugman K, Abbott D, Arle J. Thirty-day outcomes from standalone minimally-invasive surgery-transforaminal lumbar interbody fusion patients in an ambulatory surgery center vs. hospital setting. *Cureus* 2020;12(9).

Arle JE, Mei, LZ. Robustness in neural circuits, *Brain* 2019; in preparation. (Also as a chapter in *Brain and Human Body Modeling*, Makarov SN, Noetscher GM, Nummenmaa A, editors.)

Arle JE, editor (and author of 12 chapters). *The Neuromodulation Casebook*, Elsevier, Academic Press, London, 2020.

Arle JE, Shils JL, editors. *Essential Neuromodulation*, 2nd ed. Elsevier, Academic Press, London, 2021; in press.

Buhl LK, Bastos AB, Pollard RJ, Arle JE, Thomas GP, Song Y, Boone D. Neurophysiologic monitoring for spine surgery: A practical guide from past to present. *J Intensive Care Med* 2020;Sep 28 (Epub ahead of print).

Carlson KW, Shils JL, Patel S, Mei LZ, Arle JE. Computational modeling of deep brain stimulation for Parkinson's disease: A critical review. *OBM Neurobiology* 2021; in review.

Arle JE, Carlson KW, Mei LZ. Computational investigation of complexity and robustness in neural circuits. *J Theor Biol* 2021; in review.



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 diversion technology With one of the largest experiences with flow diverter technology in the world, we have added substantially to the understanding of the safety and efficacy of these devices. We have initiated prospective studies looking at symptomatic improvement with the use of flow diverters, and conducted numerous studies aimed at better dissecting specific aneurysm characteristics and how they would impact treatment outcomes. We have also collaborated with other centers to investigate the utility of flow diversion for the treatment of particular subgroups of aneurysms that usually pose treatment challenges for conventional treatment methods.

Cavernous malformations Cavernous malformation are common, yet there is a paucity of data on their natural history or treatment options. We have gathered the largest published cohort of cavernous malformations to date, and have investigated the utility of antiplatelets and statins medication 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 have published the largest series in the literature regarding its safety and efficacy, and are investigating this technique in the elderly population and defining the populations that will most benefit from it.

Subarachnoid hemorrhage We conduct multiple projects covering many aspects of aneurysmal subarachnoid hemorrhage (aSAH). Utilizing national databases, we showed that treating unruptured aneurysms leads to a reduction in the risk of aSAH presentation and discovered that treated migraine appears protective for SAH. Our research has identified the importance of maintaining a minimal blood pressure to avoid poor outcomes in SAH. We also initiated imaging studies to determine new biomarkers of SAH complications.

Artificial intelligence We have partnered with international AI firms to design new AI-powered algorithms to identify aneurysms with non-invasive imaging and hydrocephalus in neurosurgical patients.

Microsimulations Using decision analytic models and Monte Carlo microsimulation studies, we are investigating different cost-effectiveness analysis projects to study the benefits of screening for intracranial aneurysms in different subpopulations with high-risk factors and the optimal screening intervals in these populations. These include female smokers and patients with genetic-predisposing diseases. We are also studying the cost effectiveness of multiple follow-up strategies after flow diversion treatment of intracranial aneurysm.

Screening for intracranial aneurysms Our group led an institutional review of the prevalence of intracranial aneurysms in women between ages 30-60 who smoke and found that 19.1% have incidental findings of aneurysms, compared to 1.9% in non-smoker counterparts. We led a multi-institutional case control study to validate our findings, confirming the high rate of occurrence of intracranial aneurysms in women who smoke. Our team subsequently performed a decision analytic study documenting the cost effectiveness of screening women who smoke for intracranial aneurysms.

RESEARCH GROUP

Alejandro Enriquez-Marulanda, MD

Santiago Gomez, MD

Dominic Harris, MD

Mir Khorasanizadeh, MD

Franciele Kipper, PhD

Mohamed Salem, MD, MPH

Mira Salih, MD

Basic Laboratory Science

We have been exploring the hypothesis that some 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 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), which 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 treatments to facilitate and amplify BBB permeability. We have also been studying the underlying molecular alteration 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.

ACCOMPLISHMENTS 2019-2020

Invited Presentations

- Cerebral Aneurysms: Current Approaches. Keynote Speaker, Neurological Emergencies, HMS Continuing Education virtual course, Boston, MA (Dr. Ogilvy)
- Unruptured Aneurysms. Guest Professor, Mayo Neurosurgery and Neuroscience Virtual Grand Rounds, Mayo Clinic School of Continuous Professional Development, Scottsdale, AZ (Dr. Ogilvy)
- Unruptured Intracranial Aneurysms: Current Perspective. Visiting Professor, Congress of Neurological Surgeons webinar (Dr. Ogilvy)
- Current Perspectives on Unruptured Intracranial Aneurysms. 1st International Virtual Neurosurgical Conference, Bogota, Columbia (Dr. Ogilvy)
- Current Outcomes of Combined Endovascular and Operative Management of Unruptured Intracranial Aneurysms. World Federation of Neurosurgical Societies Virtual Symposium-Global Neurosurgery (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

Salem MM, Maragkos GA, Gomez-Paz S, Ascanio LC, Ngo L, Ogilvy CS, Thomas AJ, Moore JM. Trends of Ruptured and Unruptured Aneurysms Treatment in the US in Post-ISAT Era: A National Inpatient Sample Analysis. Society of Neurointerventional Surgery (oral presentation)

Salem M, Sweid A, Kuhn A, Dmytriw A, Gomez-Paz S, Maragkos G, Waqas M, Parra-Farinas C, Salehani A, Adeeb N, Brouwer P, Cognard C, Renieri L, Kan P, Limbucci N, Pereira V, Harrigan M, Puri A, Levy E, Moore J, Ogilvy C, Marotta T, Jabbour P, Thomas A. Repeat Flow Diversion for Previously Failed Flow Diversion in a Multicenter Cohort. Congress of Neurological Surgeons (oral presentation)

Maragkos GA, Ascanio LC, Salem MM, Gopakumar S, Gomez-Paz S, Enriquez-Marulanda A, Jain A, Schirmer CM, Foreman PM, Griessenauer CJ, Kan P, Ogilvy CS, Thomas AJ. Predictive Factors of Incomplete Aneurysm Occlusion after Endovascular Treatment with the Pipeline Embolization Device. AANS 2019, San Diego, CA (oral presentation)

SELECTED PUBLICATIONS

Ogilvy CS, Gomez-Paz S, Kicielski KP, et al. Women with first-hand tobacco smoke exposure have a higher likelihood of having an unruptured intracranial aneurysm than nonsmokers: A nested case-control study. *Neurosurgery* 2020;June 10 (Epub ahead of print).

Ogilvy CS, Gomez-Paz S, Kicielski KP, Salem MM, Akamatsu Y, Waqas M, Rai HH, Catapano JS, Muram S, Elghareeb M, Siddiqui AH, Levy EI, Lawton MT, Mitha AP, Hoh BL, Polifka A, Fox WC, Moore JM, Thomas AJ. Cigarette smoking and risk of intracranial aneurysms in middle-aged women. *J Neurol Neurosurg Psychiatry* 2020;91(9):985-990.

Gomez-Paz S, Salem MM, Maragkos GA, Ascanio LC, Enriquez-Marulanda A, Lee M, et al. Role of aspirin and statin therapy in patients with cerebral cavernous malformations. *J Clin Neurosci* 2020;78:246-51.

Kan P, Maragkos GA, Srivatsan A, et al. Middle meningeal artery embolization for chronic subdural hematoma: A multi-center experience of 154 consecutive embolizations. *Neurosurgery* 2021;88(2):268-277.

Foreman PM, Salem MM, Griessenauer CJ, Dmytriw AA, Parra-Farinas C, Nicholson P, Limbucci N, Kuhn AL, Puri AS, Renieri L, Nappini S, Kicielski KP, Bugarini A, Pereira VM, Marotta TR, Schirmer CM, Ogilvy CS, Thomas AJ. Flow diversion for treatment of partially thrombosed aneurysms: A multicenter cohort. *World Neurosurg* 2020;135:e164-e173.

Ascanio LC, Enriquez-Marulanda A, Maragkos GA, Salem MM, Alturki AY, Ravindran K, Fehnel CR, Hanafy K, Ogilvy CS, Thomas AJ, Moore JM. Effect of blood pressure variability during the acute period of subarachnoid hemorrhage on functional outcomes. *Neurosurgery* 2020;87(3):E430-1.

Salem MM, Ravindran K, Enriquez-Marulanda A, Ascanio LC, Jordan N, Gomez-Paz S, et al. Pipeline embolization device versus stent-assisted coiling for intracranial aneurysm treatment: A retrospective propensity score-matched study. *Neurosurgery* 2020;87(3):516-22.

Maragkos GA, Cordell S, Gomez-Paz S, Dodge LE, Salem MM, Ascanio LC, et al. Flow diversion endovascular treatment improves headaches in patients with unruptured intracranial aneurysms. *World Neurosurg* 2020;140:e140-e7.

Joyce E, Bounajem MT, Scoville J, Thomas AJ, Ogilvy CS, Riina HA, Tanweer O, Levy E I, Spiotta AM, Gross BA, Jankowitz BT, Cawley CM, Khalessi AA, Pandey AS, Ringer AJ, Hanel R, Ortiz RA, Langer D, Levitt MR, Binning M, Taussky P, Kan P, Grandhi R. Middle meningeal artery embolization treatment of nonacute subdural hematomas in the elderly: A multi-institutional experience of 151 cases. *Neurosurg Focus* 2020;49(4):E5.

Salem MM, Maragkos GA, Gomez-Paz S, et al. Trends of ruptured and unruptured aneurysms treatment in the US in post-ISAT era: A national inpatient sample analysis. *J Am Heart Assoc* 2020; in press.

Vergara-Garcia D, Gomez-Paz S, Robinson TM, Moore J, Ogilvy CS, Thomas AJ. Transition to radial approach for neurovascular procedures is safe and convenient: Characterization of a learning experience. *Oper Neurosurg* 2020;19(5):489-494.

A complete list of publications begins on page 15.



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%.

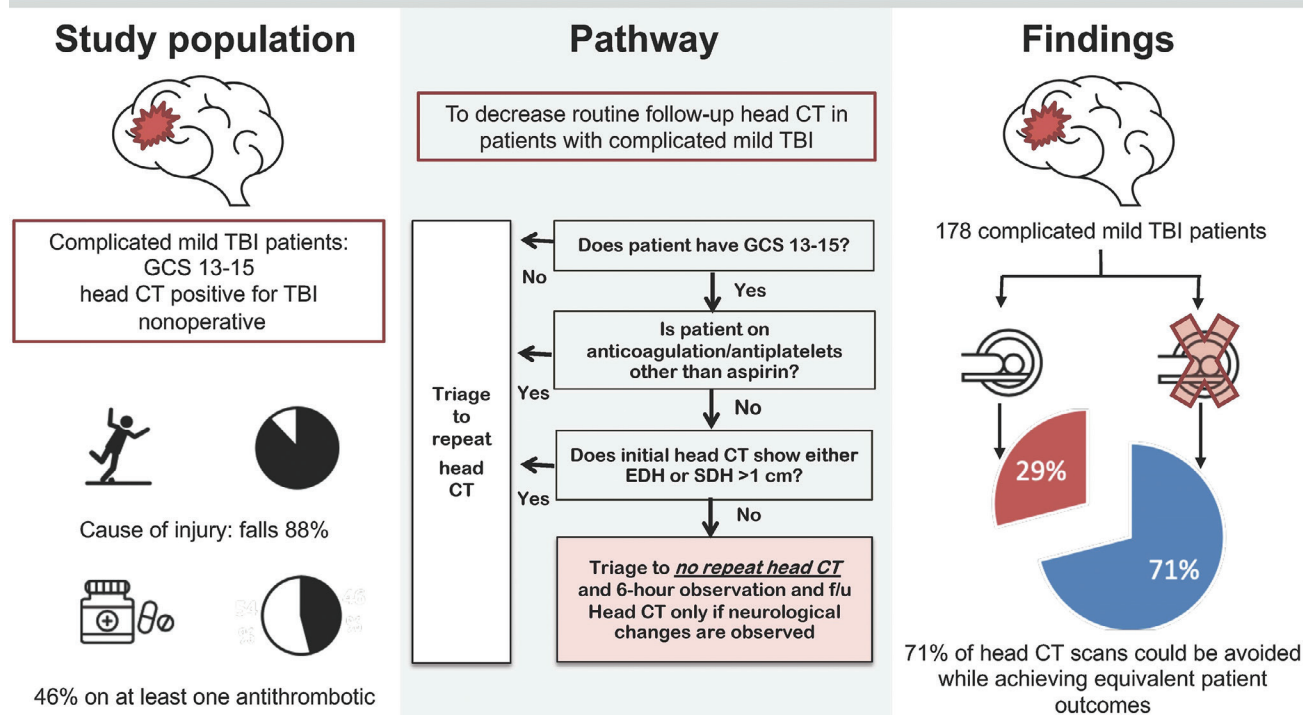
As our society is aging, increasing numbers of elderly people present with TBI. While in this patient population goal-concordant care is very important, it has been shown that few surgeons take the patient's and family's care goals into account. One of my other areas of research is to understand whether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

RESEARCH GROUP

Mary Buss, MD, MPH
Jonathan Edlow, MD
Charles Parsons, MD
Carlo Rosen, MD

▼ FIGURE: Pathway-based reduction of repeat head CT for patients with complicated mild traumatic brain injury: Implementation and outcomes. Published in *Neurosurgery*, January 2021. Martina Stippler, et al.

Pathway-based reduction of repeat head CT for patients with complicated mild traumatic brain injury: implementation and outcomes



ACCOMPLISHMENTS 2019-2020

- Completed Rabkin Fellowship in Medical Education for 2019-2020
- Became a member of the Harvard Medical Faculty Physicians (HMFP) Wellness Committee
- Continued to serve on the Board (to which I was elected in 2019) of "Think First," a national nonprofit injury-prevention organization
- Named Neurotrauma Section Editor of *Neurosurgery Open*
- Advanced to Chair of Women in Neurosurgery (WINS), Joint Section of the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS)
- Continued as an *ex officio* member of the CNS Executive Committee
- Co-led a virtual cocktail hour to celebrate 30 years of Women in Neurosurgery (WINS)
- Served on the Senior Neurosurgery Surgeons (SNS) Curriculum Subcommittee
- Served on the Planning Committee for the Women Neurosurgeons symposium series, a monthly virtual series for female neurosurgeons internationally
- Became a member of the BIDMC GME Annual Program Review Committee

TEACHING, TRAINING, AND EDUCATION

- Transitioned national neurosurgery bootcamp to a virtual course
- Initiated a Neurosurgery Town Hall and Wellness and Resilience for the Congress of Neurological Surgeons
- Led Communication Care workshop for Surgery, Critical Care, and Emergency Medicine residents
- Established virtual BIDMC Neurosurgery sub-internships
- Presented neurosurgery lecture to Harvard Medical School General Surgery Clerkship students

ABSTRACTS, POSTERS, AND EXHIBITS

Stippler M, Keith S, Parsons C, Singleton J et al. Pathway-based Reduction of Repeat Head CT for Patients with Complicated Mild Traumatic Brain Injury: Implementation and Outcomes. Annual Congress of Neurological Surgeons (abstract)

Penumaka A, Stippler M. Online Education Platform for Synchronous and Asynchronous Neurosurgery Resident Didactics. Annual Congress of Neurological Surgeons meeting (abstract)

SELECTED PUBLICATIONS

Feng R, Hoffman SE, Wagner K, Ullman JS, Stippler M, Germano I. Women neurosurgeons in academic and other leadership positions in the United States. *World Neurosurg* 2020;Dec 21 (Epub ahead of print).

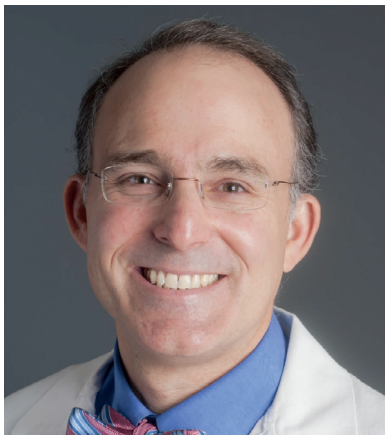
Singleton JM, Bilello LA, Greige T, Balaji L, Tibbles CD, Edlow JA, Rosen CL, Stippler M. Outcomes of a novel ED observation pathway for mild traumatic brain injury and associated intracranial hemorrhage. *Am J Emerg Med* 2020;Sep 10 (Epub ahead of print).

Maragkos GA, Nelton EB, Richter S, Stippler M. Low risk of traumatic intracranial hematoma expansion with factor Xa inhibitors without andexanet reversal. *World Neurosurg* 2020;Oct;142:e95-e100.

Corley J, Kim E, Philips CA, Stippler M, Parr AM, Sweet J, Rosseau G. One hundred years of neurosurgery: Contributions of American women. *J Neurosurg* 2020;14:1-6.

Jorge G. Arroyo, MD, MPH

Associate Professor of Ophthalmology



RESEARCH GROUP

Efren Gonzalez, MD
 Mark Kuperwaser, MD
 Colin Lemire
 Mortada Najem
 Elise Pham
 Shashvat Purohit
 Abigail Ralph
 Soobin Song
 Justin Wang

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 have presented 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: <https://www.youtube.com/watch?v=aTeMDZvNDBY>.

Less-Invasive Treatment Options

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. Recently, we have been studying the use of normobaric hyperoxia in patients with diabetic retinopathy, macular degeneration, and retinal vein occlusions. Our results from short-term three-hour trials show that hyperoxia improves vision and reduces macular edema in these patients. Currently, we are working on expanding our use of normobaric hyperoxia to longer-duration nocturnal trials in these patients. We have also been interested in how supplemental oxygen can improve outcomes in patients with retinal detachments awaiting surgery. In these cases, the photoreceptors are separated from their blood supply and can degenerate due to the hypoxic conditions. We are excited that this treatment has the potential to offer patients an inexpensive and non-invasive option to improve or preserve their vision.

ACCOMPLISHMENTS 2019-2020

Presentations

Diabetic Macular Edema: When to Treat and When to Observe. New England Ophthalmologic Society

Leadership

I am the Director of Retinal Services at BIDMC. Among my other leadership roles are serving as President 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 Retinal Service and clinical research team, including BIDMC-Lahey Hospital surgical fellows Drs. Malkit Singh and Noreen Shaikh, as well as BIDMC-Joslin Diabetes Center medical retina fellows Drs. Abdu Rageh and Cris Jacoba. We have also been joined by six Boston University master's students conducting their clinical research theses with our group. Colin Lemire is our clinical research assistant.

ABSTRACTS, POSTERS, AND EXHIBITS

Yamada K, Koch R, Atreay P, Swartz S, Maeno T, Sotozono C, Seto B, Arroyo JG. Human Laser Speckle Retinal Blood Flow Changes Associate with Exposure to Varying Concentrations of O₂ and CO₂. Association for Research in Vision and Ophthalmology (abstract)

Singh MK, Seto B, Zeng K, Koch R, Yamada K, Shahi N, Kuperwaser M, Arroyo JG. Combined Pars Plana Vitrectomy (PPV)/Posterior Endoscopic Cyclophotocoagulation (ECP) Versus Combined Phacoemulsification with Intraocular Lens Placement (CEIOL)/Anterior ECP in Patients with Glaucomatous Comorbidities. Association for Research in Vision and Ophthalmology (abstract)

Seto B, Yamada K, Koch R, Swartz S, Atreay P, Hazra N, Arroyo JG. Retinal Vascular Blood Flow in Human Subjects with Central or Branch Retinal Vein Occlusions. Association for Research in Vision and Ophthalmology (abstract)

SELECTED PUBLICATIONS

Diaz JD, Arroyo JG. Modern clinical applications of endoscopic pars plana vitrectomy in vitreoretinal surgery. *Int Ophthalmol Clin* 2020;60:25-33.

Yamada K, Maeno T, Kusaka S, Arroyo JG, Yamada M. Recalcitrant macular hole closure by autologous retinal transplant using the peripheral retina. *Clin Ophthalmol* 2020;14:2301-2306.

Yu G, Seto BK, Yamada K, Zeng K, Arroyo JG. Combined pneumatic and enzymatic vitreolysis for severe cases of vitreomacular traction. *Retin Cases Brief Rep* 2020; in press.

Nurhan Torun, MD

Chief of Ophthalmology

Assistant Professor of Ophthalmology



RESEARCH GROUP

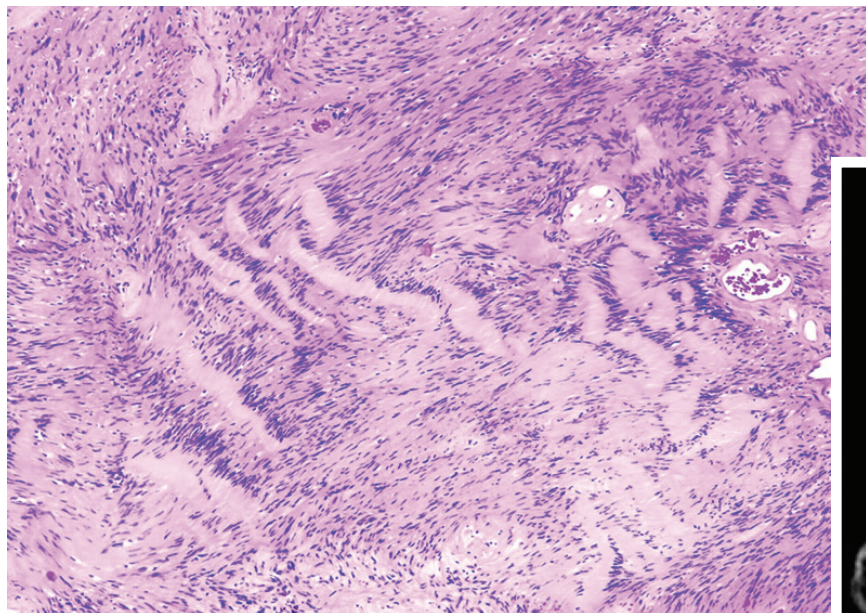
Marc A. Bouffard, MD

Konstantinos Douglas, MD, DVM, MBA

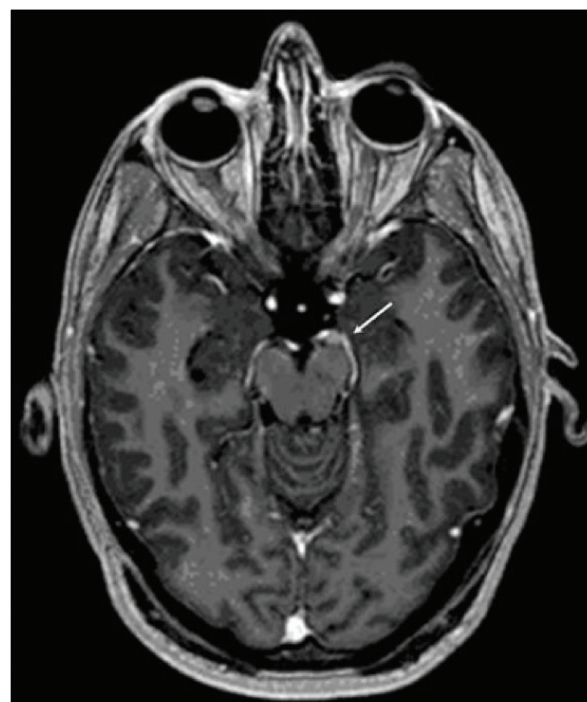
Vivian Paraskevi Douglas, MD, DVM, MBA

Edsel Ing, MD

▼ **FIGURE 1:** Clear signs of palisading and the formation of Varocay bodies can be seen in the highly cellular Antoni A region in a schwannoma biopsy (Wippold et al., 2006)



► **FIGURE 2:** T1 weighted axial MRI with gadolinium of a 46-year-old woman seen at Tufts, showing a 5 mm x 5 mm x 6 mm homogenously enhancing mass along the left CN 3 in the cistern.



RESEARCH FOCUS

My research in 2020 focused on oculomotor nerve schwannomas (ONS) originating from proliferating nerve sheath cells (Figure 1). These are rare, benign CNS tumors, with a limited number of reports (fewer than 100 cases) in the literature. Unfortunately, very few physicians have sufficient experience in treating non-vestibular schwannomas. The fact that their symptomatology can vary widely, depending on location and size of the lesion, poses an additional challenge. Given the rarity of such non-vestibular, intracranial schwannomas, many physicians may not even consider these lesions when patients present with diplopia. Management options include surgical excision, stereotactically delivered radiation therapy, and symptomatic treatment (strabismus surgery or prisms). There is currently no established management guideline that aids providers in deciding on surgical versus non-surgical management. We, therefore, set out to review the literature on the topic to identify indications for treatment as well as outcome measures (e.g., local control rates and survival rates as well as complication rates) that have been reported as associated with the various treatment modalities. Our collaboration with Tufts Medical Center also yielded four previously unreported cases of ONS that were included in this study (Figure 2). The cohort was divided into one group that had been managed with open microsurgery and a second group that was managed without surgical intervention but with stereotactically delivered radiation therapy (SRS). The data analysis is underway. Our goal is to develop an algorithm for evaluation and treatment of ONS in order to establish consensus on how these tumors should be treated.

ACCOMPLISHMENTS 2019-2020

- I was invited to the 55th Turkish National Neurology Congress in November 2019 in Antalya, Turkey to deliver the following lectures:
 - What is New in Optic Neuritis?
 - Nystagmus and Other Ocular Oscillations ("Ask an Expert" session)
- I presented the following lectures in 2020:
 - A Matter of Simple Addition: A Young Woman with Abnormal Eye Movements, Longwood Medical Area Ophthalmology Conference
 - Giant Cell Arteritis: Ophthalmologists' Perspective, Rheumatology Grand Rounds, BIDMC
- I was selected for the BIDMC Academy Award in 2020
- I accepted invitations to give lectures at Weill Cornell Ophthalmology Grand Rounds, the New England Ophthalmological Society meeting, and the Neuroophthalmology Fall Festival in 2021
- Our division transitioned in September 2020 to Nextech, an ophthalmology-specific EHR, a major step away from paper charts
- We started seeing patients in our satellite office in Chestnut Hill, MA in December 2020

TEACHING, TRAINING, AND EDUCATION

I am involved in didactic and bedside teaching of residents and fellows. I developed a curriculum of 12 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 the BIDMC and Tufts University Combined Neuroradiology Fellowship by presenting two one-hour lectures on "Clinicoanatomical Correlation in Neuro-ophthalmology." I also delivered two lectures to Neuro-ophthalmology fellows and two lectures to Joslin fellows in 2020.

ABSTRACTS, POSTERS, AND EXHIBITS

Bouffard MA, Mallery R, Liao YJ, Torun N. Incipient Optic Neuritis. 45th Annual Meeting of the North American Neuroophthalmology Society; Las Vegas, NV (poster presentation)

Frank S, Bouffard M, Dawson R, Lim A, Torun N, Malik W. Quantitative Oculomotor Biomarkers for Huntington's Disease. American Academy of Neurology meeting, virtual (poster presentation)

Abbasi B, Bouffard MA, Torun N. Transient Monocular Vision Loss following Pipeline Embolization of ICA Aneurysms. 46th Annual Meeting of the North American Neuroophthalmology Society; Amelia Island, FL (poster presentation)

SELECTED PUBLICATIONS

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* 2020;55(1):87-92.

Ing E, Miller N, tenHove M, Torun N. Diplopia and giant cell arteritis. *J Neuroophthalmol* 2019;39(4):546-547.

Nguyen HV, Gilbert AL, Fortin E, Vodopivec I, Torun N, Chwalisz BK, Cestari DM, Rizzo JF. Elevated intracranial pressure associated with exogenous hormonal therapy used for gender transition. *J Neuroophthalmol* 2020; in press.

Ing EB, Xu Q, Salimi A, Torun N. Physician deaths from coronavirus (COVID-19) disease. *Occup Med (Lond)* 2020;70(5):370-4.

Ing E, Majdedi K, Hurwitz J, Nijhawan N, Oestreicher J, Torun N. Nomenclature: Thyroid-associated orbitopathy, Graves ophthalmopathy or thyroid eye disease? *Can J Ophthalmol* 2020; in press.

Douglas VP, Chiang HH, Douglas KAA, Van Zyl T, Torun N. A matter of simple addition: A young woman with abnormal eye movements. *Digit J Ophthalmol* 2021;2(1).



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.

The onset of the COVID-19 pandemic prompted me to apply prior research experience to the development of a simulated cough-generating device for the education of trainees on the risks of aerosol-generating procedures. This device was recognized in a national competition of the American Academy of Otolaryngology. I am also collaborating with Dr. David Edwards at the Harvard John A. Paulson School of Engineering and Applied Sciences on a study investigating the effects of inhaled calcium salts on the quantity of exhaled bioaerosols in healthy individuals.

ACCOMPLISHMENTS 2019-2020

- Awarded 2nd place in the American Academy of Otolaryngology–Head and Neck Surgery Annual SimTank Competition
- Appointed to the Planning Committee, 2021 Boston Head and Neck Cancer Symposium

TEACHING, TRAINING, AND EDUCATION

- Served as course faculty for the BIDMC Surgical Program in Innovation (SPIN)
- Established the Division of Otolaryngology/Head and Neck Cancer's Surgical Simulation Program
- Produced a surgical video lecture for Harvard Medical School's Mind, Brain, and Behavior course
- Developed a patient cough-simulation device in collaboration with the BIDMC Simulation and Skills Center

ABSTRACTS, POSTERS, AND EXHIBITS

Gomez ED, Ceremsak J, Leibowitz A, Jalisi S. A Novel Cough Simulation Device for Training of Risk-Mitigation Techniques during Aerosol Generating Procedures. American Academy of Otolaryngology–Head and Neck Surgery Annual Meeting, 2020 (oral presentation)

SELECTED PUBLICATIONS

Huang VW, Jones CB, Gomez ED. State of the art of virtual reality simulation in anesthesia. *Int Anesthesiol Clin* 2020;58(4):31-35.

Gosling AF, Bose S, Gomez E, Parikh M, Cook C, Sarge T, Shaefi S, Leibowitz A. Perioperative considerations for tracheostomies in the era of COVID-19. *Anesth Analg* 2020;131(2):378-386.

Ceremsak J, Miller LE, Gomez ED. A review of otolaryngology malpractice cases with associated court proceedings from 2010 to 2019. *Laryngoscope* 2020;Nov 4 (Epub ahead of print).

Gomez ED, Chang JC, Ceremsak JJ, Brody RM, Brant JA, Rassekh CH, Weinstein GS, Newman JG. Impact of lymph node yield on survival in surgically treated oropharyngeal squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2021;164(1):146-156.

Bur AM, Villwock MR, Nallani R, Gomez ED, Varvares MA, Villwock JA, Cannady SB, Wax MK. National database research in head and neck reconstructive surgery: A call for increased transparency and reproducibility. *Otolaryngol Head Neck Surg* 2020;Jul 7 (Epub ahead of print).

Thomas WW, Calcagno HE, Azzi J, Petrisor D, Cave T, Barber B, Miles B, Gomez ED, Cannady S, Bhadkamkar M, Hanasono MM, Wax MK. Incidence of inadequate perforators and salvage options for the anterior lateral thigh free flap. *Laryngoscope* 2020;130(2):343-346.



Scharukh Jalisi, MD, MA

Chief, Otolaryngology/Head and Neck Surgery

Program Director, BIDMC/Harvard Medical School Otolaryngology/Head and Neck Surgery Residency

Director, Head and Neck Surgical Oncology, BIDMC

RESEARCH FOCUS

Our clinical research is focused on outcomes in head and neck surgical oncology, with a particular emphasis on the geriatric patient and barriers to access to care. We are engaged in research using national databases, including Vizient, Nationwide inpatient sample, and the National Cancer Database. We are also working on establishing phase 3 trials for head and neck oncology trials. Our goal is to increase patient-centered outcomes research related to outcomes in head and neck cancer surgery.

RESEARCH GROUP

David Caradonna, MD, DMD

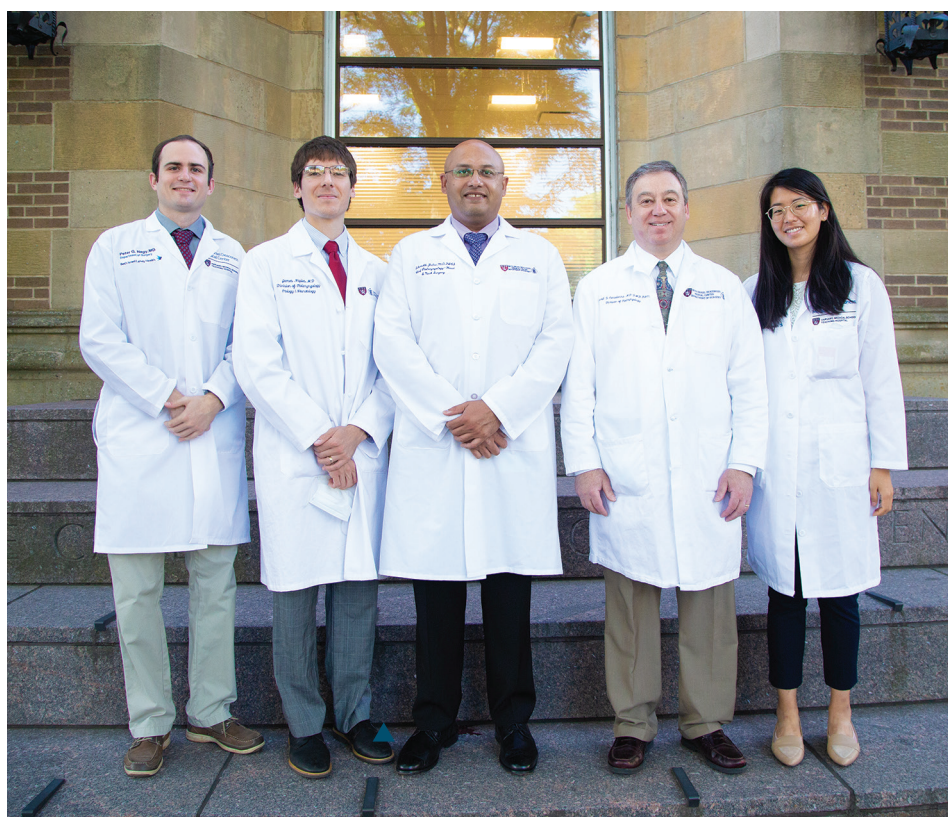
Kaashif Eazazuddin, DO

Ernest Gomez, MD, MTR

Pavan Mallur, MD

James Naples, MD

Stephanie Teng, MD



▲ The Otolaryngology/Head and Neck Surgery Residency at BIDMC/Harvard Medical School received ACGME approval in April 2020, admitting its inaugural class in June 2020. Pictured (from left) are: resident Dr. Peter Nagy, Associate Program Director Dr. James Naples, Program Director Dr. Scharukh Jalisi, Associate Program Director Dr. David Caradonna, and resident Dr. Victoria Huang. Residents in the five-year program have significant dedicated time to participate in research projects.

ACCOMPLISHMENTS 2019-2020

- Course Director: International Collaboration on Safety of ENT Surgeons during the COVID-19 Pandemic
- Course Director: Value-Based Head and Neck Oncologic Surgery in a Resource-Constrained Environment, American Academy of Otolaryngology/Head and Neck Surgery; New Orleans, LA
- Invited Lecture: Safety Protocols for ENT Surgery during the COVID-19 Pandemic. International Collaboration on Safety of ENT Surgeons during the COVID-19 Pandemic
- Invited Lecture: Airway Management in COVID-19 Patients, Saudi Arabia Society of Oral Maxillofacial Surgeons; Riyadh, Saudi Arabia

TEACHING, TRAINING, AND EDUCATION

- Established the BIDMC/Harvard Medical School Residency Program in Otolaryngology-Head and Neck Surgery
- Director, Fellowship in Head and Neck Surgical Oncology
- Core Curriculum in Resident Education: Otolaryngology/Head and Neck Surgery, BIDMC/HMS Program
- Outcomes in Head and Neck Surgical Oncology. Grand Rounds, Department of Otolaryngology/Head and Neck Surgery, Boston University School of Medicine; Boston, MA

SELECTED PUBLICATIONS

- Kim KN, Dyer MA, Qureshi MM, Shah NK, Grillone GA, Faden DL, Jalisi SM, Truong MT. Hypofractionated radiotherapy and surgery compared to standard radiotherapy in early glottic cancer. *Am J Otolaryngol* 2020;41(5):1025-44.
- Fischman V, Ivanovic V, Jalisi S. A bioresorbable fiducial for head and neck cancer. *Otolaryngol Head Neck Surg* 2020;163(3):554-556.
- Givi B, Moore MG, Bewley AF, Coffey CS, Cohen MA, Hessel AC, Jalisi S, Kang S, Newman JG, Puskas L, Shindo M, Shuman A, Thakkar P, Weed DT, Chalian A. Advanced head and neck surgery training during the COVID-19 pandemic. *Head Neck* 2020;42(7):1411-1417.
- Givi B, Schiff BA, Chinn SB, Clayburgh D, Iyer NG, Jalisi S, Moore MG, Nathan CA, Orloff LA, O'Neill JP, Parker N, Zender C, Morris LGT, Davies L. Safety recommendations for evaluation and surgery of the head and neck during the COVID-19 pandemic. *JAMA Otolaryngol Head Neck Surg* 2020;146(6):579-584.
- Patel SA, Qureshi MM, Dyer MA, Jalisi S, Grillone G, Truong MT. Comparing surgical and nonsurgical larynx-preserving treatments with total laryngectomy for locally advanced laryngeal cancer. *Cancer* 2019;125(19):3367-3377.
- Rubin SJ, Wu KY, Kirke DN, Ezzat WH, Truong MT, Salama AR, Jalisi S. Head and neck cancer complications in the geriatric population based on hospital case volume. *Ear Nose Throat J* 2021;100(2):NP62-NP68.
- Sulibhavi A, Rohlfing ML, Jalisi SM, McAneny DB, Doherty GM, Hollick MF, Noordzij JP. Vitamin D deficiency and its relationship to cancer stage in patients who underwent thyroidectomy for papillary thyroid carcinoma. *Am J Otolaryngol* 2019;40(4):536-541.
- Shah NK, Qureshi MM, Dyer MA, Patel SA, Kim K, Everett PC, Grillone GA, Jalisi SM, Truong MT. Optimal sequencing of chemoradiotherapy for locally advanced laryngeal cancer. *Laryngoscope* 2019;129(10):2313-2320.



James G. Naples, MD

Assistant Professor of Otolaryngology

RESEARCH FOCUS

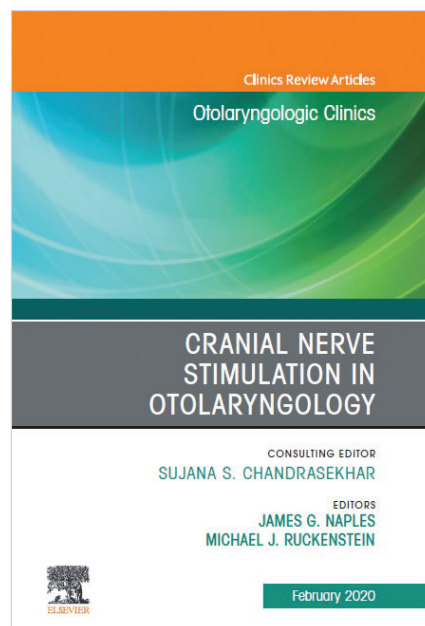
History of Otolaryngology

Some of my ongoing research involves historical research that aims to understand how medically historical concepts evolved into present day paradigms. I have multiple ongoing research projects looking into the role history played in our understanding of otologic disease. Most recently, I am working to evaluate how theories on sudden hearing loss evolved to create a standard treatment for the disorder today. In addition, I am looking into the historical role of speech-understanding tests as a tool that helped us develop current tests used to evaluate hearing.

Cochlear Implant and Cognition

One of my ongoing research efforts is to better understand the role of cognition and “brain function” in understanding outcomes following cochlear implant surgery for hearing loss. I am currently collaborating with research physicians at Ohio State University to determine if there are cognitive evaluations that perhaps offer insights to how well a patient understands speech after cochlear implant. In conjunction with some of my prior work, the goal of this research is to translate the concept of cognitive testing into the clinical setting as a tool for understanding hearing outcomes.

► James Naples, MD, and Michael Ruckenstein, MD, Penn Medicine, were guest editors of a 184-page, single-topic issue of *Otolaryngologic Clinics of North America* on “Cranial Nerve Stimulation in Otolaryngology.”



ACCOMPLISHMENTS 2019-2020

- Moderated panel at American Academy of Otolaryngology-Head and Neck Surgery National Meeting, 2020
- Selected to American Neurotology Society Young Members Committee

TEACHING, TRAINING, AND EDUCATION

- Member of the Otolaryngology and Neurotology Education Committee of the American Academy of Otolaryngology
- Member of History and Archives Committee of the American Academy of Otolaryngology
- Organized and developed curriculum for new Otolaryngology/Head and Neck Surgery Residency at BIDMC-Harvard Medical School
- Organized and developed BIDMC Advanced Clinical Elective in Otolaryngology for Harvard Medical School students

ABSTRACTS, POSTERS, AND EXHIBITS

Naples JG, Parham KP. Strong Correlation between Serum Prestin Level and ABR Thresholds 24 Hours after Cochlear Injury. American Academy of Otolaryngology-Head & Neck Surgery Annual Meeting, Boston, MA

SELECTED PUBLICATIONS

Iljazi A, Ashina H, Lipton RB, Chaudhry BA, Al-Khazali HM, Naples JG, Schytz HW, Cvetkovic VV, Burstein R, Ashina S. Vertigo and dizziness in migraine: A systematic review and meta-analysis. *Cephalgia* 2020;40(10):1095-1103.

Naples JG, Corr A, Tripathi S, Berman M, Brant JA, Ruckenstein MJ, Bosso JV. Endoscopic sinus surgery and aspirin desensitization (AD) improve otologic-specific SNOT-22 scores. *World J Otorhinolaryngol Head Neck Surg* 2020; in press.

Naples JG, Miller LE, Li D. A review of cochlear protein biomarkers as potential targets for specific drug delivery. *Drug Deliv Transl Res* 2020;10(2):368-79.

Naples J, Valdez TA. Letters to the Deaf: Present-day relevance of history's earliest social analysis of deafness. *Otolaryngol Head Neck Surg* 2020;162(3):319-21.

Naples JG, McCarty EB. Olfaction and smell identification tests: A novel test that may correlate with cochlear implant outcomes. *Med Hypotheses* 2020;135.

Kaufman AC, Naples JG, Bigelow DC, Eliades SJ, Brant JA, Kaufman HS, Ruckenstein MJ. Lateral wall electrodes increase the rate of post-activation non-auditory percepts. *Otol Neurotol* 2020;41(5): e575-9.

Naples JG, Ruckenstein MJ, Singh J, Cox BC, Li D. Intratympanic diltiazem-chitosan hydrogel as a novel otoprotectant against cisplatin-induced ototoxicity in a mouse model. *Otol Neurotol* 2020;41(1):115-22.

Naples JG, Brant JA, Ruckenstein MJ. Infections of the external ear. In: Flint PW, Francis HW, Haughey BH, et al, editors. *Cummings Otolaryngology-Head and Neck Surgery*, ed 7. Elsevier, 2021.

Naples JG, Brant JA, Ruckenstein MJ. Autoimmune inner ear disease. In: Flint PW, Francis HW, Haughey BH, et al, editors. *Cummings Otolaryngology-Head and Neck Surgery*, ed 7. Elsevier, 2021.



Stephanie E. Teng, MD

Instructor in Otolaryngology

Pavan S. Mallur, MD

Assistant Professor of Otolaryngology

RESEARCH FOCUS

Our research focus is related to clinical outcomes in laryngology with a current project on outcomes related to the use of KTP laser based on technique and settings. During the first peak of the COVID-19 pandemic, we also established collaborations across specialties and across Harvard hospitals to look at the laryngological and airway sequelae from COVID-19. These projects are currently ongoing.

We are also involved in longer-standing research collaborations with colleagues in Neurology, including the NIH-funded Dystonia Coalition with Samuel A. Frank, MD, and Luo Lan, MD.

Dr. Mallur is in preparation of the thesis required for induction to the Triological Society/ American Laryngological Association for August of 2021.

RESEARCH GROUP

David Caradonna, MD, DMD
Thomas L. Carroll, MD
Samuel A. Frank, MD
Ernest Gomez, MD, MTR
Scharukh Jalisi, MD
Luo Lan, MD
James Naples, MD
Matthew R. Naunheim, MD, MBA
Mihir S. Parikh, MD
Phillip C. Song, MD



▲ The Laryngology section of the Division of Otolaryngology/Head and Neck Surgery includes (from left): Tori Flormann, MS, CCC-SLP, Stephanie Teng, MD, Pavan Mallur, MD, and Barbara Wilson Arboleda, MS, CCC-SLP.

ACCOMPLISHMENTS 2019-2020

- Invited panelists for Massachusetts Eye and Ear Grand Rounds. Case Panel: Decision Making in Inpatient Laryngology
- Division approved for new Otolaryngology/Head and Neck Surgery Residency at BIDMC/Harvard Medical School
- Moved into the new Otolaryngology clinic space on the Shapiro Clinical Center ground floor

TEACHING, TRAINING, AND EDUCATION

We are involved in the training of otolaryngology residents (BIDMC, Combined MEEI), and the teaching of residents from other specialties and medical students through rotations in clinic, educational lectures, and engagement in research.

Dr. Teng also provides mentorship to pre-medical students through the Office of Career Services at Harvard University.

Outside of the Harvard community, in collaboration with our speech-language pathologists (Barbara Wilson Arboleda, MS, CCC-SLP, and Victoria Flormann, MS, CCC-SLP), the laryngology team has continued to perform outreach and education to the community:

- Provided education at the New England Conservatory of Music Health Fair (2020)
- Gave webinar, "Caring for the Professional Voice," to local voice teachers and speech-language pathologists (Teng and Wilson Arboleda, 2020)

ABSTRACTS, POSTERS, AND EXHIBITS

YS Cheng, SE Teng, G Har-El. Pedicled Buccal Fat Pad for Early Reconstruction after Transoral Radical Tonsillectomy. Triological Society Combined Sections Meeting, Coronado, CA (poster)

Ospina Delgado D, Mallur PS, Gangadharan SP, Parikh M, Wilson J, Kheir F, and Majid A. Characterization of Laryngeal Disorders in Patients with Central Airway Collapse. CHEST Annual Meeting, Virtual (poster)

SELECTED PUBLICATIONS

Naunheim MR, Zhou AS, Puka E, Franco Jr. RA, Carroll TL, Teng SE, Mallur PS, Song PC. Laryngeal complications of COVID-19. *Laryngoscope Investig Otolaryngol* 2020;5(6):1117-1124.

Mallur PS, Rosen CA. In: KJ Lee's Essential Otolaryngology, 12th Edition, 2020; The Larynx. p.879-921.

Mallur PS, Rosen CA. Transoral Vocal Fold Injection. *Vocal Fold Injection*, 2020 (book chapter); in press.



RESEARCH GROUP

Sivana Barron
Matthew Depamphilis
Christine Kang, MD
Amy Maselli, MD
Farzin Sadeq
Brianna Slatnick, MD

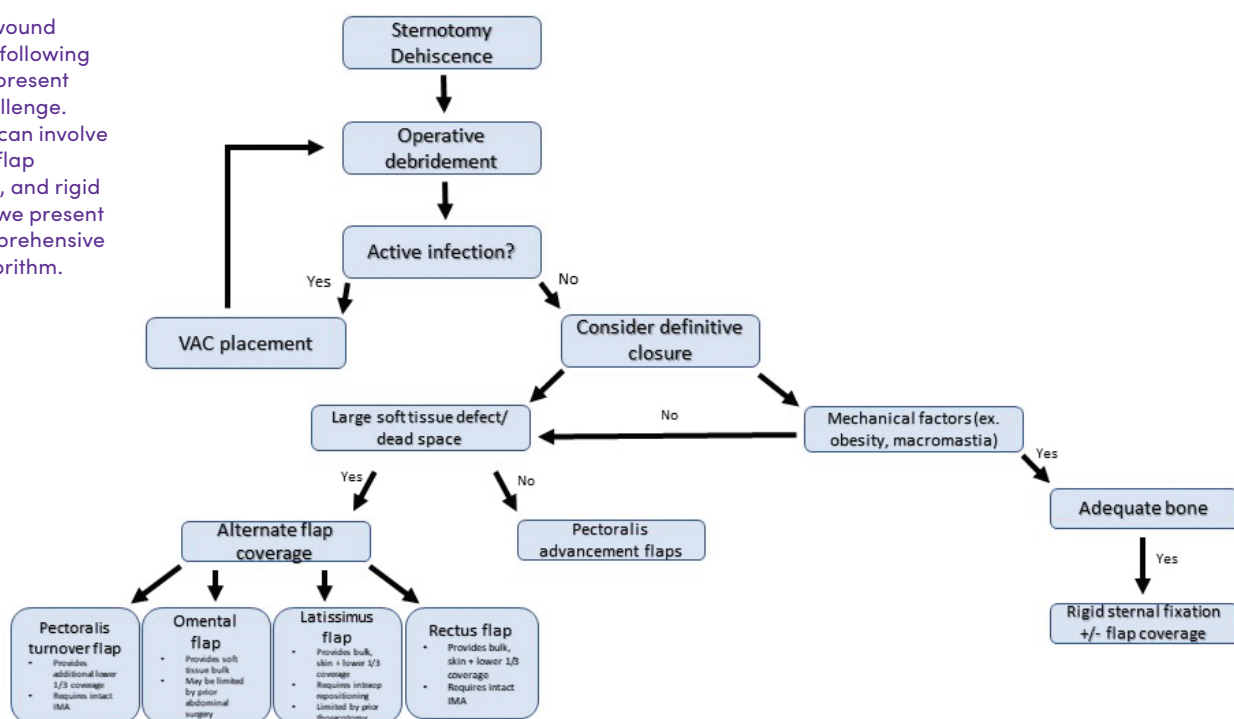
RESEARCH FOCUS

My clinical focus is complex reconstructive surgery of the head and neck, breast, thorax and lower extremity; the treatment of facial trauma, wound and burn management; and gender-affirmation surgery. I am involved in a new multidisciplinary initiative for the management of complex wounds. This program aims to be a center of excellence offering all aspects of wound and burn care, including prevention, acute care, and non-surgical treatments such as laser therapy, hyperbaric therapy, and microsurgical reconstruction.

My research interests are in health services, wound and burn surgery, microsurgical outcomes, and the optimization of surgical care in patients at high risk of wound complications. I am the principal investigator on a study of clinical efficacy, cost, and outcomes in sternal reconstruction following cardiac surgery complicated by sternal dehiscence. I have a strong interest in the use of patient reported outcome measures (PROMs) in the assessment of surgical efficacy and cost effectiveness. I am leading a study examining PROMs following gender-affirmation surgery at BIDMC—the first time these specific measures have been used in the United States for this purpose.

We are using similar PROMs to assess outcomes following common plastic surgery procedures, such as breast reductions and microvascular breast reconstruction, to optimize surgical techniques and postoperative care. Our group is also interested in studying the use of novel imaging technologies to assist in the assessment of wounds and skin flaps used in microsurgical reconstruction. We are studying ways to improve the accuracy of risk stratification in complex wounds by incorporating new technologies such as tissue oxygenation monitoring, ultrasonography, and thermal imaging. With more accurate predictive indices we hope to determine which patients may benefit from earlier surgical intervention to improve long-term outcomes.

► Deep sternal wound complications following sternotomy represent a complex challenge. Management can involve debridement, flap reconstruction, and rigid fixation. Here we present our novel comprehensive treatment algorithm.



ACCOMPLISHMENTS 2019-2020

- Completed training in the Harvard Combined Plastic Surgery Residency Program
- Completed fellowship training in Microsurgical Reconstruction at Beth Israel Deaconess Medical Center
- Achieved board certification in Plastic and Reconstructive Surgery from the American Board of Plastic Surgery and in Surgical Critical Care from the American Board of Surgery
- I am a co-investigator for a recently funded, prospectively randomized study of lymphatic reconstitution and wound healing following free tissue transfer

TEACHING, TRAINING, AND EDUCATION

I am strongly engaged in teaching plastic surgery residents in the ambulatory and operative settings. I serve as the primary clinical preceptor for the weekly plastic surgery resident-led clinic at BIDMC and staff most cases planned through the clinic. The goal of the resident clinic is to provide a thorough exposure to pre-operative planning, graded operative autonomy, and post-operative management of both aesthetic and general reconstructive surgery. I am also involved in the weekly journal club and didactics, giving lectures on flap physiology and selection, head and neck reconstruction, maxillofacial trauma, and oral board preparation. In addition, I am mentoring several medical students and general surgery residents who have developed an interest in the field of plastic surgery.

SELECTED ABSTRACTS, POSTERS, AND EXHIBITS

Sadeq F, Cauley R, Depamphilis M, Ehrlichman R, Driscoll DN. Reconstruction of Severe Burns to the Breast in Pediatric Patients: A Ten Year Experience. American Burn Association; Las Vegas, NV.

Depamphilis M, Cauley R, Sadeq F, Sheridan RL, Winograd J, Driscoll DN. Reconstruction of the Pediatric Upper Extremity Following High Voltage Electrical Burn Injury. American Burn Association; Las Vegas, NV.

SELECTED PUBLICATIONS

Depamphilis MA, Cauley RP, Sadeq F, Lydon M, Sheridan RL, Driscoll DN, Winograd JM. Surgical management and epidemiological trends of pediatric electrical burns. *Burns* 2020;Mar 31 (Epub ahead of print).

Sadeq F, Cauley R, Depamphilis MA, Driscoll DN, Ehrlichman R. Reconstruction of severe burns to the breast in pediatric patients: A 10-year experience. *J Burn Care Res* 2020;41(3):568-575.

Cauley R, Wu WW, Doval A, Chaikof E, Ho KKL, Iorio ML. Identifying complications and optimizing consultations following transradial arterial access for cardiac procedures. *Ann Vasc Surg* 2019;56:87-96.

Cuccolo NG, Cauley RP, Sieber BA, Hussain S, Chandler LK, Ibrahim A, Lin SJ. Temporoparietal fascia free flap for a large nasal septal perforation. *J Reconstr Microsurg Open* 2019;04(01): e42-e46.



A. Samandar (Sammy) Dowlatshahi, MD

Assistant Professor of Surgery

Director, Orthoplastic and Reconstructive Microsurgery Program

RESEARCH GROUP

Indeevar Beeram
Stephanie Francalancia, BA
Anna Rose Johnson, MD
Taylor Johnson, MS
Christine Kang, MD
Erin Kim
Olivia Kramer, BS
Nelson Merchan, MD
Amer Nassar, MD
Anamika Veeramani
Katiri Wagner-Nunes, ACRP, CCRC
Caroline Williams, BA
Dean Zeldich

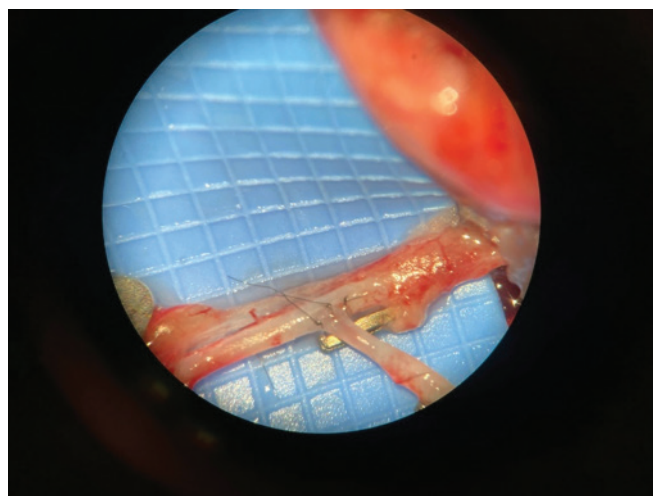
RESEARCH FOCUS

Over the last three years, my clinical and research efforts have been focused on hand and upper extremity surgery as well as orthoplastic surgery, which includes microvascular surgery, limb salvage, and peripheral nerve surgery. At the end of 2020 we initiated an Orthoplastic Surgery Research Lab that is dedicated to furthering research within this subspecialty area.

In terms of hand and upper extremity research, we are currently looking at socioeconomic factors that affect the delivery of hand surgical care for routine hand conditions and the role of local anesthetics in ultrasound-guided joint injections.

Our orthoplastic research projects include: looking at outcomes of gastrocnemius muscle flaps, minimally invasive flap dissection using an endoscopic technique, patient-reported outcomes in limb salvage surgery, readability of limb salvage patient-information materials, outcomes and incidence of infection in acute compartment syndrome patients, and outcomes of surgical management for popliteal artery entrapment syndrome. We have also established a collaboration with the musculoskeletal neurology group at BIDMC and are in the process of putting together research protocols to look at patients with cubital tunnel syndrome.

▼ 500 micron supermicrosurgical end-to-side anastomosis for finger revascularization.



ACCOMPLISHMENTS 2019-2020

I am the founding Director of the BIDMC Orthoplastic and Reconstructive Microsurgery Program, which is the second program of its kind in the United States. The program includes collaboration with a large interdisciplinary team including anesthesia, infectious diseases, neurology, general surgery, vascular surgery, podiatry, radiology, pathology, oncology, nutrition, rehabilitation, mental health, case management, and social work. It also encompasses the Orthoplastic Research Laboratory, which focuses on clinical outcomes and basic science research. In addition, the program will offer an educational curriculum for orthopedic, plastic, vascular, and podiatric surgery residents and fellows at BIDMC and BILH affiliates.

Patent

Patent for surgical retractor designed for extremity surgery (U.S. Patent No. 10,624,622 B2), April 2020

Invited Presentations

- Orthoplastic Surgery: Fertile Ground for Interdisciplinary Innovation and Collaboration. Harvard Combined Orthopaedic Grand Rounds, Brigham and Women's Hospital; Boston, MA
- Influence of BMI on Distal Radius Fracture Outcomes. American Association for Surgery of the Hand; Palm Desert, CA
- Changing Markets in Hand and Upper Extremity Surgery (Panel). American Association of Plastic Surgeons Annual Meeting; Baltimore, MD
- Distal Radius Fractures (Instructional Course). American Society for Surgery of the Hand Annual Meeting; Las Vegas, NV
- Critical Analysis of an Office-Based Procedure Room: Logistics, Workflow and Financial Considerations (Panel). Northeastern Society of Plastic Surgeons Annual Meeting; Pittsburgh, PA

TEACHING, TRAINING, AND EDUCATION

I am one of the core faculty for the BIDMC Microsurgery Fellowship, the BIDMC Plastic and Reconstructive Surgery Residency Program, the Harvard Combined Orthopedic Residency Program, and the BIDMC Hand Fellowship Program. I also mentor several medical students from Harvard Medical School as well as other schools in the United States. Within the Hand Fellowship Program, I have been offering an annual microvascular surgery course which has been well received and is now in its third iteration.

SELECTED PUBLICATIONS

- Harper CM, Dowlatshahi AS, Rozental TD. Challenging dogma: Optimal treatment of the "fight bite." *Hand (NY)* 2020;15(5):647-50.
- Johnson AR, Doval AF, Granoff MD, Egeler SA, Bravo MG, Dowlatshahi AS, Lin SJ, Lee BT. Comparative multimetric assessment of English and Spanish carpal tunnel syndrome materials. *J Surg Res* 2019;238:64-71.
- Hall M, Ostergaard P, Dowlatshahi AS, Harper CM, Earp B, Rozental TD. The impact of obesity and smoking on outcomes after volar plate fixation of distal radius fractures. *J Hand Surg Am* 2019;44(12):1037-1049.
- Harper CM, Dowlatshahi AS, Rozental TD. Evaluating outcomes following open fractures of the distal radius. *J Hand Surg Am* 2020;45(1):41-47.
- Daly LT, Doval AF, Lin SJ, Tobias A, Lee BT, Dowlatshahi AS. Role of CTA in women with abdominal scars undergoing DIEP breast reconstruction: Review of 1,187 flaps. *J Reconstr Microsurg* 2020;36(4):294-300.
- Akyurek M, Dowlatshahi AS, Quinlan RM. Two-stage prosthetic breast reconstruction with latissimus flap: Prepectoral versus subpectoral approach. *J Plast Reconstr Aesthet Surg* 2020;73(3):501-506.
- Dowlatshahi AS, Constantian MB, Deng A, Fudem G. Defining the histologic support structures of the nasal ala and soft triangle: Toward understanding the cause of iatrogenic alar retraction. *Plast Reconstr Surg* 2020;146(3):283e-291e.



Bernard T. Lee, MD, MBA, MPH

Professor of Surgery

Chief, Plastic and Reconstructive Surgery

Director, Peter Jay Sharp Microsurgery Fellowship Program

RESEARCH GROUP

Ryan Cauley, MD, MPH

Danielle Chuang

Diana Del Valle, MD

Christine Kang, MD, MHS

Amy Maselli, MD

Anamika Veeramani (Harvard Medical School)

RESEARCH FOCUS

Our research laboratory focuses 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. Other collaborative projects have evaluated near infrared imaging of lymphatic vessels in a large animal model.

Our clinical research group is examining outcomes and patient satisfaction after breast cancer and reconstructive surgery. We have also been examining patient access, health literacy, and readability of resources for plastic surgery in collaboration with Dr. Rima Rudd (Harvard T. H. Chan School of Public Health).

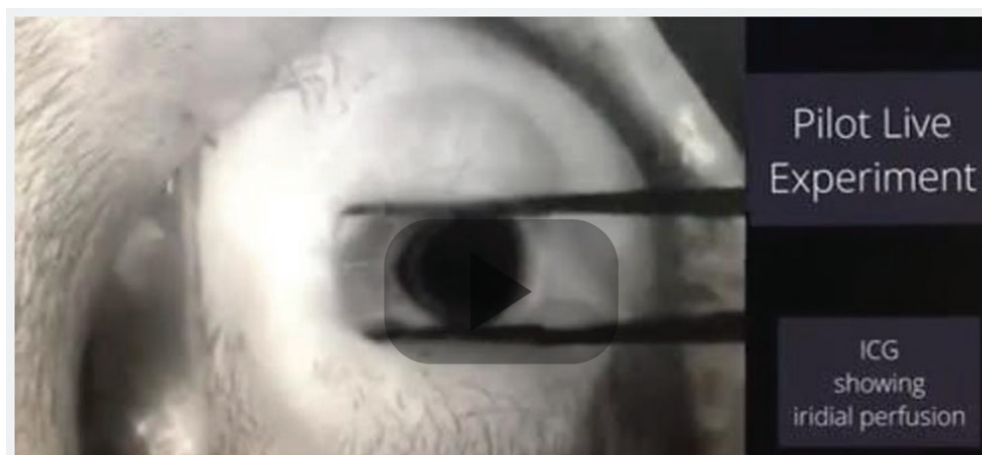
Near Infrared Imaging Systems

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. This work serves as the basis for future studies examining vascular composite allotransplantation of the eye in a large animal model.

Patient Access and Health Literacy in Plastic and Reconstructive Surgery

In 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 have been 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. This extends to patient education through telehealth, which has been extensively used during the COVID-19 pandemic, but not studied.

► FIGURE 1: Near infrared imaging showing iridial perfusion in a swine model.



ACCOMPLISHMENTS 2019-2020

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 as the President-Elect of the Plastic Surgery Foundation. I have given multiple (virtual) lectures this past year as a visiting professor at universities including Northwestern, Duke, University of Michigan, and the University of Wisconsin. I am also a Director for the American Board of Plastic Surgery and was on the planning committee of the recent virtual oral board exam.

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

- The Profunda Artery Perforator Flap, Duke Flap Course
- The Superior Gluteal Artery Perforator Flap, Duke Flap Course
- Lower Extremity Reconstruction and Super-Thin Flaps, American Society of Plastic Surgeons
- Prophylactic Lymph Node Transfer, American Society of Reconstructive Microsurgery
- Surgical Ergonomics, Mountain West Society of Plastic Surgeons meeting
- Improving Outcomes in Breast Reconstruction, Virtual Grand Rounds, Northwestern, University of Michigan, Rutgers, Saudi Plastic Surgery Society
- How to Ace a Zoom Interview, American Society of Academic Plastic Surgeons
- Plastic Surgery and Publication Trends, University of Wisconsin
- The Value of Ultrasound in Reconstructive Surgery, Ultrasound in Reconstructive Microsurgery Virtual Course
- COVID-19 and Plastic Surgery in the United States, Plastic and Reconstructive Surgery Korea meeting

TEACHING, TRAINING, AND EDUCATION

I have been training medical students, general surgery and plastic surgery residents, clinical fellows, and research fellows for over 18 years. We have had multiple students from Harvard Medical School (HMS) as well as international students working on our research team. I serve on the Faculty Council and Promotions Committee at Harvard Medical School. 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, the BIDMC Department of Surgery Clinical Research Mentorship Award in 2017, and the A. Clifford Barger Excellence in Mentoring Award at Harvard Medical School in 2020.

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

Ruan QZ, Rinkinen JR, Doval AF, Scott BB, Tobias AM, Lin SJ, Lee BT. Safety profiles of fat processing techniques in autologous fat transfer for breast reconstruction. *Plast Reconstr Surg* 2019;143(4):985-991.

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* 2020;145(1):67-75e.

Chen DH, Johnson AR, Ayyala H, Lee E, Lee BT, Tran BNN. A multimetric health literacy analysis of autologous versus implant based breast reconstruction. *Ann Plast Surg* 2020; in press.

Kokosis G, Dellon LA, Hollenbeck ST, Lee BT, Coon D. Prevalence of musculoskeletal symptoms and ergonomics among plastic surgery residents: Results of a national survey and analysis of contributing factors. *Ann Plast Surg* 2020; in press.

Chi D, Chen AD, Ha AY, Yaeger LH, Lee BT. Comparative effectiveness of transversus abdominis plane blocks in abdominal autologous breast reconstruction: A systematic review and meta-analysis. *Ann Plast Surg* 2020; in press.

Crystal DT, Cuccolo NG, Plewinski MJ, Ibrahim AMS, Sinkin JC, Lin SJ, Agag RL, Lee BT. Assessment of opioid prescribing practices in breast augmentation: Future directions for prescribing guidelines. *Ann Plast Surg* 2020; in press.

Johnson AR, Lainez SS, Santos HJ, Chen AD, Lainez C, Lin SJ, Agag RL, Lee BT. Beyond the tip of the blade: An investigation of upper extremity machete injuries in Honduras. *J Reconstr Microsurg* 2020; in press.

Chi D, Chen AD, Dorante MI, Lee BT, Sacks JM. Plastic surgery in the time of novel coronavirus COVID-19. *J Reconstr Microsurg* 2020; in press.

Atia A, Langdell HC, Hollins A, Shammass RL, Glenner AD, Marks C, Lee BT, Phillips BT. Microsurgery fellowship website and social media presence: Are programs optimizing recruitment strategy. *J Reconstr Microsurg* 2020; in press.



Samuel J. Lin, MD, MBA

Associate Professor of Surgery

Program Director, BIDMC/Harvard Medical School Plastic Surgery Residency

Co-Director, BIDMC/Harvard Aesthetic and Reconstructive Surgery Fellowship

RESEARCH FOCUS

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

RESEARCH GROUP

Carly D. Comer, MD

Samuel M. Manstein, MD

Eric Shiah, BA

Elizabeth Laikhter, BA

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. Our primary focus 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 nerve stimulation thresholds to aid in paralysis/paresis and/or block nerve firing, and to reduce pain for conditions such as facial nerve paralysis, chronic pain, and nerve dysfunction syndromes.

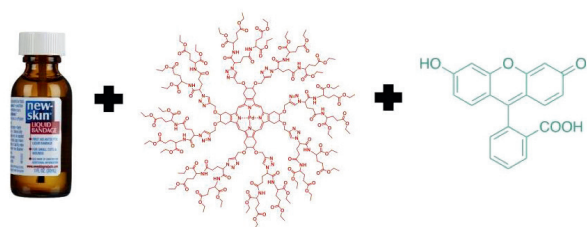
Use of Silk-Based Orthopedic Devices to Modulate Healing

I am co-principal investigator on this R01 funded project, which is a collaborative effort with scientists and engineers at Tufts University. We are developing degradable silk protein-based orthopedic devices (screws and plates). Our pilot data was published in *Nature Communications* in March 2014 and an updated report was published in *Nature Materials* in January 2020. These devices may be able to provide immediate surgical stabilization for orthopedic repair, promote active repair, reduce infections by releasing therapeutics, and degrade fully, thereby reducing the need for future removal surgery.

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 (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. Results of our first human trial for DIEP flap reconstruction were published in *Science Advances* in December 2020. This technology may be able to address limitations in current 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.

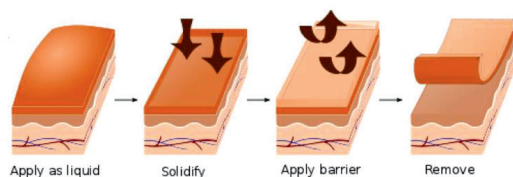


3D Printing in Plastic Surgery

We have 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 have an active clinical research group examining outcomes, techniques, and patient satisfaction following reconstructive and aesthetic plastic surgery procedures. 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 examined risk factors for complications, trends over time, healthcare disparities, and performed cost analysis.



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ACCOMPLISHMENTS 2019-2020

- Over the last year, I have expanded my involvement in professional societies. For the American Society of Plastic Surgeons (ASPS), I served as the American College of Surgeons representative, moderator of the session 'Mini versus Maxi: Selecting the Right Facelift for the Right Patient' at the 2020 Annual Meeting, and serve as a member of the Audit and Conflict-of-Interest Committees.
- I continue to serve as a research grant reviewer of the Plastic Surgery Foundation (PSF) Study Section, and a study section reviewer for multiple National Institutes of Health/Musculoskeletal Oral and Skin Sciences (NIH/MOSS) studies.
- My editorial activities include: serving on the Editorial Board for *Journal of Reconstructive Microsurgery*, and *Plastic and Reconstructive Surgery*; as Outcomes Section Editor for *Plastic and Reconstructive Surgery*; as Academic Editor for *Public Library of Science*; and as Associate Editor for *Plastic and Reconstructive Surgery-Global Open*.
- I have continued my commitment as ad hoc reviewer for: *Plastic and Reconstructive Surgery*, *Annals of Plastic Surgery*, *The Laryngoscope*, *Microsurgery*, *International Journal of Surgery Case Reports*, and the *International Journal of Surgery*.
- I have continued efforts to educate patients and the lay community. Through the *Plastic and Reconstructive Surgery* Journal Club, I created an educational video on Facebook about the opioid crisis in ambulatory plastic surgery. I have also written multiple educational articles about popular plastic surgery topics which can be found on multiple media sources.

Selected Regional, National, and International Presentations

- Rhinoplasty, Visiting Professor, Queen Victoria Hospital, West Sussex, UK
- Is Out-of-Network a Threat to Global Reimbursement?, Panel Discussant. 2020 American Society of Reconstructive Microsurgery Annual Meeting, Fort Lauderdale, FL
- Head and Neck Reconstruction, Grand Rounds Speaker (Virtual), Northwestern Plastic Surgery
- Parotid Tumors/Head and Neck Cancer; Nasal and Lip Reconstruction; Basics of Rhinoplasty, Harvard Plastic Surgery Shriners Virtual Grand Rounds
- Rhinoplasty Cases, Speaker (virtual), Northwestern Plastic Surgery

TEACHING, TRAINING, AND EDUCATION

I have been training medical students, general surgery and plastic surgery residents, and clinical and research fellows for the past 14 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 BIDMC/Harvard 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, MBA

SELECTED PUBLICATIONS

Guo C, Li C, Vu H, Hanna P, Lechtig A, Qiu Y, Mu X, Ling S, Nazarian A, Lin SJ, Kaplan D. Thermoplastic moulding of regenerated silk. *Nat Mater* 2020;19(1):102-108.

Li C, Guo C, Fitzpatrick V, Ibrahim A, Zwierstra M, Hanna P, Lechtig A, Nazarian A, Lin SJ, Kaplan D. Design of biodegradable, implantable devices towards clinical translation. *Nat Rev Mater* 2020;5(1):61-81.

Johnson AR, Lainez SS, Santos HJ, Chen AD, Lainez C, Lin SJ, Agag RL, Lee BT. Beyond the tip of the blade: An investigation of upper extremity machete injuries in Honduras. *J Reconstr Microsurg* 2020; in press.

Blankensteijn L, Sparenberg S, Crystal D, Ibrahim A, Lee BT, Lin SJ. Racial disparities in outcomes of reconstructive breast surgery: An analysis of 51,362 patients from the ACS-NSQIP. *J Reconstr Microsurg* 2020; in press.

Cuccolo N, Crystal D, Ibrahim A, Lin SJ. Single-payer health care in the United States: Implications for plastic surgery. *Plast Reconstr Surg* 2020;145(6):1089e-1096e.

Crystal D, Blankensteijn L, Ibrahim A, Brownstein G, Reed L, Watts D, Lin SJ. Quantifying the crisis: Opioid-related adverse events in outpatient ambulatory plastic surgery. *Plast Reconstr Surg* 2020;145(3):687-695.



Dhruv Singhal, MD

Associate Professor of Surgery
Co-Director, Boston Lymphatic Center
Director, Lymphatic Surgery, BIDMC

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.

Our research program continues to grow with the unparalleled support from the BIDMC FIRST (Facilitating Innovative Research & Surgical Trials) team. As we evaluated our 1000th new patient in the BIDMC Lymphatic Center this past summer, our robust quality improvement database continues to grow. Similarly, our biorepository houses more than 300 samples of healthy and diseased lymphatic tissue.

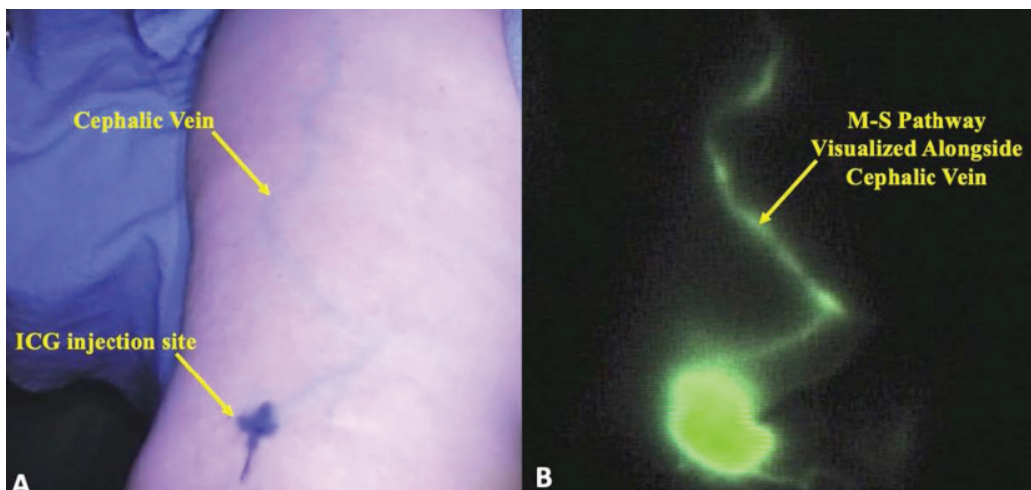
Our clinical research this past year focused on defining anatomic variations of the lymphatic system, especially of the upper extremity. Moreover, we continued our study on immediate lymphatic reconstruction with a cost-effectiveness article published in *Annals of Surgery*.

In the laboratory, we continue to refine our animal model to investigate the physiology of preventing lymphedema surgically at the time of lymphadenectomy. Specifically, we are utilizing unique lymphatic-specific dyes to report real-time changes in lymphatic flow from an extremity.

RESEARCH GROUP

Aaron Fleishman, MPH
Melisa Granoff, BA
Christine Kang, MD
Leo Magrini, BS
Chris Mistretta, RN
Jaime Pardo, MD

► M-S pathway visualized coursing along the cephalic vein. (A) Location of ICG injection over the cephalic vein 4 cm proximal to the antecubital crease. The cephalic vein course can be grossly visualized in the upper arm. (B) M-S pathway visualized coursing along the cephalic vein utilizing ICG imaging. (Johnson AR, Granoff MD, Suami H, Lee BT, Singhal D. Real-time visualization of the Mascagni-Sappey pathway utilizing ICG lymphography. *Cancers* (Basel) 2020;8;12(5):1195).



ACCOMPLISHMENTS 2019-2020

In June 2020, the BIDMC Lymphatic Center joined with the Boston Children's Hospital Lymphedema Program to become the Boston Lymphatic Center. We were subsequently named one of 11 Comprehensive Centers of Excellence for the treatment of lymphatic disorders in the world by the Lymphatic Education and Research Network (LE&RN).

In the fall of 2019, we held our third annual Boston Lymphatic Symposium at the Joseph B. Martin Conference Center at Harvard Medical School, which was geared to patients. Highlights of the sold-out conference included a talk from Chuck Ehrlich, author of "Lymphedema and Lipedema Nutrition Guide." A keynote address was given by 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. The 2020 Boston Lymphatic Symposium was cancelled secondary to the pandemic but will return in a virtual format in 2021 (visit: bostonlymphaticsymposium.org).

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

- Immediate Lymphatic Reconstruction: Update on Research. World Society of Reconstructive Microsurgery; Bologna, Italy
- BIDMC Lymphatic Center. Visiting Professor, Tata Memorial Hospital; Mumbai, India
- Immediate Lymphatic Reconstruction. International Confederation of Plastic Surgery Societies/Webinar SMH Series; London, England
- Surgical Options for Lymphedema. Association of Surgeons of India, Odisha Chapter; Odisha, India
- Liposuction for Advanced Lymphedema. European School of Reconstructive Microsurgery; Barcelona, Spain
- Immediate Lymphatic Reconstruction. 9th World Symposium for Lymphedema Surgery; Barcelona, Spain
- Second Best Microsurgical Breast Reconstruction Option after DIEP: The SGAP Flap. Barcelona Breast Meeting; Barcelona, Spain
- Surgery for Lymphedema. 18th Annual Conference of the Diabetic Foot Society of India; Chennai, India
- Immediate Lymphatic Reconstruction in Breast Cancer Management. 13th Breast-Gynecological & Immuno-oncology International Cancer Conference; Cairo, Egypt

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

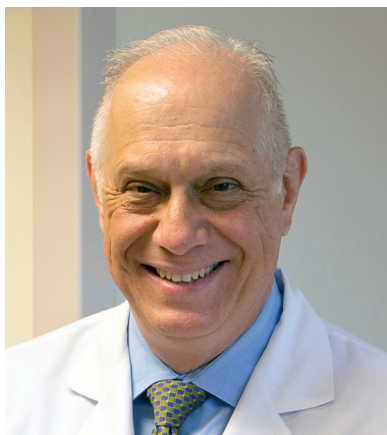
Lymphatic Reconstitution in Microvascular Breast Reconstruction. BIDMC FIRST Program, 2019-present; PI: Dhruv Singhal, MD

Evaluating Real-Time Changes in Lymphatic Flow Utilizing Optical Imaging. Lymphatic Education and Research Network (LE&RN) and American Society for Reconstructive Microsurgery (ASRM), 2018-present; PI: Dhruv Singhal, MD

SELECTED PUBLICATIONS

- Jhaveri VV, Singhal D, Riedel S, Rowley CF, Nathaviharana RR. Surgical cure of clarithromycin resistant mycobacterium chelonae breast implant infection: A case report and review of the literature. *J Clin Tuberc Other Mycobact Dis* 2020;Sep 5.
- Granoff MD, Guo L, Singhal D. Lipofilling after breast conserving surgery: A plastic surgery perspective. *Gland Surg* 2020;9(3):617-619.
- Johnson AR, Granoff MD, Suami H, Lee BT, Singhal D. Real-time visualization of the Mascagni-Sappey pathway utilizing ICG lymphography. *Cancers (Basel)* 2020;8;12(5):1195.
- Kim G, Smith MP, Donohoe KJ, Johnson AR, Singhal D, Tsai LL. MRI staging of upper extremity secondary lymphedema: Correlation with clinical measurements. *Eur Radiol* 2020;30(8):4686-4694.
- Johnson AR, Asban A, Granoff MD, Kang CO, Lee BT, Chatterjee A, Singhal D. Is immediate lymphatic reconstruction cost-effective? *Ann Surg* 2019; in press.
- 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.
- 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(9):e2436.
- Granoff MD, Johnson AR, Lee BT, Padera TP, Bouta EM, Singhal D. A novel approach to quantifying lymphatic contractility during indocyanine green lymphangiography. *Plast Reconstr Surg* 2019;144(5):1197-1201.
- 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* 2020;36(1):28-31.

A complete list of publications begins on page 15.



John M. Giurini, DPM

Associate Clinical Professor of Surgery
Chief, Division of Podiatric Surgery

RESEARCH GROUP

Kevin Buczkowski, DPM
Juan Ceja-Solorio, DPM
Thanh Dinh, DPM
Amish Dudeja, DPM
Tommy Ho, DPM
Casey Lewis, DPM
John Martucci, DPM
Kevin L. Riemer, DPM
Barry I. Rosenblum, DPM
Christopher Sullivan, DPM
Lowell Tong, DPM
Aristidis Veves, MD, DSc

RESEARCH FOCUS

The Division of Podiatric Surgery participates in translational as well as clinical research. Translational ("bench to bedside") research focuses on causes of neuropathy and impaired wound healing and is led by Aristidis Veves, MD, DSc, a leading scientist and researcher. Dr. Veves has been the recipient of several NIH grants and works collaboratively with the Wyss Institute for Biologically Inspired Engineering of Harvard University. His work has been published in prestigious journals such as *Diabetes*, *Circulation* and *The Lancet*.

The rest of our faculty members are involved in clinical research that largely focuses on diabetes and its complications. They also participate in outcomes research that address surgical and clinical conditions for which there are no clear treatment algorithms. This research draws from our own clinical cases and experience. With the assistance of the Department of Surgery's FIRST program, we have been able to expand our ability to conduct this type of research. A major focus of our clinical research is to involve all of our residents and to instill in them a mentality of research, to ask questions, and to work toward answers. This begins in their first year.

In 2020, we initiated three studies examining clinical questions that are encountered every day but do not have clear answers. Two of these studies are being conducted collaboratively with two other departments at BIDMC (Orthopedic Surgery and Anesthesia). During 2020 we are continuing our work on four other studies, which are in various stages of completion. We expect to submit our results for publication for two of these studies in 2021.

Ongoing Research Projects

- Reconstructive surgery in patients with Charcot joint disease
- Hallux amputation in patients with diabetes and osteomyelitis
- Clinical and chemical biomarkers to predict diabetic foot ulcer (DFU) healing
- Retrospective review of 5th metatarsal fractures
- Are immediate postoperative X-rays of value in foot surgery patients?
- Outcomes of hallux rigidus surgery: 1st MTPJ fusions versus joint sparing procedures
- Is monitored anesthesia care safe in patients undergoing foot and ankle surgery in the prone position?

ACCOMPLISHMENTS 2019-2020

- Board member, Community Leadership Board, American Diabetes Association, New England Division (Dr. John Giurini)
- President-elect, American College of Foot & Ankle Surgeons (Dr. Thanh Dinh)
- Elected to Board of Directors, American College of Foot & Ankle Surgeons (Dr. Barry Rosenblum)
- Peer reviewer, *Journal of Foot & Ankle Surgery* (Dr. Kevin Riemer)
- Moderator, The Diabetic Foot and Osteomyelitis, APMA Online CECH Summer Series (Dr. John Giurini)

TEACHING, TRAINING, AND EDUCATION

The Division of Podiatric Surgery sponsors a three-year residency program accredited by the Council on Podiatric Medical Education (CPME) of the American Podiatric Medical Association. Two residents are selected each year, consistently drawing the top candidates from the nine podiatric medical schools in the U.S.

- Received full 5-year accreditation of residency program, Council on Podiatric Medical Education
- Didactic lectures to Department of Surgery residents (Drs. Giurini and Rosenblum)
- Established formal podiatric surgical rotation at VA Boston to enhance ankle surgery

ABSTRACTS, POSTERS, AND EXHIBITS

Martucci JA, Riemer KL. Gas-Producing Infections in the Foot at a Large Academic Medical Center: A 10-Year Retrospective Review. APMA Scientific Conference; Boston, MA (poster)

Dudeja A, Giurini JM. Long-term Functional Outcomes of Hallux Amputations at Various Anatomical Levels. Annual Scientific Conference, ACFAS; San Antonio, TX (poster)

Giurini, JM. Diagnosing Osteomyelitis in the Diabetic Foot. APMA Online CECH Summer Series; Boston, MA (oral video presentation)

SELECTED PUBLICATIONS

Veves A, Giurini JM, Guzman R, Editors. *The Diabetic Foot: Medical and Surgical Management*. Humana Press, 2018.

Migonis A, Murano R, Stillman I, Iorio M, Giurini JM. A case report and literature review: Intraneural ganglion cyst causing tarsal tunnel syndrome. *J Foot Ankle Surg* 2019;58(4):795-801.

Dinh T, Lewis C. Amnion applications in the foot and ankle. *Clin Podiatr Med Surg* 2019;36(4):563-576.

Martucci JA, Migonis AM, Rosenblum BI. Subtalar arthroereisis implantation in acquired neuropathic pes planus: A preliminary report detailing a minimally invasive approach to healing medial column ulcerations. *J Foot Ankle Surg* 2020;59(3):611-615.

Jhaveri VV, Sullivan C, Ward A, Giurini J, Karchmer AW, Stillman I, Davis RB, Freed JA, Lasalvia M, Stead W. More specialties, less problems: Creating collaborative competency between the Infectious Disease, Podiatry, and Pathology departments in the management of diabetic foot infection. *J Amer Pod Med Assoc* 2020; in press.



Aristidis Veves, MD, DSc

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

RESEARCH GROUP

Lihong Chen, MD, PhD
Jie Dong, MD, PhD,
Navin Jayaswal, BS
Ikram Mezghani, MS
George Theodoridis, 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 time is dedicated to research, five percent to teaching, and five percent to administrative and other professional activities.

Translational research is a major part of my research activities. My work mainly focuses on the pathogenesis 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 departments throughout BIDMC and investigators from other institutions, such as the Wyss Institute at Harvard University, Joslin Diabetes Center, MIT, Boston University, and Brigham and Women's Hospital.

I conduct investigator-initiated research studies that examine the effects of various FDA-approved medications on cardiovascular function. These industry-funded studies have been conceived, designed, and executed by my unit and focus on possible new mechanisms by 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.

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 at BIDMC and is funded by NIH grants. I also collaborate with Dr. David Mooney's laboratory at the Wyss Institute and the Harvard School of Engineering and Dr. Jonathan Garlick's laboratory at Tufts University School of Medicine. The main aim of our collaboration, which has resulted in NIH funding, is the development of new wound-healing products.

The results of my research have been published in prestigious medical journals, including *Lancet*, *Diabetes*, and *Circulation*. According to Google Scholar as of December 2020, my work has resulted in more than 22,300 citations; an h-index of 74 and i10-index of 177.

I have also served as Director of the Rongxiang Xu, MD Center for Regenerative Therapeutics since its establishment in 2015. The center was established with 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.

ACCOMPLISHMENTS 2019-2020

This year we continued to focus on understanding the pathophysiology of impaired diabetic wound healing. To this end, we applied a combined understanding of single cell transcriptome and proteome levels that 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. We have almost completed the study; the first data analysis has provided very interesting insight regarding the role of specific cell types, such as a subgroup of fibroblasts, in promoting wound healing. A patent application is under development.

We already performed transcriptomic analysis in a portion of the collected samples and published our results, which showed that there are similarities in the gene expression between the forearm and foot skin specimens of the same subjects. We will conduct additional studies to further investigate the role of various genes in the development of chronic, non-healing wounds.

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. Work is progressing well and we expect the first results soon.

We have almost completed 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 recruit macrophages and then direct these cells to the M2 phenotype to enhance diabetic wound healing.

Finally, we initiated a new project to develop advanced wound healing products. I am a co-PI of this project, funded by DARPA, which is led by Columbia University and includes investigators from MIT, Virginia University, Northwestern University, and IBM. I also participate in an SBIR grant that evaluates the efficacy of RNA interference in promoting wound healing in diabetes.

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. Currently, I participate as editor in the third edition of the textbooks *Diabetic Neuropathy* and *Diabetes and Cardiovascular Disease*.

SELECTED RESEARCH SUPPORT

Skin Inflammatory Phenotypes as Biomarkers of Myocardial and Vascular Remodeling. NIH, 2016–2021; Co-PI/Contact PI: Aristidis Veves, MD, DSc

Proteomic and Transcriptomic Single Cell Analysis in DFU Patients. DiaComp, 2018–2020; PI: Aristidis Veves, MD, DSc

A Novel sshRNA-antimiR Combination Therapy for Accelerating Healing of Diabetic Foot Ulcers. NIH, 2018–2020; PI: Aristidis Veves, MD, DSc

TRAUMAS: Treatment and Recovery Augmented with Electrical and Ultrasound-Mediated Actuation and Sensing. DARPA, 2020–2024; Co-PI: Aristidis Veves, MD, DSc

The Skin of Naked Mole Rats as a Model for Scar-Free Wound Healing. NIH, 2020–2023; Co-PI: Aristidis Veves, MD, DSc

SELECTED PUBLICATIONS

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* 2020;140(4):901-911.

Bakker JP, Baltzis D, Tecilazich T, Chan RH, Manning WJ, Neilan TG, Wallace ML, Hudson M, Malhotra A, Patel SR, Veves A. The effect of CPAP on vascular function and cardiac structure in diabetes and sleep apnea: A randomized controlled trial. *Ann Am Thorac Soc* 2020;17(4):474-483.

Jones JD, Ramser HE, Woessner AE, Veves A, Quinn KP. Quantifying age-related changes in skin wound metabolism using *in vivo* multiphoton microscopy. *Adv Wound Care* 2020;1;9(3):90-102.

Theocharidis G, Baltzis D, Roustit M, Tellechea A, Dangwal S, Khetani R, Shu B, Zhao W, Fu J, Bhasin S, Kafanas A, Hui D, Sui S, Patsopoulos N, Bhasin M, Veves A. Integrated skin transcriptomics and serum multiplex assays reveal novel mechanisms of wound healing in diabetic foot ulcers. *Diabetes* 2020;69:2157-2169.

Dong J, Chen L, Zhang Y, Jayaswal N, Mezghani I, Zhang W, Veves A. Mast cells in diabetes and diabetic wound healing. *Adv Ther* 2020;37:4519-4537.

Veves A: Repair, regeneration and the future. *J Wound Care* 2020;29:539.



Benjamin C. James, MD, MS

Assistant Professor of Surgery

Section Chief, Endocrine Surgery

Associate Surgery Clerkship Director, BIDMC

Director of Resident Research

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.

RESEARCH GROUP

Jordan Broekhuis, MD

Natalia Chaves, MD

Hao Wei Chen, BA

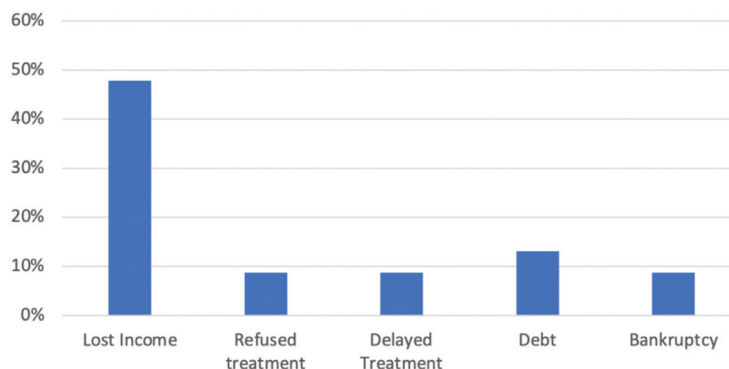
Richard D. Cummings, PhD

Per-Olof Hasselgren, MD, PhD

Leo Magrini, BA

Michiya Nishino, MD, PhD

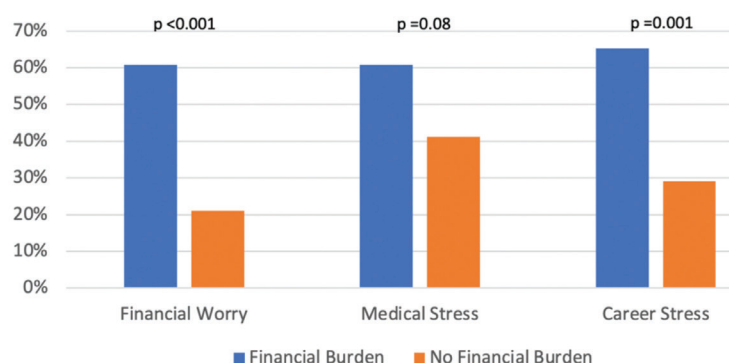
Financial Burden of Thyroid Cancer



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 systematically 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-glycans and Extra HexNAc (bisected) N-glycans were seen in papillary thyroid cancer. Based on these findings, we will continue to evaluate

Psychological and Financial Hardship of Thyroid Cancer Patients



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.

Quality of Life and Economic Impact of Thyroid Cancer Diagnosis

Cancer care expenditure in the U.S. 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 evaluation using the Agency for Healthcare Research and Quality Medical Expenditure Panel Survey (MEPS), we 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 of the financial burden associated with a diagnosis of thyroid cancer (*Surgery* 2020). As a result of these findings, we evaluated our own population of thyroid cancer survivors over the past 20 years at BIDMC and found a significant number of survivors report lost income, financial worry, medical stress, and career stress related to their diagnosis. These 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.

ACCOMPLISHMENTS 2019-2020

- Editorial Board of the *Journal of Surgical Research*
- Research Committee, American Association of Endocrine Surgeons
- Appointed to the Membership Committee, Association for Academic Surgery
- Appointed Director of the Advanced Surgery Elective, BIDMC
- Director of Resident Research

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 2019.

SELECTED PUBLICATIONS

Nagarur A, McEvoy JW, Hirsh DA, James BC. Words Matter: Removing the word pimp from medical education discourse. *Am J Med* 2019;132(12):e813-e814.

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

Barrows CE, Belle JM, Fleishman A, Lubitz CC, James BC. Financial burden of thyroid cancer in the United States: An estimate of economic and psychological hardship among thyroid cancer survivors. *Surgery* 2020;167(2):378-384.

McKinley S, Cassidy D, Mansur A, Saillant N, Ghosh A, Evenson A, Askari R, Haynes A, Cho N, James BC, Olasky J, Rangel E, Petrusa E, Phitayakorn R. Identification of special targets to improve the student surgical clerkship experience. *J Surg Research* 2020;254:49-57.

Roth EM, Lubitz CC, Swan JS, James BC. Patient-reported quality of life outcomes measures in the thyroid cancer population. *Thyroid* 2020;30(10):1414-1431.

Wachtel H, Roses RE, Kuo LE, Lindeman BM, Nehs MA, Tavakkoli A, Parangi S, Hodin RA, Fraker DL, James BC, Carr AA, Wang TS, Solorzano CC, Lubitz CC. Adrenalectomy for secondary malignancy: Patients, outcomes, and Indications. *Ann Surg* 2020;May 18 (Epub ahead of print).

Kent TS, Freischlag J, Minter R, Hawn M, Al-Refaie W, James BC, Eskander M, Chu D. Overcoming a hostile work and learning environment in academic surgery-tools for change at every level. *J Surg Res* 2020;252:281-284.

James BC, Angelos P, Grogan RH. Transoral endocrine surgery: Considerations for adopting a new technique. *J Surg Onc* 2020;122(1):36-40.



Ted A. James, MD, MHCM

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

Sonali V. Pandya, MD, MS

Instructor in Surgery
Director, BreastCare Center at BID-Needham

Monica Valero, MD

Instructor in Surgery
Director, Hispanic Breast Cancer Program



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.

RESEARCH GROUP

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

* No longer at BIDMC

ACCOMPLISHMENTS 2019-2020

- 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

Pardo JA, Fan B, Mele A, Serres S, Valero M, Emhoff I, Alapati A, James T. The role of Oncotype DX recurrence score in predicting axillary response after neoadjuvant chemotherapy in breast cancer. *Ann Surg Oncol* 2020; in press.

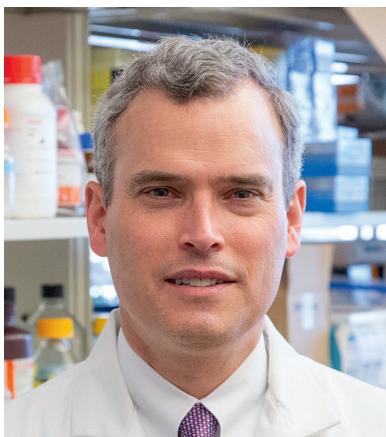
Whitlock AE, Allar BG, James T. Pausing for the pandemic? The impact of deferring breast cancer surgery. *Breast J* 2020;Oct 23 (Epub ahead of print).

Pardo JA, Fan B, Valero M, Alapati A, Emhoff I, Mele A, Serres S, Davis RB, James TA. Impact of geographic distribution of accredited breast centers. *Breast J* 2020;Oct 13 (Epub ahead of print).

Fan B, Pardo JA, Serres S, Alapati AC, Szweczyk J, Mele A, James TA. Role of sentinel lymph node biopsy in microinvasive breast cancer. *Ann Surg Oncol* 2020;27(11):4468-4473.

James TA, Palis B, McCabe R, Pardo JA, Alapati A, Ukandu O, Serres SK, Zhang J, Mele A, Facktor M, Shulman LN. Evaluating the role of sentinel lymph node biopsy in patients with DCIS treated with breast conserving surgery. *Am J Surg* 2020;220(3):654-659.

Fan B, Pardo JA, Alapati A, Hopewood P, Mohammad Virk Z, James TA. Analysis of active surveillance as a treatment modality in ductal carcinoma in situ. *Breast J* 2020;26(6):1221-1226.



A. James Moser, MD

Professor of Surgery, Harvard Medical School

Co-Director, BIDMC Pancreas and Liver Institute

RESEARCH GROUP

Project Survival

Corinne DeCicco

William E. Gooding, MS

Wendy Hori, RN

Genesis Perez-Melara

Tori Singer

Multidimensional Outcomes of Surgery for Pancreatic Cancer

Michiel Francken

Kevin Kennedy, PhD

Juanita Rodriguez, MD

Wald Van der Vliet, MD

Ronald van Dam, MD, PhD

Koen Verkoulen

RESEARCH FOCUS

Our multicenter research program focuses on validating novel diagnostic and therapeutic biomarkers for pancreatic cancer. 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 Pancreas and Liver Institute (PLI) Biorepository Core, these programs and data support collaborations with Maastricht 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.

Here at BIDMC, we are working with David Avigan, MD, and the Immunooncology Institute to develop and test a novel autologous DC fusion vaccine for patients with pancreatic cancer.

These efforts are supported through large industry and society grants, as well as the enduring generosity of numerous grateful patient family foundations whose vision and partnership are critical to supporting the many people committed to interdisciplinary research excellence.

ACCOMPLISHMENTS 2019-2020

- Chair, Project Survival Joint Steering Committee
- Director, PLI Disease Registry and Biorepository Core Facility
- Boston's Top Doctors, Castle Connolly and *Boston Magazine*

TEACHING, TRAINING, AND EDUCATION

Co-Director of Pancreaticobiliary Multidisciplinary Management Conference, a weekly CME-approved course of Harvard Medical School (50 hours)

SELECTED RESEARCH SUPPORT

Project Survival: Multisite Identification and Validation of Prognostic Biomarkers for Pancreatic Cancer Detection and Treatment. Berg Pharma, LLC: 2015-2022; PI: A. James Moser, MD

Does Surgical Approach Affect Pain and Narcotic Consumption After Upper Abdominal Oncological Surgery? Intuitive Surgery Research Foundation, 2020-2021; PI: A. James Moser, MD

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: A. James Moser, MD

SELECTED PUBLICATIONS

Rice MK, Hodges JC, Bellon J, Borrebach J, Al Abbas AI, Hamad A, Knab LM, Moser AJ, Zureikat AH, Zeh HJ, Hogg ME. Association of mentorship and a formal robotic proficiency skills curriculum with subsequent generations' learning curve and safety for robotic pancreaticoduodenectomy. *JAMA Surg* 2020;155(7):607-15.

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* 2020;22(4) 563-569.

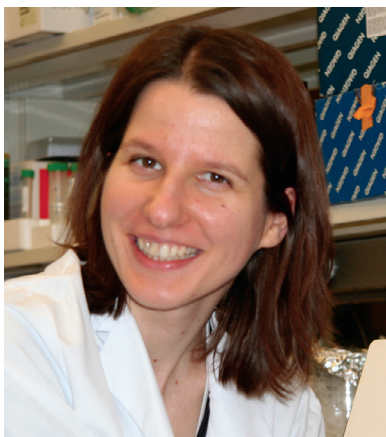
Tolstikov V, Moser AJ, Sarangarajan R, Narain NR, Kiebish MA. Current status of metabolomic biomarker discovery: Impact of study design and demographic characteristics. *Metabolites* 2020;10(6).

Zwart MJW, Jones LR, Balduzzi A, Takagi K, Vanlander A, van den Boezem PB, Daams F, Rosman C, Lips DJ, Moser AJ, Hogg ME, Busch ORC, Stommel MWJ, Besselink MG, Dutch Pancreatic Cancer Group. Added value of 3D-vision during robotic pancreatoduodenectomy anastomoses in biotissue (LAEBOT 3D2D): A randomized controlled cross-over trial. *Surg Endosc* 2020; in press.

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;21(11):1585-91.

Schawkat K, Tabah N, Tridente D, Schlechter BL, Singer T, DeCicco C, Moser AJ, Mortelet KJ. Incidental pulmonary embolism in pancreatic ductal adenocarcinoma: Impact of tumor and AJCC stages at initial staging CT. *Pancreatol* 2019;19(7):979-84.

Zureikat AH, Beane JD, Zenati MS, Al Abbas AI, Boone BA, Moser AJ, Bartlett DL, Hogg ME, Zeh HJ 3rd. Five hundred minimally invasive robotic pancreatoduodenectomies: One decade of optimizing performance. *Ann Surg* 2019; in press.



RESEARCH GROUP

Giacomo Canesin, PhD

Eva Csizmadia, MSc

Lubica Janovicova, MSc

RESEARCH FOCUS

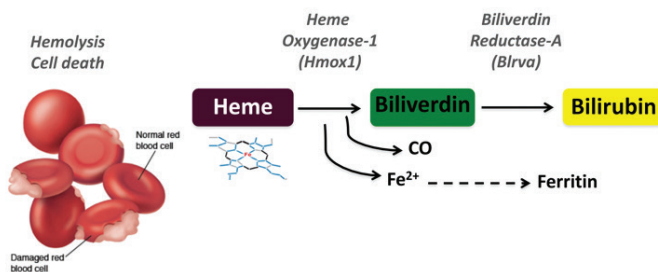
My research focuses on the heme metabolic pathway allowing for removal of labile heme by activities of heme oxygenase-1 (HO-1) and biliverdin reductase (BLVRA) (Figure 1). The generated metabolites—carbon monoxide, iron, and bile pigments—are signaling molecules and critical regulators of innate inflammatory responses and macrophage phenotype during organ injury, hematopoiesis, and carcinogenesis (prostate and lung cancer). As part of the Fibrosis and Endometriosis Research Program (FERP), my laboratory dissects the alterations of immune niche and heme pathway in endometriosis and ovarian carcinoma. Our work has implications for understanding novel targets and potential therapeutics for treatment of cancer and beyond.

Below are examples of the ongoing projects in my laboratory:

1. We study the role of labile heme and its scavenger, hemopexin (Hx), in tumor microenvironment as well as a role of heme:G4 complexes in gene regulation. We have recently discovered that sequestration of labile heme by Hx may block heme-driven tumor growth and metastases, suggesting a potential strategy to prevent and/or arrest cancer dissemination. This work was published in *Cell Reports* (Canesin, Di Ruscio et al, 2020) and featured on the journal cover (Figure 2). We demonstrated that labile heme promotes tumor growth and metastases in an orthotopic murine model of prostate cancer, with the most aggressive phenotype detected in mice lacking Hx. Mechanistically, labile heme accumulated in the nucleus and modulated specific gene expression via interacting with guanine quadruplex (G4) DNA structures to promote colony growth. In this work we identified c-MYC as an heme:G4-regulated gene and a major player in heme-driven cancer progression. Numerous implications that arise from this study include: 1) the potential use of heme levels as a biomarker for prostate cancer patients; 2) the reclassification of heme (i.e., red meat or treatment with heme arginate) as a DNA intercalating agent able to turn on oncogene expression and metastatic gene expression profile via interaction with G4; 3) the use of Hx and BG4 as clinical biomarkers associated with cancer dissemination in prostate malignancies.

2. Much of our efforts over the years 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. We continue work on the role of HO-1 and BVR in tumor microenvironment and its impact on anti-cancer responses to immunotherapy. 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*. 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).

3. We study the role of sterile- and bacteria-induced inflammation in organ injury and cancer. Our prior work showed the role of exogenous CO and HO-1 in models of sterile and bacterial infection (Wegiel et al, *JCI* 2013). Recently, we discovered that the protective effects of CO and HO-1 in models of sterile or bacteria-induced prostate inflammation are, in part, via induction of the lipid metabolic enzyme, ACSL1. Lipid metabolism is an emerging target during cancer progression and inflammation. Our



▲ FIGURE 1

findings may drive possible development of drugs targeting metabolic reprogramming in context to early inflammatory and proliferative changes in the prostate.

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 and genotoxic stress
- Metabolic control of inflammation in cancer and the role of HO-1 metabolic pathway in controlling responses to immunotherapy
- The role of biliverdin reductase and bile pigments in cancer and sterile inflammation-induced organ injury
- DNA damage, replication, and gene expression regulation by heme and secondary structures of DNA in cancer and diseases
- Role of heme in endometriosis through the collaborative efforts via FERP across Harvard

ACCOMPLISHMENTS 2019-2020

- Ad-hoc reviewer of NIH (Transplant Tolerance Tumor Immunology TTT, special emphasis panels) and DOD
- Member of American Association for Cancer Research, BIDMC Cancer Research Institute, and Dana-Farber/ Harvard Cancer Center (DF/HCC)
- Editorial Board member, *American Journal of Pathology*, *Gastrointestinal and Liver Biology*
- Guest Associate Editor, special edition: "Oxidative Stress, Antioxidants, Transcription Factors, and Assimilation of Signal Transduction Pathways in Obesity-Related Disorders," *Frontiers in Pharmacology*
- Section Editor-in-Chief of Cancer Immunology Immunotherapy, *Cancers* (Basel)
- Honorary Lecturer in Molecular Oncology, Aston University, UK

TEACHING, TRAINING, AND EDUCATION

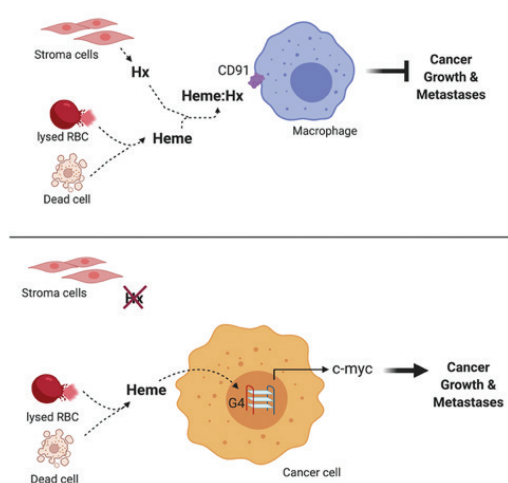
During the last two years, I have been a supervisor for one PhD student, and one junior faculty member (Instructor). I am involved in teaching experimental design, molecular and biochemical techniques, and data acquisition and analysis, as well as manuscript and grant preparation

SELECTED RESEARCH SUPPORT

Role of Biliverdin Reductase During Sterile Inflammation in the Liver. NIH, R01, 2016–2021; PI: Barbara Wegiel, PhD, DSc

Fibroids and Endometriosis Program. BIDMC Chief Academic Office funds, 2016–2019; PI: Barbara Wegiel, PhD, DSc

Determining the Role of Gas Metabolite in Response to Immunotherapy. NIH, R21, 2020–2022, PI: Barbara Wegiel, PhD, DSc



▲ FIGURE 2



SELECTED PUBLICATIONS

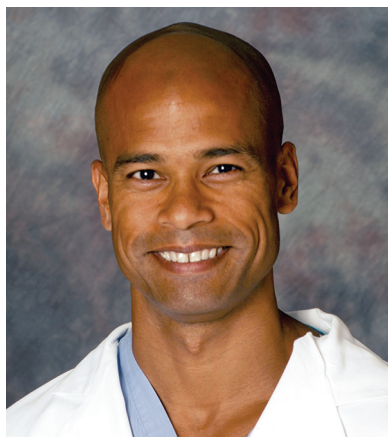
Canesin G, Di Ruscio A, and Li M and Hedblom A, Choudhury R, Krzyzanowska A, Ummarino S, Csizmadia E, Palominos M, Stiehm A, Ebralidze A, Chen S-Y, Bassal M, Zhao P, Tolosano E, Hurley L, Bjartell A, Tenen DG, Wegiel B. Scavenging of labile heme by hemopexin is a key checkpoint in cancer growth and metastases. *Cell Rep* 2020;32(12):108181 (on a cover of *Cell Reports*).

Canesin G, Hejazi M, Swanson K, Wegiel B. Heme-derived metabolic signals dictate immune responses. *Front Immunol* 2020;11:66.

Lilljebjorn LV, Csizmadia E, Hedblom A, Canesin G, Kalbasi A, Li M, Kramer F, Bronfeldt KE, Wegiel B. A role of the heme degradation pathway in shaping prostate inflammatory responses and lipid metabolism. *Am J Pathology* 2020;190(4):830–843.

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.

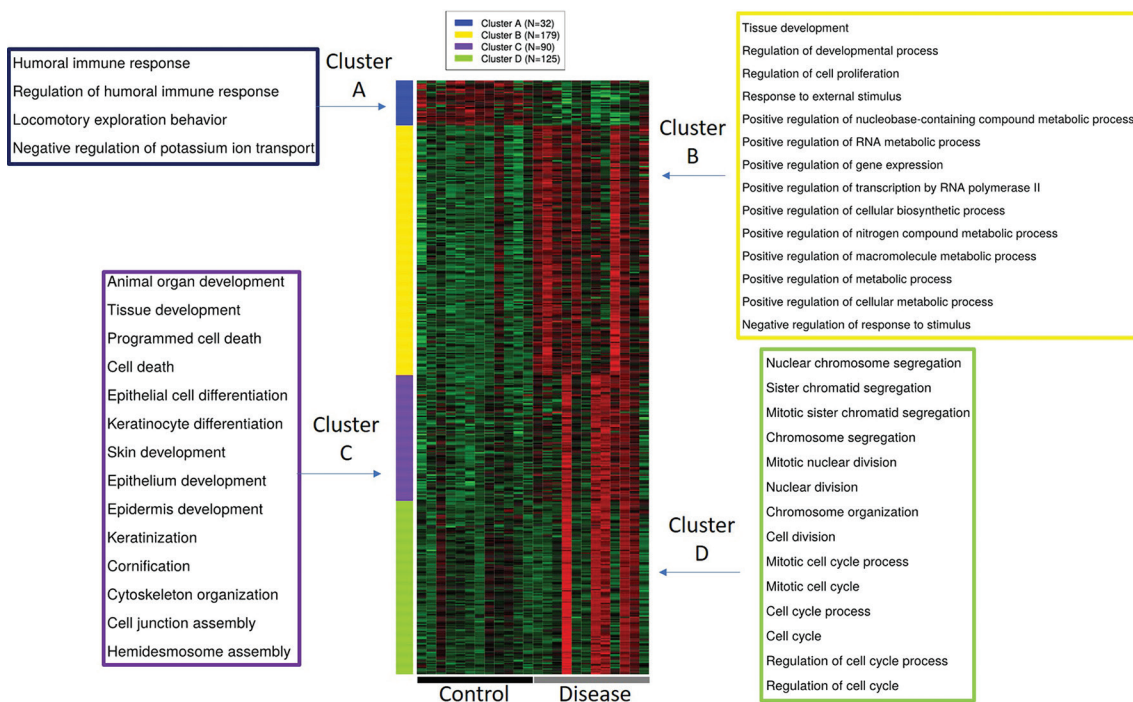
A complete list of publications begins on page 15.



RESEARCH GROUP

Christine Conley, ACRP
Christopher Digesu, MD
Mary Farquhar, RN
Jayden Garcia, HMS2
Michael Kent, MD
Daniel Ospina, MD
Jorge Ruiz de Somocurcio, MD
Rani Singh, PhD
Ammara Watkins, MD, MPH
Richard Whyte, MD, MBA
Jennifer Wilson, MD

▼ FIGURE 1: TBP and changes in airflow characteristics using new modeling skills.



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.

Our group is keenly interested in understanding the processes that lead to the pathologic laxity in the central airway walls that is a hallmark of TBM. In collaboration with Paul Vanderlaan, MD, PhD, in the Department of Pathology, we analyzed resected tracheal specimens including TBM and different diseases and identified unique pro-remodeling and pro-inflammatory gene expression signatures in those with TBM. Building on this, Dr. Rani Singh has generated a first-in-human TBM transcriptomic signature for TBM (Figure 1) using bulk tissue RNA sequencing (RNAseq) on airway biopsies. Among other differentially expressed genes (+ 2-fold, $p < 0.05$), categories related to epithelium biomechanical properties and keratinocyte differentiation—including small proline-rich proteins (SPRR) and keratin (KRT) gene family were enriched. The downregulated genes in TBM suggest their role in the dysregulation of humoral immune response and potassium ion transport, which might influence B-cell development, activation, and differentiation. Further investigation is underway to validate the transcriptomic signature we have obtained using biopsy tissue of TBM and non-TBM subjects. The plan is to confirm the gene expression signatures of candidate genes from RNAseq at mRNA level by using qRT-PCR and at protein level by performing Western blotting, immunohistochemistry, and flow cytometry assays on the biopsy tissues and tracheobronchial (TB) wash cells of TBM and non-TBM subjects. In addition, given that the bulk RNA sequencing and pathway analysis results suggest that SPRR and

KRT proteins may be the end products rather than components of the initial inflammatory events, we are planning to study whether mRNA-based gene signatures captured in RNAseq are translated and detectable at the protein level and if there are specific upstream pathway regulators in tracheobronchial wash and serum of TBM patients.

We continue to collaborate 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. This phase 2 study has been published and was presented at the 2020 Annual Meeting of the Society of Thoracic Surgeons, winning the J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery. The phase 3 study has just opened at BIDMC.

ACCOMPLISHMENTS 2019-2020

- Boston's Top Doctors, Thoracic and Cardiac Surgery; Castle Connolly and *Boston Magazine*, 2020
- Chair, Department of Surgery Committee on Diversity, Equity, and Inclusion

Invited Presentations

- Excessive Dynamic Airway Collapse: State-of-the-Art. Invited speaker, Clinical Controversy Session, American College of Chest Physicians (CHEST) annual conference; *virtual meeting*
- My iPhone as My Stethoscope (Cough-O-Meter). Invited speaker, Tech-Con General Thoracic Potpourri session, Society of Thoracic Surgeons annual meeting; New Orleans, LA
- Cardiothoracic Surgical Education and Professional Development. Moderator, Society of Thoracic Surgeons annual meeting; New Orleans, LA
- Tech-Con General Thoracic: Innovations in Lung Cancer Care, Moderator, Society of Thoracic Surgeons annual meeting; New Orleans, LA
- Pitfalls and Solutions in Virtual Interviews. Invited speaker, Thoracic Surgery Directors Association meeting, *virtual meeting*
- Surgical Placebo Effect, Grand Rounds, Department of Surgery, Beth Israel Deaconess Medical Center

TEACHING, TRAINING, AND EDUCATION

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

SELECTED RESEARCH SUPPORT

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)

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* 2020;27(2):128-134.

McCarty JC, Parker RK, Vidri RJ, Robinson KA, Lipsitz S, Gangadharan SP, Iyer P. A retrospective cohort study of endoscopic therapy and esophagectomy for stage 1 esophageal cancer: Less is more. *Gastrointest Endosc* 2020;92(1):23-30.

De Lima A, Vidal B, Kheir F, VanderLaan PA, Mallur PS, Gangadharan SP, Majid A. Thermoablative techniques for excessive central airway collapse: An ex vivo pilot study on sheep tracheal tissue. *J Bronchology Interv Pulmonol* 2020;27(3):195-9.

Fligor SC, Wang S, Allar BG, Tsikis ST, Ore AS, Whitlock AE, Calvillo-Ortiz R, Arndt KR, Gangadharan SP, Callery MP. Gastrointestinal malignancies and the COVID-19 pandemic: Evidence-based triage to surgery. *J Gastrointest Surg* 2020;24(10):2357-73.

Chaudhary O, Baribeau Y, Urits I, Sharkey A, Rashid R, Hess P, Krumm S, Fatima H, Zhang Q, Gangadharan S, Mahmood F, Matyal R. Use of erector spinae plane block in thoracic surgery leads to rapid recovery from anesthesia. *Ann Thorac Surg* 2020; in press.

Chow OS, Sudarshan M, Maxfield MW, Seese LM, Watkins AA, Fleishman A, Gangadharan SP. National survey of burnout and distress among cardiothoracic surgery trainees. *Ann Thorac Surg* 2020; in press.

Gangadharan S, Sarkaria I, Rice D, Murthy S, Braun J, Kucharczuk J, Predina J, Singhal S. Multi-institutional phase 2 clinical trial of intraoperative molecular imaging of lung cancer. *Ann Thorac Surg* 2020;Nov 19 (Epub ahead of print).

Robinson KA, Shin B, Gangadharan SP. A comparison between in-person and virtual fellowship interviews during the COVID-19 pandemic. *J Surg Educ* 2020;Nov 20 (Epub ahead of print).

Fligor SC, Tsikis ST, Wang S, Ore AS, Allar BG, Whitlock AE, Calvillo-Ortiz R, Arndt K, Callery MP, Gangadharan SP. Time to surgery in thoracic cancers and prioritization during COVID-19: A systematic review. *J Thorac Dis* 2020;12(11):6640-6654.



Adnan Majid, MD

Associate Professor of Medicine

Associate Professor of Surgery*

Chief, Section of Interventional Pulmonology

RESEARCH GROUP

Alvaro Ayala, MD
Christine Conley, BS
Mary Farquhar, RN
Erick Flores, MScPH
Fayez Kheir, MD
Daniel Ospina, MD
Mihir Parikh, MD
Rani Singh, PhD
Juan Pablo Uribe, MD

* Secondary appointment

RESEARCH FOCUS

Our research, which is clinical in nature, aims to improve care for patients with lung, airway, and pleural disorders. Our research areas include the following:

Lung Cancer

PRECISE Trial (Principal Investigator). This is a multicenter prospective evaluation of the clinical utility and early performance of the Ion Endoluminal System to bronchoscopically approach and facilitate the sampling of pulmonary nodules suspicious for malignancy. The benefits of this system may include a higher diagnostic yield than existing bronchoscopic biopsy modalities to the diagnosis of lung cancer.

ALTITUDE Trial (Co-Investigator). This is a multicenter, randomized controlled trial that prospectively evaluates the clinical utility of the Nodify XL2 proteomic classifier in incidentally discovered low to moderate risk lung nodules and the Nodify XL2 test results in the decision-making process when planning the management of lung nodules in order to reduce the number of unnecessary surgical and biopsy procedures.

Multicenter Registry for Patients Treated with Photodynamic Therapy (PDT) (Principal Investigator). The purpose of this research is to collect demographics, clinical data with disease specific information, procedural characteristics, survival and complications of patients who are treated with endobronchial photodynamic therapy (PDT). Data will be used to describe the baseline characteristics of patients treated with PDT and their treatment short and long-term outcomes.

A Phase 2 Randomized, Placebo-Controlled, Double-Blind, Dose-Ranging Study Evaluating LTI-01 (Single-Chain Urokinase Plasminogen Activator, Scupa) in Patients with Infected, Non-Draining Pleural Effusions (Co-Investigator). This study is a multicenter trial being done to identify an effective dose of LTI-01 for the treatment of infected, non-draining pleural effusions. Three different doses of the study drug, LTI-01, will be tested and compared against placebo.

Chronic Obstructive Pulmonary Disease (COPD)

Gala Early Feasibility Study of RheOx (Principal Investigator). This is a multicenter prospective observational study evaluating the safety and clinical utility of RheOx on patients with chronic bronchitis in the U.S.

RejuvenAir System Clinical Trial (Principal Investigator). This is a prospective, multicenter, 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.

COMPLETE-1 Clinical Trial (Principal Investigator). This is a randomized controlled feasibility clinical trial. The objective is to show that combining inter-lobar fissure completion via video assisted thoracoscopic surgery with endobronchial valves placement for the treatment of patients with severe heterogeneous emphysema and collateral ventilation improves lung function, exercise capacity, and quality of life.

Tracheobronchomalacia (TBM)

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

Airway Stents for Excessive Dynamic Airway Collapse: A Randomized Trial (Principal Investigator). 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.

Effect of Endoscopic Argon Plasma Coagulation (APC) on the Tracheobronchial Tree in Patients with Focal Airway Malacia (Principal Investigator). This is a pilot study to evaluate the safety and effectiveness of argon plasma coagulation (APC) when applied to the posterior wall of the trachea of patients with severe (>90%) symptomatic excessive dynamic airway collapse (EDAC) who are not candidates for corrective surgery of the airways (tracheobronchoplasty).

ACCOMPLISHMENTS 2019-2020

- Elected to American Association for Bronchology and Interventional Pulmonology (AABIP) Board of Directors
- Boston's Top Doctors, Castle Connolly, and *Boston Magazine*, 2019, 2020

Invited Presentations

- Endobronchial Valves: From Randomized Clinical trials to Clinical Practice. American College of Chest Physicians International meeting; New Orleans, LA
- Endobronchial Ultrasound and Lung Cancer Staging. National Cancer Meeting; Paracas, Peru
- Solitary Pulmonary Nodule, Diagnosis and Treatment. World Congress for Bronchology and Interventional Pulmonology (WCBIP), INER y Hospital ABC; Mexico City, Mexico
- Medical Thoracoscopy: An Update. World Congress for Bronchology and Interventional Pulmonology (WCBIP), INER y Hospital ABC; Mexico City, Mexico
- Endoscopic Therapies for COPD. Lung Force Expo American Lung Association, Framingham, MA
- Endoscopic Treatments for Patients with Severe COPD: Introduction to Bronchoscopy and Pulmonary Procedures, BIDMC, Boston, MA
- Percutaneous Tracheostomy: A Modified Technique. International Webinar, Pulmonary Procedures during COVID-19; Latin-American Thoracic Society (ALAT)
- Experiencing the Full Impact of Robotics on Lung Cancer Care in a Major Academic Center. 3rd American Association for Bronchology and Interventional Pulmonology (AABIP) Annual Conference, Tampa, FL
- Adult Tracheomalacia: An Update. 11th International Meeting 2020, St. Vincent's University Hospital, Dublin, Ireland
- Advances in Bronchoscopic Treatment of Emphysema: Complication Management. American College of Chest Physicians International Conference, Chicago, IL

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 four physicians into the competitive one-year program.

In 2012, I was appointed Director (and a major teacher) of the Interventional Pulmonology rotations for residents and the 20-24 pulmonary/critical care fellows who rotate through the Interventional Pulmonary service at BIDMC each year. In 2014, I launched the advanced diagnostic bronchoscopy fellowship, which now trains four senior

pulmonary fellows each year in advanced bronchoscopic techniques such as endobronchial ultrasound and navigation bronchoscopy. Also in 2014, I launched and now lead the Interventional Pulmonology Clinical Research Fellowship Program at BIDMC. This program provides four postdoctoral students each year with mentored, individualized research training to prepare them for careers in academic medicine.

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" and "Introduction to Pulmonary and Pleural Procedures" courses.

ABSTRACTS, POSTERS, AND EXHIBITS

Ospina-Delgado D, Kheir F, Vidal B, Beattie J, VanderLaan P, Majid A. Argon Plasma Coagulation for the Treatment of Excessive Dynamic Airway Collapse: An Animal Pilot Study. ACCP Conference, New Orleans, LA (oral presentation)

Uribe Becerra J, Ayala A, Carreiro M, Ospina-Delgado D, Kheir F, Gangadharan S, Wilson J, Parikh MS, Chee AC, Majid A. Description of Comorbidities in Excessive Central Airway Collapse (ECAC) Patients. ATS 2020 Conference; Philadelphia, PA (poster presentation)

Ospina-Delgado D, Parikh M, Gangadharan SP, Wilson JL, Kheir F, Chee AC, Majid A. Predictors of Complications during Stent Evaluation for Excessive Central Airway Collapse. ATS 2020 Conference; Philadelphia, PA (poster presentation)

Uribe Becerra J, Chee AC, Parikh MS, Majid A. Introducing Endoscopic Lung Volume Reduction with Endobronchial Valves for the Treatment of Severe Emphysema: Impact on Patient Volume and Use of Ancillary Services. ATS 2020 Conference; Philadelphia, PA (poster presentation)

Ayala A, Patel P, Kheir F, Chee AC, Parikh MS, Martinez R, Majid A. Intrapleural Instillation of tPA Alone Vs tPA and DNase for Loculated Malignant Pleural Effusions. ATS 2020 Conference; Philadelphia, PA (poster presentation)

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* 2020;27(2):128-34.

Majid A, Labarca G, Uribe JP, Kheir F, Pacheco C, Folch E, Jantz MA, Mehta HJ, Patel NM, Herth FJF, Fernandez-Bussy S. Efficacy of the Spiration Valve System in patients with severe heterogeneous emphysema: A systematic review and meta-analysis. *Respiration* 2020;9(1):62-72.

Majid A, Rivera E, Sisniega C, Husta B, Chee A, Parikh M, Holden V, Kheir F. Fluid infusion through chest tube to facilitate pleural procedures: A feasibility study. *J Bronchology Interv Pulmonol* 2020;27(3):190-4.

de Lima A, Vidal B, Kheir F, VanderLaan PA, Mallur PS, Gangadharan SP, Majid A. Thermoablative techniques for excessive central airway collapse: An ex vivo pilot study on sheep tracheal tissue. *J Bronchology Interv Pulmonol* 2020;27(3):195-9.

Holden VK, Ospina-Delgado D, Chee A, Parikh MS, Carreiro MM, Alape Moya D, Fernandez-Bussy S, Herth FJF, Majid A. Safety and efficacy of the tracheobronchial Bonastent: A single-center case series. *Respiration* 2020;99(4):353-9.

Kheir F, Thakore S, Mehta H, Jantz M, Parikh M, Chee A, Kaphle U, Sisniega C, Fernandez-Bussy S, Majid A. Intrapleural fibrinolytic therapy versus early medical thoracoscopy for treatment of pleural infection: Randomized clinical trial. *Ann Am Thorac Soc* 2020;17(8):958-64.

Chee A, Sierra-Ruiz M, Parikh MS, Majid A. Comparison of flexible 3D printed stenotic airway model versus standard model for therapeutic bronchoscopy training: A proof of concept. *J Bronchology Interv Pulmonol* 2020; in press.

Majid A, Ayala A, Uribe JP, Abdelghani R, Patel P, Chee A, Parikh M, Kheir F. Protective strategies in a simulated model when performing percutaneous tracheostomies in the COVID-19 era. *Ann Am Thorac Soc* 2020;17(11):1486-1488.



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 2019-2020

- Named Site Director of the Harvard Combined BIDMC/MGH Interventional Pulmonology Fellowship Program
- Selected to Rabkin Fellowship in Medical Education
- Invited speaker at CME course: Principles of Critical Care Medicine
- Multiple published manuscripts and conference presentations (see following page)



- ▲ In January 2020, the Division of Thoracic Surgery and Interventional Pulmonology hosted a daylong course, "Updates in Interventional Pulmonology," led by course director Alex Chee, MD, and course co-directors Mihir Parikh, MD, and Adnan Majid, MD. The course was attended by 40 clinicians from around the country.

TEACHING, TRAINING, AND EDUCATION

I am one of the core training faculty for the Interventional Pulmonology Fellowship Program at BIDMC. I am also Site Director of the Harvard Combined BIDMC/MGH Interventional Pulmonology Fellowship and Program Director of the Advanced Diagnostic Bronchoscopy Fellowship Program at BIDMC. In addition, I 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, which is attended by incoming 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

Beattie J, Uribe-Becerra J, 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

Holden V, Ospina-Delgado D, Chee A, Parikh M, Carreiro M, Alape D, Fernandez-Bussy S, Herth F, Majid A. Safety and efficacy of the tracheobronchial Bonastent: A single-center case series. *Respiration* 2020;99(4):353-359.

Kheir F, Rivera E, Sisniega C, Parikh M, Holden V, Chee A, Majid A. Fluid infusion through chest tube to facilitate pleural procedures: A feasibility study. *J Bronchology Interv Pulmonol* 2020;27(3):190-194.

Gosling AF, Bose S, Gomez E, Parikh M, Cook C, Sarge T, Shaefi S, Leibowitz A. Perioperative considerations for tracheostomies in the era of COVID-19. *Anesth Analg* 2020;131(2):378-386.

Kheir F, Thakore S, Mehta H, Jantz M, Parikh M, Chee A, Kaphle U, Sisniega C, Fernandez-Bussy S, Majid A. Intrapleural fibrinolytic therapy versus early medical thoracoscopy for treatment of pleural infection: A randomized controlled clinical trial. *Ann Am Thorac Surg* 2020;17(8):958-964.

Sierra-Ruiz M, Parikh M, Majid A, Chee A. Comparison of flexible 3D printed stenotic airway model versus standard model for therapeutic bronchoscopy training: A proof of concept study. *J Bronchology Interv Pulmonol* 2020;Jul 24 (Epub ahead of print).

Majid A, Ayala A, Uribe JP, Abdelghani R, Patel P, Chee A, Parikh M, Kheir F. Protective strategies in a simulated model when performing percutaneous tracheostomies in the COVID-19 era. *Ann Am Thorac Soc* 2020;17(11):1486-1488.



Jennifer L. Wilson, MD, MPH

Assistant Professor of Surgery

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 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

RESEARCH GROUP

Anastasia Bogdanovski, MD
Brian Campos, MD
Christopher Digesu, MD
Sidhu Gangadharan, MD, MHCM
Michael Kent, MD
Adnan Majid, MD
Mihir Parikh, MD
James Rodrigue, PhD
James Wallace, MD

ACCOMPLISHMENTS 2019-2020

- Completed the Harvard T. H. Chan Master's in Public Health-Clinical Effectiveness Program
- Served on the Promotions Committee
- Served on the Department of Surgery Diversity, Equity, and Inclusion Parental Leave Committee
- Served as a Harvard Surgery Research Day Committee Member

TEACHING, TRAINING, AND EDUCATION

Weekly thoracic surgery resident and fellow preoperative conference is held 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

Ascanio J, Pawlowski J, Mikhailov B, Kelly M, Kaneko M, Ruiz J, Ott Q, Pasley S, Wilson J, Kent M, Gangadharan SP. A Multidisciplinary Quality Improvement Project Can Significantly and Sustainably Reduce Wasted Time Prior to Starting Thoracic Surgical Operations. Accepted for oral presentation, American Association for Thoracic Surgery 2020 meeting (*canceled due to COVID-19*)

Singh R, Wang Z, Ascanio J, Chee A, Wilson JL, Majid A, Ospina-Delgado D, An T, Otsuka S, Zhang LT, Gangadharan SP. Quantification of the Airflow Effects After Tracheobronchoplasty By Computational Fluid Dynamics Modeling Is More Accurate Than Standard Spirometric Testing. Accepted for oral presentation, American Association for Thoracic Surgery 2020 meeting (*canceled due to COVID-19*)

Buitrago DH, Wilson JL, Bezuidenhout F, Litmanovich D, Parikh M, Chee A, Majid A, Gangadharan SP. Tracheobronchoplasty Provides Long-term Anatomic, Functional, and Subjective Benefit for Patients with Severe, Diffuse Tracheobronchomalacia. CHEST Annual Meeting 2019; New Orleans, LA

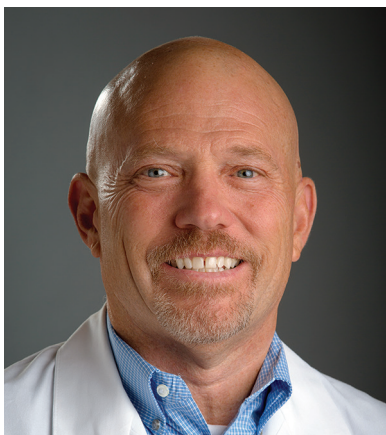
SELECTED PUBLICATIONS

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;29(12):1561-1564.

Watkins AA, Kent MS, Wilson JL. Surgical adjuncts during esophagectomy. *Thorac Surg Clin* 2020;30(3):315-20.

Chow O, Wilson JL, Gangadharan SP. Neurogenic tumors of the posterior mediastinum. In: Sugarbaker DJ, editor. *Adult Chest Surgery: Concepts and Procedures*, 3rd ed. New York: McGraw-Hill; 2020; p.1422-1430.

Maxfield MW, Wilson JL, Gangadharan SP. Overview of benign pleural conditions: Anatomy and physiology of pleura. In: Sugarbaker DJ, editor. *Adult Chest Surgery: Concepts and Procedures*, 3rd ed. New York: McGraw-Hill; 2020; p. 1172-1179.



Devin E. Eckhoff, MD

Professor of Surgery

Chief, Division of Transplant Surgery

Director, BIDMC Transplant Institute

RESEARCH GROUP*

Douglas J. Anderson, MD

David K.C. Cooper, MD, PhD

Hidetaka Hara, MD, PhD

Hayato Iwase, MD, PhD

Takayuki Yamamoto, MD

**University of Alabama (UAB)*

RESEARCH FOCUS

I was recruited to BIDMC and Harvard Medical School from the University of Alabama (UAB) in the Fall of 2020, therefore the research and accomplishments on these pages largely reflect my tenure at UAB. I am excited to continue this work in collaboration with colleagues at BIDMC and Harvard Medical School and the rich research environment of which they are a part, as well as with my colleagues at UAB.

There is an inadequate supply of organs from deceased human donors, which severely limits the number of organ transplants that can be performed each year. Xenotransplantation—using pigs as sources of organs—if successful, would resolve this continuing problem. However, the primate immune response to a pig organ has proven to be rapid and severe, and overcoming this barrier has been the focus of this research group. Progress has been made, largely through the availability of increasingly sophisticated genetically engineered pigs, and the introduction of novel immunosuppressive agents. The basic strategies employed in designing these genetically engineered pigs is the deletion of antigens that are targeted by the immune response and/or the addition of “protective” genes.

ACCOMPLISHMENTS 2019–2020

- Upgraded UAB’s xenotransplantation pig research facility for producing a small number of genetically modified pigs for use in a pilot clinical trial
- Co-authored several manuscripts examining the results in preclinical xenotransplantation trials and met the criteria to initiate a clinical trial
- Delivered Grand Rounds at BIDMC: “Xenotransplantation: Can It Solve the Organ Shortage?”
- Secured Designated Pathogen-Free (DPF) Operating Agreement, United Therapeutics
- Delivered Grand Rounds presentation on Xenotransplantation: Current Status and Future Prospects. Scripps Solid Organ Transplant Workshop, San Diego, CA
- Presented research at several regional, national, and international scientific conferences
- Elected as Councilor-at-Large on the Board of Directors of the American Society of Transplant Surgeons
- Named Chief of Transplant Surgery in the Department of Surgery and Director of the Transplant Institute at Beth Israel Deaconess Medical Center (BIDMC)
- Abstract reviewer for 2021 American Transplant Congress (Tolerance in Transplantation)

TEACHING, TRAINING, AND EDUCATION

At BIDMC, I continue to provide training and mentorship to medical students, surgical residents, and surgical faculty. At UAB, I served as a member of the Faculty Mentorship Program and was the recipient of the Department of Surgery Medical Student Teaching Award.

SELECTED RESEARCH SUPPORT

Genetically Engineered Pig Organ Transplantation in Baboons: Immunological and Functional Studies. NIH U19, 2020–2025; PI: David Cooper, MD, PhD; Co-Investigators: Hayato Iwase, MD, PhD, Eric Judd, MD, Devin E. Eckhoff, MD

A Multicenter Randomized Controlled Trial to Compare the Efficacy of *Ex-Vivo* Normothermic Machine Perfusion with Static Cold Storage in Human Liver Transplantation. OrganOx Ltd., 2017–2020; Site PI: Devin E. Eckhoff, MD

Completion of Experimental Kidney Xenotransplantation Program using Revivicor Pigs as a Preliminary to a Clinical Trial. United Therapeutics (2020); PI: Devin E. Eckhoff, MD; Co-Investigator: David Cooper, MD, PhD

SELECTED PUBLICATIONS

Mustian MN, Kumar V, Stegner K, Mompoin-Williams D, Hanaway M, Deierhoi MH, Young C, Orandi BJ, Anderson D, MacLennan PA, Reed RD, Shelton BA, Eckhoff D, Locke JE. Mitigating racial and sex disparities in access to living donor kidney transplantation: Impact of the nation's longest single-center kidney chain. *Ann Surg* 2019;270(4):639–646.

Hurst DJ, Padilla LA, Walters W, Hunter JM, Cooper DKC, Eckhoff DM, Cleveland D, Paris W. Paediatric xenotransplantation clinical trials and the right to withdraw. *J Med Ethics* 2020;46(5):311–315.

Hurst DJ, Padilla LA, Trani C, McClintock A, Cooper DKC, Walters W, Hunter J, Eckhoff D, Cleveland D, Paris W. Recommendations to the IRB review process in preparation of xenotransplantation clinical trials. *Xenotransplantation* 2020;27(2):e12587.

Cannon R, Goldberg DS, Eckhoff DE, Anderson DJ, Orandi BJ, Locke JE. Early outcomes with the liver-kidney safety net. *Transplantation* 2020; in press.

Cooper DKC, Hara H, Iwase H, Yamamoto T, Jagdale A, Kumar V, Mannon RB, Hanaway MJ, Anderson DJ, Eckhoff DE. Clinical pig kidney xenotransplantation: How close are we? *J Am Soc Nephrol* 2020;31(1):12–21.

Yamamoto T, Hara H, Iwase H, Jagdale A, Bikhel MH, Morsi MA, Cui Y, Nguyen HQ, Wang ZY, Anderson DJ, Foote J, Schuurman HJ, Ayares D, Eckhoff DE, Cooper DKC. The final obstacle to successful pre-clinical xenotransplantation? *Xenotransplantation* 2020;27(5).

James R. Rodrigue, PhD

Professor

Vice Chair, Clinical Research



RESEARCH GROUP

Matt Boger, MS
 Amanda Calvo, BA
 Stephanie Cohen, MD
 Vanessa Cowan, MD
 Sarah Duncan, ALB
 Amy Evenson, MD, MPH
 Mario Feranil, BS
 Aaron Fleishman, MPH
 Sara Hawthorne, BA
 Leo Magrini, BS
 Christopher Mistretta, RN, BSN
 Amber Nieves, BA
 Jessica Shenkel, MA
 Joanna Sullivan, RN, BSN

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 causes 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 2019-2020

- Continuation of research grants from the Health Resources and Services Administration to evaluate strategies to effectively increase organ donor registrations in veterans; the NIDDK to evaluate the effectiveness of reimbursing living donor lost wages on rates of live donor kidney transplantation; and Patient-Centered Outcomes Research Institute (PCORI) to evaluate the differential effectiveness of Transplant House Calls and Peer Mentorship on rates of live donor kidney transplantation in Black patients
- Published 20 peer-reviewed manuscripts focused primarily on outcomes related to transplantation and living donation
- Delivered several invited presentations on disparities in kidney transplantation at the American Society of Transplantation's Cutting Edge of Transplantation (CEOT) meeting in Phoenix, AZ; the American Foundation for Donation and Transplantation's Living Donation Conference in Clearwater, FL; the American Transplant Congress in Boston, MA; and the European Society of Transplantation in Copenhagen, Denmark

- Department of Surgery FIRST Program staff contributed to more than 30 scientific papers

Other Recent Accomplishments Include

- Abstract reviewer for 2020 American Transplant Congress (Disparities in Outcome and Access to Healthcare)
- Co-authored the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation
- Appointed Member of the American Society of Transplantation's Inclusion, Diversity, Equity Task Force

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
- Director of the FIRST Program's bi-weekly Clinical Research Seminar, an interactive venue for clinical research sharing, learning, collaboration, and engagement in the department
- Chair of the Department of Surgery Appointment, Re-appointments, and Promotions Committee

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, 2015-2021; PI: James Rodrigue, PhD (Co-Investigators: Amy Evenson, MD, MPH, Derek DuBay, MD)

Increasing VCA Donation Knowledge, Attitudes, Willingness, and Designations in Veterans. HRSA, 2017-2021; 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

Berrigan M, Austrie J, Fleishman A, Tercyak KP, Pollak MR, Pavlakis M, Rohan V, Baliga PK, Kayler LK, Feeley TH, Rodrigue JR. Opinions of African-American adults about the use of apolipoprotein L1 (ApoL1) genetic testing in living kidney donation and transplantation. *Am J Transplant* 2020; in press.

Ward S, Boger M, Fleishman A, Shenkel J, Calvo A, Pomahac B, Zwolak R, Krishnan N, Rodrigue JR. Attitudes toward organ, tissue and vascularized composite allograft (VCA) donation and transplantation: A survey of United States military veterans. *Transplantation* 2020; in press.

Sokas CM, Berrigan MT, Fligor SC, Fleishman AJ, Raven KE, Rodrigue JR. Is social distancing keeping patients from the ED? *Am J Emerg Med* 2020; 16:S0735-6757(20)30616-1.

Carroll AJ, Christon LM, Rodrigue JR, Fava JL, Frisch MB, Serber ER. Implementation, feasibility, and acceptability of quality of life therapy to improve positive emotions among patients with implantable cardioverter defibrillators. *J Behav Med* 2020;43:968-978.

Fleishman A, Khwaja K, Schold JD, Comer CD, Morrissey P, Whiting J, Vella J, Kayler LK, Katz D, Jones J, Kaplan B, Pavlakis M, Mandelbrot DA, Rodrigue JR, and the KDOC Study Group. Pain expectancy, prevalence, severity, and patterns following donor nephrectomy: Findings from the KDOC Study. *Am J Transplant* 2020;20:2522-2529.

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* 2020;20:181-189.

Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, Kumar D, Oberbauer R, Pascual J, Pilmore HL, Rodrigue JR, Segev DL, Sheerin NS, Tinckam KJ, Wong G, Balk EM, Gordon CE, Earley A, Rofeberg V, Knoll GA. Summary of the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. *Transplantation* 2020;104:708-714.

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.



Peter Chang, MD, MPH

Assistant Professor of Surgery

Director, BIDMC Prostate Cancer Center

Director, BID-Milton Robotic Surgery Program

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. As Director of the BIDMC Prostate Cancer Center, I will describe my research efforts to optimize quality-of-life in prostate cancer patients. I also am very active clinically in the surgical treatment of bladder cancer, and have a more recent research focus on radical cystectomy.

RESEARCH GROUP

Catrina M. Crociani, MPH

Da David Jiang, MD

Allison Kleeman

Yu-Chen Liu

Andrew Wagner, MD

Adrian Waisman, MD

Prostate Cancer

Quality-of-life assessment in prostate cancer patients

At BIDMC, we are committed to giving every patient with prostate cancer a chance to have the best quality of life possible. Unfortunately, prostate cancer treatment can cause significant side effects, and doctors tend to underestimate how bad these are, potentially leaving patients with long-lasting quality of life problems. My research focuses on accurate and objective measurement of prostate cancer quality of life using patient-reported outcome questionnaires. I developed a new questionnaire called "EPIC for Clinical Practice (EPIC-CP)," designed to be used by clinicians rather than researchers (Chang P et al, J Urol, Sep 2011). I recently showed that EPIC-CP can allow a doctor to estimate the chances of a patient recovering sexual function after prostate cancer surgery (Chipman et al, J Urol, Mar 2014). Due to its development here at BIDMC, our institution is at the forefront of using EPIC-CP as part of prostate cancer care. I 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), and the instrument continues to be used as both a clinical and research tool throughout the nation.

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

ACCOMPLISHMENTS 2019-2020

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. A larger study comparing outcomes between open and robotic surgery is pending publication.

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.

I was selected to be a faculty member for the 18th 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

BIDMC Department of Surgery Pilot Randomized Controlled Trial Award, 2021-2022; 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.

Chang P, Renehan P, Taylor KN, Dewey LE, McAnally KC, Hyde S, Crociani CM, Carneiro A, Beaulieu LT, Wagner AA. Societal costs of localized renal cancer surgery. *Can J Urol* 2018;25(4):9401-9406.

Einstein DJ, Patil D, Chipman J, Regan MM, Davis K, Crociani CM, Wagner AA, Sanda MG, Chang P. Expanded Prostate Cancer Index Composite-26 (EPIC-26) online: Validation of an internet-based instrument for assessment of health-related quality of life after treatment for localized prostate cancer. *Urology* 2019;127:53-60.

Stensland KD, Chang P, Wagner AA. The urologist's role in the opioid epidemic. *Curr Opin Urol* 2019;29(4):466-468.

Delto JC, Chang P, Hyde S, McAnally K, Crociani C, Wagner AA. Reducing pseudoaneurysm and urine leak after robotic partial nephrectomy: Results using the early unclamping technique. *Urology* 2019;132:130-135.

Althaus AB, Chang P, Mao J, Olugbade K, Taylor K, Dewey L, Percy A, Crociani C, McAnally K, Wagner AA. Patient-reported quality of life and convalescence after minimally invasive kidney cancer surgery. *Urology* 2020;144:123-129.



RESEARCH GROUP

Peter Chang, MD, MPH
 Issa Dahabreh, MD, MS, ScD
 Aaron Fleishman, MPH
 Sumedh Kaul, MS
 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.

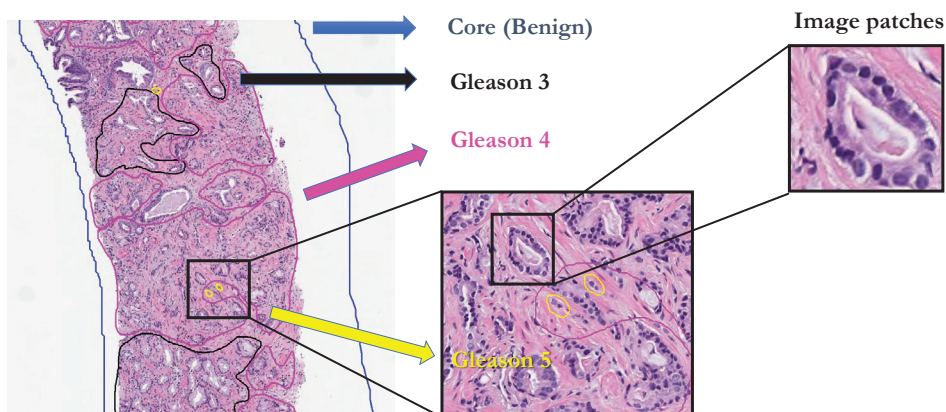
Using Observational Data for Comparative Effectiveness Research When Clinical Trial Evidence is Limited

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 are applying the emulation framework to the study of kidney, prostate, and bladder cancer. For example, in one completed 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.

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.



▲ FIGURE 1: Classification of core biopsy specimen patches as benign versus Gleason 3 versus Gleason 4 versus Gleason 5.

ACCOMPLISHMENTS 2019-2020

- I was selected to the Society of Urologic Oncology Young Urologic Oncologists Steering Committee in 2020.
- In 2020, I started the EXPLORE (Experiential Learning Opportunity in Research) Program, which pairs medical students with faculty mentors for an experiential learning process that teaches applied research methods in a problem-based approach.
- I continue to serve as a peer reviewer for multiple journals, including *Annals of Internal Medicine*, *Lancet*, *European Urology*, *Journal of Urology*, and *Urologic Oncology*.
- I served as a member of the 2020 Program Committee for the New England section of the American Urological Association annual meeting.
- I was invited to present 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."
- I served as an invited peer reviewer for the 2019 AUA Guideline on the Diagnosis and Treatment of Early Stage Testicular Cancer.

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. Working together with a group of medical students in 2020, I co-led an effort to a urology question deck for the popular flashcard app, Anki. Finally, I provide training in research and statistical methods through mentorship of medical students and residents in clinical research projects.

ABSTRACTS, POSTERS, AND EXHIBITS

Reitblat C, Fleishman A, Kaplan I, Stensland K, D'Amico A, Olumi A, Wagner A, Chang P, Kim S, Korets R, Gershman B. Emulating a Clinical Trial of Radical Prostatectomy versus External Beam Radiation Therapy for High-Grade, Clinically Localized Prostate Cancer. American Urological Association annual meeting; Washington, DC (oral presentation by Chanan Reitblat)

Unadkat P, Fleishman A, Olumi A, Wagner A, Chang P, Kim S, Korets R, Gershman B. Examining the Survival Benefit of Inguinal Lymph Node Dissection in Men with cN0 Penile Cancer. American Urological Association annual meeting; Washington, DC (poster presentation)

Kott O, Li S, Linsley D, Amin A, Golijanin B, Golijanin D, Serre T, Gershman B. A Deep Learning Algorithm for the Diagnosis and Gleason Grading of Whole Slide Images of Prostate Cancer Core Biopsies. American Urological Association annual meeting; Washington, DC (oral presentation by Ohad Kott)

Monfared S, Fleishman A, Korets R, Chang P, Wagner A, Bubley G, Kaplan I, Olumi A, Gershman B. The Impact of Pre-Treatment PSA on Risk Stratification in Men with Gleason 6 Prostate Cancer: Implications for Active Surveillance. New England Section, American Urologic Association annual meeting (oral presentation by Sina Monfared)

Ramos F, Fleishman A, Korets R, Johnson M, Olumi A, Tsai L, Gershman B. Predicting Cancer Detection Rates from Multiparametric Prostate MRI: Refining the PI-RADS Categorization System. New England Section, American Urologic Association annual meeting (poster presentation)

SELECTED PUBLICATIONS

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 Oncol* 2020;38(3):76.e19-76.e28.

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* 2020;38(5):1243-52.

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* 2020;6(2):305-312.

Bacic J, Liu T, Thompson RH, Boorjian SA, Leibovich BC, Golijanin D, Gershman B. Emulating target clinical trials of radical nephrectomy with or without lymph node dissection for renal cell carcinoma. *Urology* 2020;140:98-106.

Morrison JC, Gershman B, Konety B, Cost N, Kim SP. Centralization of health care to facilitate greater use of nephron-sparing surgery for localized renal tumors: Identifying appropriate health care delivery. *Ann Surg Oncol* 2020;27(6):1735-6.

Unadkat P, Olumi AF, Gershman B. The role of lymphadenectomy in patients with advanced renal cell carcinoma (RCC). *Urol Clin North Am* 2020;47(3):371-7.

Nguyen DD, Reitblat C, Andino JJ, Couture F, Sui W, Cone EB, Gershman B, Haleblan GE, Kathrins MN, Korets R, Kraft KH, Perrotte P, Scarpato KR, Singla A, Lee JY, Bhojani N. Virtual 'matchmaking' without visiting electives: Overview of the early U.S. experience and potential applications to the 2021 Canadian Urology match. *Can Urol Assoc J* 2020; in press.

A complete list of publications begins on page 15.

Ruslan Korets, MD

Assistant Professor of Surgery

Associate Program Director, Urology Residency Program



RESEARCH GROUP

Peter Steinberg, MD

RESEARCH FOCUS

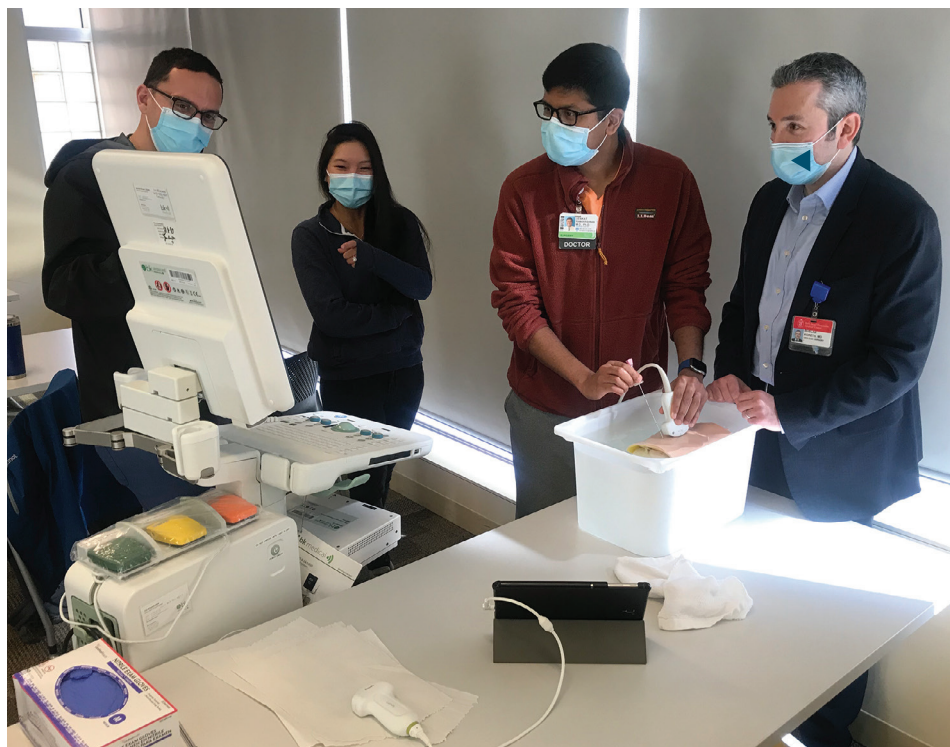
Clinical Outcomes in Surgical Treatment of Nephrolithiasis

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 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 have also initiated 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.

- Teaching ultrasound-guided access to urology residents from Boston urology residency programs.



ACCOMPLISHMENTS 2019-2020

Teaching and surgical education continue to be important aspects of my career and practice. Over the last two years I have been involved in establishing an independent Urology residency program at Beth Israel Deaconess Medical Center, recruiting our first two residents, and successfully matching another two residents earlier this year. In my role as the Associate Program Director, I oversee academic and clinical programs for training the next generation of urologic surgeons.

TEACHING, TRAINING, AND EDUCATION

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.

In 2019, 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

Ramos F, Korets R, Fleishman A, Johnson M, Olumi A, Gershman B. Comparative Effectiveness of MRI-U/S Fusion Versus In-bore MRI-targeted Prostate Biopsy. New England Section, American Urological Association annual meeting (virtual); Burlington, VT (abstract)

Monfared S, Fleishman A, Korets R, Chang P, Wagner A, Olumi A, Gershman B. The Impact of Pre-Treatment PSA on Risk Stratification in Men with Gleason 6 Prostate Cancer: Implications for Active Surveillance. New England Section, American Urological Association annual meeting (virtual); Burlington VT (virtual)

SELECTED PUBLICATIONS

Childs B, Manganiello M, Korets R. Novel education and simulation tools in urologic training. *Curr Urol Rep* 2019;20(12):81.



◀ Dr. Korets lecturing (pre-COVID) at the Ukrainian Urologic Forum on Percutaneous Renal Surgery Techniques, which was held in Kiev. Dr. Korets was co-chair of the forum.

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, Urologic Surgery

RESEARCH GROUP

Andrew Chang
Xingbo Long, MD
Christina Sharkey, BA
Zongwei Wang, PhD
Xiaobo Wu, 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. In our research, we clinically evaluate the mechanisms of resistance to 5 α -reductase inhibitor, finasteride, one of the more common drugs used to manage BPH and associated LUTS.

Ongoing work in our lab has focused on steroid 5 α -reductase 2 (SRD5A2, aka: 5 α -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. Our studies indicate that: 1) methylation of the *SRD5A2* is regulated by direct binding of the DNA-methyl transferase 1 (DNMT1) protein to the *SRD5A2* promoter; 2) the inflammatory mediators TNF- α , NF- κ B, and IL-6 regulate *DNMT1* binding and subsequent methylation of the *SRD5A2* promoter region; 3) clinical conditions associated with increased inflammation, age, and obesity are associated with decreased expression of SRD5A via epigenetic modification; 4) in the absence of prostatic SRD5A2, where androgenic pathways are blocked, alternate estrogenic pathways are upregulated, leading to an androgenic-to-estrogenic switch in the prostate gland, thus creating alternate pathways for prostatic growth. 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.

To demonstrate the clinical significance of epigenetic changes to *SRD5A2* and confirm its role in regulating sensitivity to 5ARI treatment, we propose the following aims: *Specific Aim 1*: To assess the role of 5-AR2 expression in the development of resistance to 5ARI therapy. *Specific Aim 2*: To demonstrate that SRD5A2 methylation turns on estrogen pathways and affects sensitivity to 5ARI therapies in men with BPH. *Specific Aim 3*: To determine that prostatic inflammation is associated with methylation of SRD5A2 promoter. Our findings have broad implications for the development of predictive biomarker assays that can be used to evaluate resistance to BPH-related therapies and allow clinicians to select alternate therapies for managing the most common proliferative disorder affecting men worldwide.

ACCOMPLISHMENTS 2019-2020

- Received funding for NIH/R01 grant; 2020-2025; Title: 5-Alpha Reductase 2 as a Marker of Resistance to 5ARI Therapy; direct and indirect total: \$1.84 million
- Society of Basic Urologic Research: 2020 Distinguished Service Award recipient

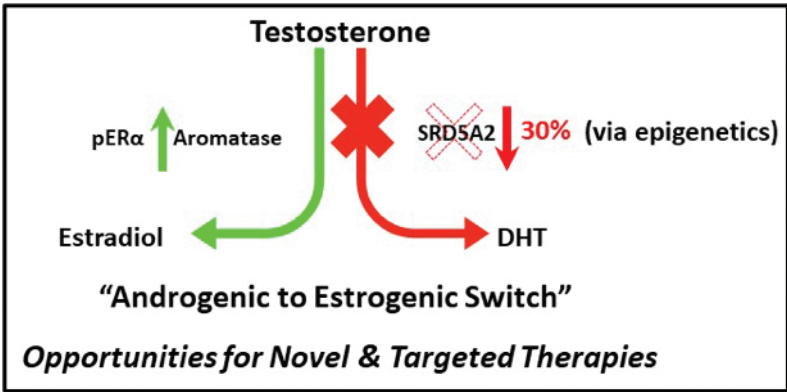
TEACHING, TRAINING, AND EDUCATION

- BIDMC Urology faculty, in partnership with medical students at HMS and other schools across the nation, developed the BIDMC Urology Anki flashcard app to help prepare medical students for sub-internships. Thus far, the popular app has had over 730 downloads nationally.
- BIDMC, Brigham and Women’s Hospital, and Massachusetts General Hospital Urology programs collaborated to hold a virtual sub-internship rotation for Harvard Medical School students.

SELECTED RESEARCH SUPPORT

- 5-Alpha Reductase 2 as a Marker of Resistance to 5ARI Therapy. NIH/R01, 2020-2025; PI: Aria F. Olumi, MD
- 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

▼ FIGURE 1: Opportunities for novel and targeted therapies



SELECTED PUBLICATIONS

Zhang H, Frendl D, Wang Z, Olumi AF. High real-world medication adherence and durable clinical benefit in Medicare patients treated with 5-alpha reductase inhibitors for benign prostatic hyperplasia. *J Urol* 2020;204(2):325-331.

Xue B, Wu S, Sharkey C, Tabatabaei S, Wu CL, Tao Z, Cheng Z, Strand D, Olumi AF, Wang Z. Obesity-associated inflammation induces androgenic to estrogenic switch in the prostate gland. *Prostate Cancer Prostatic Dis* 2020;23(3):465-474.

Wang Z, Deng T, Long X, Lin X, Wu S, Wang H, Ge R, Zhang Z, Wu CL, Taplin ME, Olumi AF. Methylation of SRD5A2 promoter predicts a better outcome for castration-resistant prostate cancer patients undergoing androgen deprivation therapy. *PLoS One* 2020;15(3):e0229754.

Liu D, Shoag JE, Poliak D, Goueli RS, Ravikumar V, Redmond D, Vosoughi A, Fontugne J, Pan H, Lee D, Thomas D, Salari K, Wang Z, Romanel A, Te A, Lee R, Chughtai B, Olumi AF, Mosquera JM, Demichellis F, Elemento O, Rubin MA, Sboner A, Barbieri CE. Integrative multiplatform molecular profiling of benign prostatic hyperplasia identifies distinct subtypes. *Nat Commun* 2020;11(1):1987.

Wu S, Lin X, Lin SX, Lu M, Deng T, Wang Z, Olumi AF, Dahl DM, Wang D, Blute ML, Wu CL. Impact of biopsy perineural invasion on the outcomes of patients who underwent radical prostatectomy: A systematic review and meta-analysis. *Scand J Urol* 2019; Aug 10:1-8 (Epub ahead of print).

Wu S, Lin SX, Wirth GJ, Lu M, Lu J, Subtelny AO, Wang Z, Olumi AF, Dahl DM, Blute ML, Wu CL. Long-term oncologic impact of positive anterior and posterior surgical margins after radical prostatectomy. *Am J Clin Oncol* 2020; in press.

Heidi J. Rayala, MD, PhD

Assistant Professor of Surgery



RESEARCH GROUP

Alejandro Abello, MD
 Heather Faulkner, MD
 Taisha Joseph
 Suprita Krishna, MD
 Rumel Mahmood, MA, MSc
 Ketan Sheth, MD

RESEARCH FOCUS

Cancer Screening Disparities in Health Safety Net Populations

In collaboration with colleagues at Cambridge Health Alliance, we identified patient populations within a Health Safety Net health system that were at risk in screening for breast, cervical, and colorectal cancer. Our current work is focused on assessing factors that contribute to reduced screening for colorectal cancer in a Health Safety Net population. We are studying how a patient's "race" differs from "ethnicity," and querying whether broadly grouping ethnicities within the small census-defined "race" categories can obfuscate important differences. We have found that our non-English-speaking patients have higher colorectal screening rates when compared to their English-speaking counterparts, and are analyzing whether factors such as substance abuse and mental health may contribute to reduced screening in this unique patient population.

Impact of Language Barriers on Patient Satisfaction in a Health Safety Net Population

We seek to assess patient satisfaction and understanding in our non-English-speaking patients in an ambulatory clinic setting through a text message-based platform. Areas of interest include how language barriers impact a patient's satisfaction with an ambulatory encounter and the patient's assessment of the success of the medical team in communicating the medical plan.

Medical Student Education and Early Exposure to Surgical Careers

As an instructor for courses and workshops at Harvard Medical School, I have continued to promote surgery as a field of medicine that can provide a supportive and nurturing career path. In my role as Co-Director for Harvard Medical School's Introduction to Suturing, my colleagues and I are now assessing student interest in surgery before and after the workshop to determine whether the workshop has a positive impact on students' interest in the field of surgery.

ACCOMPLISHMENTS 2019-2020

Educational Instruction

- Course Instructor for the Harvard Medical School Practice of Medicine Introduction to the GU exam
- Co-Director of the Harvard Medical School Suturing Workshop

Other Accomplishments

- Harvard Medical School Admissions Committee Member
- Promotion to Assistant Professor of Surgery
- Boston's Top Doctors, Urology; Castle Connolly and *Boston Magazine*, 2020

TEACHING, TRAINING, AND EDUCATION

In 2020, I began my role as supervising attending for the resident-run Genitourinary Clinic. In this unique role, I am able to merge my interest in providing the best possible care to underserved patients with my love of teaching. During our busy weekly clinic, I work with the residents to teach methods for smooth clinic flow, clinic documentation, billing, and time management. I support their education on general urology topics that they might not be exposed to in the operating room. Most importantly, I share my joy in caring for these underserved patients.

In my private clinics, I offer a longitudinal urology clinic experience for internal medicine residents interested in pursuing primary care. I mentor a rotating series of residents, providing tips and tools for approaching the medical management of common urologic problems.

INVITED PRESENTATIONS

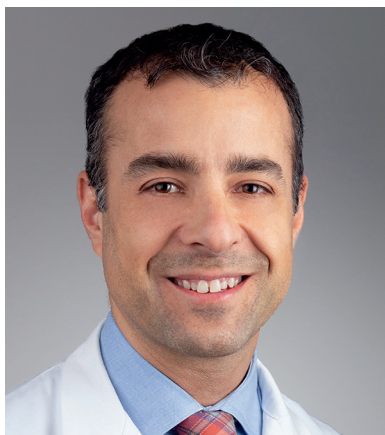
- Medical Management of BPH, Harvard Primary Care Internal Medicine CME Course, Boston, MA
- Prostate Cancer Screening: System-based Workflows. Department of Family Medicine Grand Rounds, Cambridge Health Alliance, Cambridge, MA
- The Pesky Prostate: Update on PSA Screening Guidelines. Department of Internal Medicine Grand Rounds, Cambridge Health Alliance, Cambridge, MA
- Invited Guest on "Health Corner," a Haitian language radio show in partnership with Universités de Haiti. The topic was "The Many Reasons for Frequent Urination"

Andrew A. Wagner, MD

Associate Professor of Surgery

Director, Minimally Invasive Urologic Surgery

Director, Minimally Invasive Urologic Surgery Fellowship Program



RESEARCH GROUP

Peter Chang, MD, MPH

Catrina Crociani, MPH

Da David Jiang, MD

Allison Kleeman, BS

Yuchen Liu, BS

Adrian Waisman, MD

RESEARCH FOCUS

Kidney Cancer

Using prospectively collected, patient-reported quality-of-life data after kidney surgery we can now provide detailed recovery expectations for our patients. We recently published our findings evaluating recovery trends after minimally invasive partial nephrectomy and radical nephrectomy, finding patients routinely require at least six weeks for full recovery. We also presented our multicenter study evaluating the use of aspirin during robotic partial nephrectomy, a surgery notorious for bleeding risk. We found a slightly higher risk of bleeding and complications in these patients, however the continuation of aspirin appeared to be safe.

Our team is also interested in non-operative approaches to small renal masses. A collaboration with researchers at 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. Our 10-year outcomes were recently presented and submitted for publication, demonstrating that 16% of patients initially choosing active surveillance cross over to intervention—usually partial nephrectomy. Therefore over 80% were spared surgery. There was no difference in cancer-specific survival between active surveillance and primary intervention.

Bladder Cancer

We are the first urology team in Boston to regularly perform radical cystectomy and urinary diversion entirely robotically. Through our membership in the IRCC (International Radical Cystectomy Consortium), we have published on a variety of issues, including the rates of cancer recurrence after robotic cystectomy and the impact of perioperative chemotherapy on survival after robotic cystectomy.

We also have recent funding and IRB approval for a randomized trial at BIDMC to evaluate the use of home IV fluids after cystectomy. Bladder cancer patients have a high readmission rate due to dehydration and this study will evaluate the utility of this type of preventive treatment.

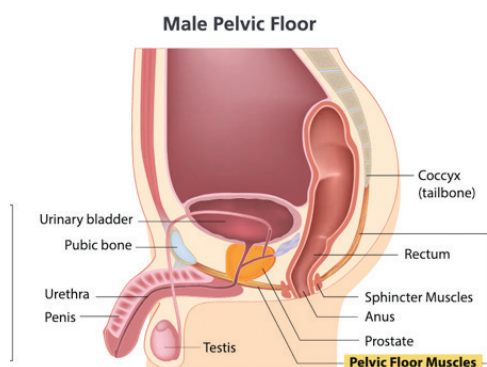
Prostate Cancer

We continue to investigate a novel method of identifying positive margins in real time during robotic prostatectomy using a non-linear microscope (NLM) and have begun a pilot study evaluating prostatectomy specimens immediately after surgery using NLM. Information gained through this IRB-approved pilot study will be used to design a randomized trial to evaluate the ability of NLM to improve our rate of nerve-sparing and reduce final positive margins.

We are one of the area's leaders in the field of prostate cancer active surveillance. 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 more than 2,000 patients enrolled. This project was recently awarded an NIH UO1 grant to support research infrastructure for the next five years.

As part of our ongoing interest in quality of life after prostatectomy, we evaluated the importance of preoperative pelvic floor physical therapy in our robotic radical prostatectomy database. We found that pelvic sphincter endurance measured preoperatively was predictive of early recovery of continence.

▼ FIGURE 1: Pelvic floor muscles evaluated during a preoperative physical therapy visit prior to robotic radical prostatectomy.



Model (n = 144)

	Adjusted OR (95% CI)	p-value
Age	0.96 (0.89,1.03)	0.25
BMI	0.94 (0.86,1.04)	0.23
D'Amico risk classification for prostate cancer		0.54
Low Risk (ref)	--	--
Intermediate Risk	0.81 (0.22,2.78)	--
High Risk	0.50 (0.11,2.08)	--
Nerve Sparing		0.45
Bilateral Non-Nerve Sparing	0.52 (0.09,2.78)	--
Unilateral/Bilateral Complete or Partial Nerve Sparing (ref)	--	--
Prostate Volume (cc)	0.98 (0.96,1.00)	0.036
Pelvic Floor Resting Tone (microV)	1.06 (0.82,1.36)	0.64
Pelvic Floor Working Tone (microV)	0.98 (0.94,1.03)	0.45
Pelvic floor endurance		0.015
Yes	2.70 (1.23,6.25)	--
No	--	--
Dominant Hand Grip Strength	1.01 (0.99,1.04)	0.17

ACCOMPLISHMENTS 2019-2020

- We began our pilot study evaluating the NLM microscope during robotic radical prostatectomy
- We trained our seventh Minimally Invasive Urology Fellow, Kola Olugbade, MD
- We presented our multicenter experience evaluating the use of aspirin during robotic partial nephrectomy at the national AUA meeting in 2020
- We identified factors measurable during a preoperative pelvic floor therapy visit that can predict early return of continence after robotic radical prostatectomy
- We received funding for a pilot study, randomizing patients after cystectomy to receive home IVF vs standard of care
- We have enrolled over 280 patients in the prospective Prostate Cancer Active Surveillance Study (Canary-PASS)

TEACHING, TRAINING, AND EDUCATION

In addition to training our BIDMC urology residents, in 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, named in honor of our Chief of Urology for more than 25 years. 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

Althaus AB, Chang P, Mao J, Olugbade K, Taylor K, Dewey L, Percy A, Crociani C, McNally K, Wagner AA. Patient-reported quality of life and convalescence after minimally invasive kidney cancer surgery. *Urology* 2020;144:123-129.

Cooperberg MR, Zheng Y, Faino AV, Newcomb LF, Zhu K, Cowan JE, Brooks JD, Dash A, Gleave ME, Martin F, Morgan TM, Nelson PS, Thompson IM, Wagner AA, Carroll PR, Lin DW. Tailoring intensity of active surveillance for low-risk prostate cancer based on individualized prediction of risk stability. *JAMA Oncol* 2020; in press.

Cahill LC, Wu Y, Yoshitake T, Ponchiardi C, Giacomelli MG, Wagner AA, Rosen S, Fugimoto JG. Nonlinear microscopy for detection of prostate cancer: Analysis of sensitivity and specificity in radical prostatectomies. *Mod Pathol* 2020;33(5):916-23.

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Schenk JM, Newcomb LF, Zheng Y, Faino AV, Zhu K, Nyame YA, Brooks JD, Carroll PR, Cooperberg MR, Dash A, Filson SP, Gleave ME, Liss M, Martin FM, Morgan TM, Nelson PS, Thompson IM, Wagner AA, Lin DW. African-American race is not associated with risk of reclassification during active surveillance: Results from the Canary Prostate Cancer Active Surveillance Study. *J Urol* 2020;203(4):727-33.

Lin DW, Zheng Y, McKenney JK, Brown MD, Lu R, Crager M, Boyer H, Tretiakova M, Brooks JD, Dash A, Fabrizio MD, Gleave ME, Kolb S, Liss M, Morgan TM, Thompson IM, Wagner AA, Tsiaatis A, Pingitore A, Nelson PS, Newcomb LF. 17-gene genomic prostate score test results in the Canary Prostate Active Surveillance Study (PASS) cohort. *J Clin Oncol* 2020;38(14):1549-57.

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Elliot L. Chaikof, MD, PhD

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

RESEARCH GROUP

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Richard Cheng, PhD
Erbin Dai, MD
Pradheep Eradi, PhD
Sayo Eweje
Carolyn A. Haller, PhD
Oki Ham, PhD
Revanth Kosaraju
Liyang Liu, MD
Appi Reddy Mandhapati, PhD
Torsten B. Meissner, PhD
David Miranda Nieves, PhD
Diane (Dayoung) Park, PhD
Simon Park, PhD
Rae Rokosh, MD
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, including novel synthetic heparins, 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. We use genome editing to generate “hypoimmunogenic” stem cells that evade the human immune system.

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 without disrupting hemostatic mechanisms or increasing the risk of bleeding.

Genome Editing

Design of delivery systems for in vivo genome editing

Genome editing raises the transformative possibility of curing genetic diseases and installing protective alleles. But major challenges limit the clinical translation of this technology, foremost of which is the difficulty of delivering editing agents to somatic cells *in vivo*. We are developing new delivery technologies to enable selective editing of target cells with high efficiency and DNA specificity.

ACCOMPLISHMENTS 2019-2020

Ongoing collaborations with David Liu, PhD (Broad Institute/Harvard University) have led to a new program directed at the design of delivery systems for *in vivo* genome editing as part of the **NIH Somatic Cell Genome Editing Consortium (SCGE)**.

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 are a member of an **NHLBI Consortium Linking Oncology with Thrombosis (CLOT)** to determine the underlying biological mechanisms that 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 an ongoing 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).

We were awarded a \$1M **Blavatnik Therapeutics Challenge Award** from Harvard Medical School to develop selectin inhibitors for prevention of cancer-associated venous thromboembolism. Ongoing drug discovery efforts include 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.

- Chair for Section 01 (Physical Sciences [Physics/Chemistry], Mathematical Sciences, Computer/Information Sciences, Engineering Sciences), 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 (CESTI), National Academy of Medicine
- Member, National Materials and Manufacturing Board, Roundtable on Biomedical Engineering Materials and Applications (BEMA), National Academies of Science, Engineering, and Medicine
- Member, Association of American Physicians

TEACHING, TRAINING, AND EDUCATION

Recipient of the Harvard Medical School Class of 2020 Outstanding Faculty Mentor Award

Presented Robert M. Zollinger Lecture, Ohio State University

Presented Ramon Berguer Lecture, University of Michigan

SELECTED RESEARCH SUPPORT

Biomarkers and Mechanisms in Cancer-Associated Thrombosis. NIH/NHLBI, 2018–2023 (\$4,465,000); MPI: Elliot Chaikof, MD, PhD; Robert Flaumenhaft, MD, PhD; Jeffrey Zwicker, MD, PhD

The Harvard Translational Glycobiology Career Development Program: Bridging Glycoscience and Clinical Medicine. NIH, 2018–2023 (\$4,802,020); MPI: Elliot Chaikof, MD, PhD; Richard D. Cummings, PhD; Robert Sackstein, MD, PhD

Clot-targeted Antithrombotics for Venous Thromboprophylaxis. NIH, 2019–2023 (\$1,780,793); PI: Elliot Chaikof, MD, PhD

Delivery Technologies for *in Vivo* Genome Editing. NIH, 2019–2022 (\$2,260,670); PI: Elliot Chaikof, MD, PhD

Selectin Inhibitors for Prevention of Cancer-Associated Venous Thromboembolism. Blavatnik Therapeutics Challenge Award, Harvard Medical School, 2020–2022 (\$1,000,000); MPI: Elliot Chaikof, MD, PhD; Lijun Sun, PhD; Richard D. Cummings, PhD

Immuno-evasive Engineered Living Blood Vessels. Harvard Stem Cell Institute, 2018–2020 (\$100,000); MPI: Elliot Chaikof, MD, PhD; Torsten Meissner, PhD

SELECTED PUBLICATIONS

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.

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.

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):e99329.

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.

McNamara S, Brudno Y, Miller A, Ham O, Aizenberg M, Chaikof EL, Mooney DJ. Regenerating antithrombotic surfaces through nucleic acid displacement. *ACS Biomater Sc Eng* 2020;6(4):2159–2166.

Malladi S, Miranda-Nieves D, Leng L, Grainger SJ, Tarabanis C, Nesmith AP, Kosaraju R, Haller CA, Parker KK, Chaikof EL, *Guenther A. *Continuous formation of ultrathin, strong collagen sheets with tunable anisotropy and compaction. *ACS Biomater Sc Eng* 2020;6(7):4236–4246. *co-senior authors

Bienvenu LA, Maluenda A, McFadyen J, Searle AK, Yu E, Malan E, Haller C, Chaikof EL, Peter K, Wang X. Combined antiplatelet/anticoagulant drug for cardiac ischemia/reperfusion injury. *Circ Res* 2020;127(9):1211–1213.

Park DD, Chen J, Kudelka MR, Jia N, Haller CA, Kosaraju R, Premji AM, Galizzi M, Nairn AV, Moreman KW, Cummings RD, Chaikof EL. Resident and elicited murine macrophages differ in expression of their glycomes and glycan-binding proteins. *Cell Chem Biol* 2020; in press.

Wong DJ, Miranda-Nieves D, Nandivada P, Patel MS, Hashimoto DA, Kent D, Gomez-Marquez J, Lin SJ, Feldman HJ, Chaikof EL. The Surgical Program in Innovation (SPIN): A design and prototyping curriculum for surgical trainees. *Acad Med* 2020; in press.

Krishanu S, Sontheimer EJ, Brooks PJ, Dwinell MR, Gersbach CA, Liu DR, Murray SA, Tsai SQ, Wilson RC, Anderson DG, Asokan A, Banfield JF, Bankiewicz KS, Bao G, Bulte JWM, Bursac N, Campbell J, Carlson DF, Chaikof EL, et al. Towards safe and effective genome editing therapeutics: The NIH somatic cell genome editing consortium. *Nature* 2021; in press.

A complete list of publications begins on page 15.



RESEARCH GROUP

Cleide Angolano, PhD
Mauricio Contreras, MD
Lauren Dunavant
John Gigoli, MD
Nyah Patel
Anant Shah, PhD
Maryam Shamloo, PhD
Jacqueline Wade, MD

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 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- κ B (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- κ B heart of inflammation, but also beyond to control Interferon γ 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 disease models that share inflammation as a central pathogenic component, focusing on the three fields below.

Vascular Diseases

Our data qualifies A20 as a potent “atheroprotective” and “modulator of angiogenesis” molecule, as evidenced in animal models of:

- neointimal hyperplasia post-balloon angioplasty
- transplant arteriosclerosis, the pathognomonic feature of chronic allograft rejection
- accelerated atherosclerosis of diabetes
- vein graft and prosthetic arterial graft failure
- proliferative retinopathies, and blinding eye diseases

Liver Regeneration and Repair

We have 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 toxic hepatitis, lethal radical hepatectomy where 90% of the liver is resected, prolonged warm liver ischemia, and orthotopic liver transplantation using marginal grafts.

We uncovered an unsuspected phenotype in A20 heterozygous mice, whereby a benign 2/3 hepatectomy caused a staggering 50% lethality. These data imply that single nucleotide polymorphisms that negatively impact A20 expression and/or function could inform the risk of extensive liver resections for donation or tumor.

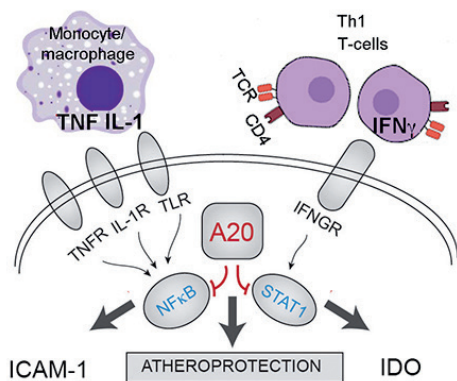
We lately discovered that A20 regulates lipid metabolism in a way that improves fatty liver disease in a mouse model of human non-alcoholic fatty liver disease.

Current pre-translational studies in pigs using clinically safe gene therapy platforms to induce A20 expression in the liver are 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: 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 1 diabetes. Remarkably, this effect was long-lasting and insulin independent. We are exploring clinical translation of this finding into a first-in-class anti-diabetic modality.



▲ FIGURE 1: The atheroprotective umbrella of A20

ACCOMPLISHMENTS 2019-2020

Administrative

- Elected member and Subcommittee on Climate Change member: HMS Faculty Council
- Member: Committee for Senior Appointment, BIDMC
- Member: Promotion and Reappointment Committee, Department of Surgery, BIDMC
- Member: Search Committee for Director of the Cancer Center, BIDMC, HMS
- Member: Search Committee for Director of the Cell and Gene Therapy Center, BWH, 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: NIH T32 Training Grants study section

Invited Presentations and Visiting Professorships

A20 Gene Therapy for Diabetes and its Vascular Complications 1.0 to 2.0: A Tale of Discovery and Translation. Lecture, annual retreat, Center for Vascular Biology Research, BIDMC, and the BWH Vascular Biology Center, HMS; Boston, MA

A20: A Homeo-Dynamic Regulator of Allografts Fate. Lecture, eGenesis Bio; Cambridge, MA

A20: A Tale of a Versatile Allograft Shield. Visiting Professor, MGH Transplantation grand rounds

Awards

Christiane Ferran, MD, PhD, received one of five (5/87) inaugural Blavatnik Therapeutics Challenge Awards from HMS, which are aimed at accelerating clinical translation of promising scientific projects.

Cleide Angolano, PhD, was the recipient of a multi-PI Trailblazer Award from the NIH.

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/Angolano, 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-Principal Investigator, Longwood-Harvard T32 in Vascular Surgery (Multi-PI: Frank LoGerfo, MD, Leena Pradhan-Nabzdyk, PhD, MBA, 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 RESEARCH SUPPORT

Novel Therapies to Achieve Glycemic Control. Juvenile Diabetes Research Foundation, 2016-2020; PI: Christiane Ferran, MD, PhD (Co-I: Cleide Angolano, PhD)

Bioengineering of Vein Graft to Resist Intimal Hyperplasia. NIH, 2018-2021; PI: Christiane Ferran, MD, PhD (Co-I: Mauricio Contreras, MD)

Mechanisms of Prosthetic Arterial Graft Failure. NIH, 1987-2022; 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, Manoj Bhasin, PhD

Novel Insulin-Independent Therapy to Treat Type I Diabetes. Blavatnik Foundation/Harvard Medical School BTCA, 2021-2023. PI: Christiane Ferran, MD, PhD

Understanding the Relationships Between FUS-BBB Opening, Neuroinflammation and the Neurovascular Response. NIH, 2020-2023; Multi-PIs: Cleide Angolano, PhD; Nicholas Todd, PhD

SELECTED PUBLICATIONS

Todd N, Angolano C, Ferran C, Devor A, Borsook D, N McDannold. Secondary effects on brain physiology caused by focused ultrasound-mediated disruption of the blood-brain barrier. *J Control Release* 2020;324:450-459.

Kipper FC, Angolano C, Vissapragada R, Contreras MA, Moore J, Bhasin M, Ferran C,* Thomas AJ.* Embryonic periventricular endothelial cells demonstrate a unique pro-neurodevelopment and anti-inflammatory gene signature. *Scientific Reports* 2020;10:20393. **co-last authors*

Haque O*, Cloonan D*, McIntosh E, Ferran C. Xenotransplantation 1.0 to 2.0. In: Hakim N, Haberal M, Maluf D, editors. *Transplantation surgery*, 2nd ed. Springer; 2020. Chapter 18, p. 279-304. **equal contributors*



RESEARCH GROUP

Mauricio Contreras, MD
Jennifer Li, MD
Navneet Momi, PhD
Kimberly Piper, MS, MA

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 the 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 2019-2020

Based on our previous work, the LoGerfo-Pradhan group has identified gene targets that are altered 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 Drs. Christiane Ferran and 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. Based on these preliminary results, our group successfully renewed its R01 funding for this project. Additionally, the metabolomics results have backed these genomic alterations and efforts made to increase the overall sample size. During the pandemic, a meta-analysis study was conducted on vein graft failure research aiming to discover signature genome targets for IH prevention. 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 Drs. Christiane Ferran of BIDMC and Dr. David Mooney (Harvard John A. Paulson School of Engineering and Applied Sciences), is focused on developing Click-Hydrogels that can be coated on clinically used prosthetic grafts as dacron to deliver siRNA at the anastomotic site in an *in vivo* rat carotid angioplasty model. The group is also working on designing a double-sided tape to secure the gel for improved siRNA delivery and optimizing its flexibility and impermeable backing *in vitro*. The results from this project have been presented at national and international meetings by postdoctoral fellows Cindy Hyunh, Patric Liang, and Jennifer Li.

Additionally, human aortic thrombus specimens have been collected and biobanked for ongoing aortic aneurysm thrombus evaluation for inflammatory markers and microbiome analysis.

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 and have gained special interest from industrial companies regarding inhibitor IC50s. 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 eight trainees (seven surgical residents and one PhD postdoctoral fellow) mentored in different labs in the Longwood Medical Area. Trainees from around the country apply to this program and, thus far, 87 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 eighth 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, 50 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 (oral presentation)

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 (oral presentation)

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 (poster)

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 (poster)

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, 16th Academic Surgical Congress, Orlando, FL (oral presentation)

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, 2007-2022; PIs: Frank W. LoGerfo, MD, Christiane Ferran, MD, PhD, Manoj Bhasin, PhD; Co-Investigator: Leena Pradhan-Nabzdyk, PhD, MBA

Harvard-Longwood Research Training in Vascular Surgery. NIH, 1993-2024; PI: Frank W. LoGerfo, MD; Executive Committee: Leena Pradhan-Nabzdyk, PhD, MBA

Harvard-Longwood Short-Term Research Training 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, Huynh 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.



Marc L. Schermerhorn, MD

George H.A. Clowes, Jr. Professor of Surgery
Chief, Vascular and Endovascular Surgery

RESEARCH GROUP

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Jennifer Li, MD
Patric Liang, MD
Jinny Lu, MD
Christina Marcaccio, MD
Thomas F.X. O'Donnell, MD
Priya B. Patel, MD
Alexander Pothof, MD
Peter A. Soden, MD
Lucas Souza-Mota, 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. We also compared the accuracy of administrative versus quality improvement data for AAA demographics and outcomes. 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.

ACCOMPLISHMENTS 2019-2020

With more than 34 peer-reviewed publications and more than 40 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.

**Society for Vascular Surgery, Vascular Annual Meeting (10 presentations in 2019; 5 presentations in 2020). The Society for Clinical Vascular Surgery, Vascular Annual Symposium (7 presentations in 2019; 2020 meeting cancelled due to COVID-19). New England Society of Vascular Surgery (4 presentations in 2019; 2 presentation in 2020). Vascular Society Group of New England (6 presentations in 2019). European Society for Vascular Surgery (6 presentations in 2020).*

TEACHING, TRAINING, AND EDUCATION

Under my mentorship, our research group has welcomed a number of tremendously productive 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 Hamdan, MD)

Harvard/Longwood Training Grant in Vascular Surgery. NIH, 1993-2024; Co-Investigator: Marc L. Schermerhorn, MD (PI: Frank LoGerfo, MD)

Agency for Healthcare Research and Quality F32 Grant. NIH, 2020-2022; Sponsor: Marc L. Schermerhorn, MD (PI: Christina Marcaccio, MD)

SELECTED PUBLICATIONS

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;70(4):1254-1262.

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**Co-first authorship*

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