SAC 2019 Theme:

Mass General's Most Valuable Research Resource: Our Faculty

71st Meeting of the
MGH Scientific Advisory Committee

SAC 2019

April 3 & 4, 2019
Simches Auditorium
185 Cambridge Street, 3rd Floor

MASSACHUSETTS GENERAL HOSPITAL
RESEARCH INSTITUTE

Welcome

Welcome to the 71st Meeting of the MGH Scientific Advisory Committee (SAC) on April 3 & 4 of 2019. Dr. Richard O. Hynes has graciously agreed to chair our SAC meeting this year.

As in past years, we will begin our two-day SAC meeting with a Celebration of Science at MGH. Our poster sessions begin at 10:00 am on Wednesday, April 3, followed by an afternoon Research Symposium from 2:00 pm to 5:00 pm. David E. Fisher, MD, PhD, will begin the symposium with a report on the past year of research at MGH through the lens of the Executive Committee on Research (ECOR). The outstanding MGH researchers who will then be presenting their work are the 2019 Howard Goodman Award recipient, Marcela Maus, MD, PhD, and the 2019 Martin Research Prize recipients, Tanuja Chitnis, MD, and Robert M. Anthony, PhD.

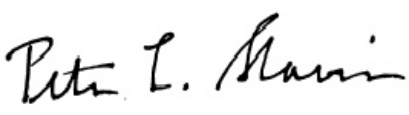
The theme of SAC this year will be *Mass General's Most Valuable Research Resource: Our Faculty.* We are honored to have as our keynote, Lawrence S. Bacow, President of Harvard University. In place of a traditional keynote address, Linda Pizzuti Henry, Managing Director of the Boston Globe and STAT, has graciously agreed to interview President Bacow and we will begin our morning on Thursday, April 4 with this interview.

Following the interview, the remainder of the day will be dedicated to highlighting the challenges facing academic biomedical researchers in the current era and identifying solutions to maintain the extraordinary trajectory of science at Mass General.

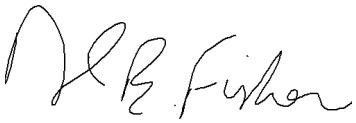
Also on Thursday, SAC members will have the opportunity to meet and hear from MGH investigators in small, unstructured, informal conversations during lunch.

To maximize the time for discussion during the day, the annual MGH Research Institute Executive Report and financials for FY19 have been provided in these printed materials (starting on page 12) for your review in advance of the meeting. Dr. Fisher will highlight some of this information in his annual ECOR Report.

We look forward to an engaging and stimulating two days of discussion and appreciate your participation.



Peter L. Slavin, MD
President



David E. Fisher, MD, PhD
Chair, Executive Committee on Research (ECOR)

Harry W. Orf, PhD
Senior Vice President for Research

Agenda

Wednesday, April 3, 2019
Simches 3.110

Celebration of SCIENCE

10:00 am - 1:30 pm **POSTER SESSION** *Simches, Floor 2*
10:00 - 11:30 am Session 1
12:00 - 1:30 pm Session 2

2:00 - 5:00 pm **CELEBRATION OF SCIENCE** *Simches, 3.110*

Welcome and Opening Remarks
Peter L. Slavin, MD, President, MGH

2:15 - 2:55 pm **Introduction to SAC 2019 & Research at MGH**
David E. Fisher, MD, PhD, Chair, Executive Committee on Research (ECOR)

2:55 - 3:30 pm **2019 Martin Prize for Clinical Research**
Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis
Tanuja Chitnis, MD

3:30 - 3:50 pm **Break**

3:50 - 4:25 pm **2019 Martin Prize for Fundamental Research**
Engineered Sialylation of Pathogenic Antibodies In Vivo Attenuates Autoimmune Disease
Robert M. Anthony, PhD

4:25 - 5:00 pm **2019 Howard M. Goodman Fellowship**
Combinations of Molecular Engineering Strategies in Immune Cell Design
Marcela V. Maus, MD, PhD

Agenda

Thursday, April 4, 2019
Simches 3.110

8:00 am	**Welcome and Introduction** *Peter L. Slavin, MD*
8:05 – 8:40 am	**Interview of Harvard University President Bacow** *Lawrence S. Bacow, JD, MPP, PhD, President, Harvard University* *Linda Henry, Managing Director of the Boston Globe and STAT*
8:40 – 10:00 am	**Current State of MGH Research Faculty** **Introduction** *David E. Fisher, MD, PhD* **Research Quality of Life Survey** *Karen Donelan, ScD, EdM* **CNY Quality of Life Committee** *David M. Langenau, PhD* **Stories from our Faculty** *Yakeel Quiroz-Gaviria, PhD; Miguel N. Rivera, MD; Bakhos A. Tannous, PhD; Karen K. Miller, MD*
10:00 - 10:20 am	**Discussion**
10:20 - 10:35 am	**Break**
10:35 - 11:30 am	**Facilitating Career Development** **The Center for Faculty Development (CFD)** *Anne Klibanski, MD, Director, CFD* *Dennis Brown, PhD, Director, Office for Research Career Development (ORCD)* *Nancy A. Rigotti, MD, Director, Office for Women's Careers (OWC)* *Rochelle Walensky, MD, MPH, 2002 Claflin Awardee*
11:30 - 11:50 am	**Discussion**
12:00 - 1:15 pm	**Faculty Lunch**

Agenda

Thursday, April 4, 2019
Simches 3.110

1:30– 2:15 pm	**Attracting and Engaging a Diverse Research Workforce** **The Center for Diversity and Inclusion (CDI)** *Winfred Williams, MD, Founding Director, CDI* *Elena Olson, JD, Executitve Director, CDI* *Oluwaseun Johnson-Akeju, MD, 2011 Physician-Scientist Development Awardee* *Elsie Taveras, MD, MPH, Pediatrics and the Kraft Center for Community Health*
2:15 – 2:30 pm	**Discussion**
2:30 - 2:45 pm	**Faculty Retention in a Soft Money Environment** **Bridging the NIH Funding Gap** *Robert E. Kingston, PhD*
2:45 - 3:00 pm	**Discussion**
3:00 - 3:30 pm	**Sustaining our Talent** *Susan A. Slaugenhaupt, PhD, Scientific Director, Mass General Research Institute* *Jennifer S. Temel, MD, Hostetter MGH Research Scholar* *Mike McNally, Vice President for Development*
3:30 - 3:45 pm	**Discussion**
3:45 - 3:50 pm	**Looking Ahead**
3:50 - 4:20 pm	SAC Member Session *(closed)*
4:20 - 5:00 pm	Open Discussion & Debrief: Hospital/Research Leadership & SAC Members *(closed)*

Martin Research Prizes

2018 Martin Research Prize for Clinical and Fundamental Research

The Martin Research Prizes were established to honor Joseph B. Martin, MD, PhD, who was Dean of Harvard Medical School from July 1997 to July 2007. Prior to becoming Dean, Dr. Martin was Chief of the Neurology Service at MGH. Each year, ECOR awards two $100,000 Martin Research Prizes to recognize outstanding research papers published by MGH investigators in Fundamental research and Clinical research.

Clinical Research
Tanuja Chitnis, MD
Professor, Neurology

Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis
Multiple sclerosis affects almost 1 million Americans, with typical onset in young adulthood. Over the past 10 years, there has been an increasing recognition that children and teenagers are also afflicted by MS, and in fact have a more inflammatory form of disease than adults, resulting in disability at an early age. There are currently no FDA approved treatments for children and teenagers with MS. Dr. Chitnis and her team of investigators led the first completed phase 3 study to investigate a treatment for children with multiple sclerosis. This study compared the study drug oral fingolimod to the current standard of care for children with MS, which is injectable interferon beta-1a. In the study, 215 children were enrolled, and 107 were assigned to fingolimod, and 108 to interferon beta-1a, and treated with either medication for up to 2 years. The primary outcome measure was rate of relapses per year (adjusted annualized relapse rate). The children on fingolimod treatment had 0.12 relapses/year, while the children in the interferon beta-1a arm had 0.67 relapses/year. This represented an 82% relative difference in relapse rates between fingolimod and interferon beta-1a. The accumulation of new lesions on magnetic resonance imaging scans was similarly reduced in the fingolimod arm compared to interferon beta-1a. Overall, there were few serious adverse events with both drugs. This study led to the FDA approval of fingolimod for pediatric MS patients 10 years of age or older in May 2018. Approval of this medication for pediatric MS has also been granted by the EMA, and in several other regions of the world.

Fundamental Research
Robert M. Anthony, PhD
Assistant Professor, Medicine, Rheumatology, Allergy & Immunology
Center for Immunology and Inflammatory Diseases

Engineered Sialylation of Pathogenic Antibodies In Vivo Attenuates Autoimmune Disease
IgG antibodies exhibit well-known paradoxical properties. They are potent initiators of inflammation, offering protecting from infection and cancer, and harm when directed against self as seen in some autoimmune diseases, including system lupus erythematosus (SLE). Surprisingly, IgG also exhibit immunomodulatory ability, and are used to treat autoimmune and inflammatory diseases in the clinic in the form of high dose intravenous immunoglobulin (IVIG). Studies have demonstrated that a small proportion of IgG in IVIG with a specific carbohydrate modification called sialylation are responsible for the general anti-inflammatory activity of IVIG. This study by Pagan, Kitaoka, and Anthony describes development of soluble enzymes that sialylate IgG. Administration of these engineering enzymes ameliorated autoimmune disease in two models of rheumatoid arthritis (RA) and SLE. The enzymes were effective at a 400-fold lower dose than IVIG. No toxicology or off-target effects following administration of the soluble enzymes were detected. Surprisingly, no increased sialylation was observed on IgG in circulation following administration of the enzymes. However, IgG recovered from the sites of inflammation, the joints from the RA model and the kidney from the SLE model, was found to be sialylated following enzyme administration. The authors then demonstrated that platelets were responsible for the inflammation-specific sialylation, by provide sialic acid donors selectively at sites of inflammation. Taken together, this study demonstrates in vivo engineering of antibodies by sialylation is controlled by platelets and attenuates autoimmune disease.

Howard M. Goodman Fellowship

2019 Howard M. Goodman Fellowship

The Howard M. Goodman Fellowship honors Howard M. Goodman, PhD, founder of the Department of Molecular Biology at Massachusetts General Hospital in 1982 and chief of that department until 2004. Dr. Goodman's guiding principle was that great science should not be encumbered by the continual need to convince the world concerning the merit of an individual scientific vision. He believed in choosing scientists of demonstrated excellence and giving them the resources to pursue their goals with vigor, a model that was resoundingly successful. Each year a Goodman Fellow is chosen from the MGH community to honor that legacy and to support the pursuit of excellence by young scientists of uncommon passion and ability.

Marcela V. Maus, MD, PhD
Assistant Professor, Medicine, Cancer Center

Combinations of Molecular Engineering Strategies in Immune Cell Design

Immune therapies have the potential to cure cancer. When T cells from patients with some forms of leukemia are genetically engineered with chimeric antigen receptors (CARs) and re-infused, and they can induce long-term remissions in many patients. However, the CAR T cells can cause serious side effects and sometimes the tumors come back in a way that specifically avoids being targeted by the CAR T cells. We propose to design and test new engineering strategies so that the tumors have a harder time escaping the CAR T cells and so that the CAR T cells cause fewer side effects. We also aim to improve our understanding of how T cells work, so that better T cell therapies can used to treat patients with multiple myeloma and perhaps other cancers.

Keynote Speaker

Lawrence S. Bacow is the 29th President of Harvard University.

One of higher education's most widely experienced leaders, President Bacow is committed to supporting scholarship and research, encouraging civic engagement, and expanding opportunity for all. From 2001 to 2011, he was president of Tufts University, where he fostered collaboration and advanced the university's commitment to excellence in teaching, research, and public service. Prior to Tufts, he spent 24 years on the faculty of the Massachusetts Institute of Technology, where he held the Lee and Geraldine Martin Professorship of Environmental Studies and served as Chair of the Faculty (1995-97) and as Chancellor (1998-2001).

An expert on non-adjudicatory approaches to the resolution of environmental disputes, President Bacow received an S.B. in economics from MIT, a J.D. from Harvard Law School, an M.P.P. from the Harvard Kennedy School of Government, and a Ph.D. in public policy from the Graduate School of Arts and Sciences. Prior to his election to the Harvard presidency in February 2018, he served as a member of the Harvard Corporation (2011-18), the Hauser Leader-in-Residence at the Harvard Kennedy School of Government (2014-18), and a President-in-Residence at the Harvard Graduate School of Education (2011-14).
President Bacow was raised in Pontiac, Michigan, by parents who were both immigrants. He and his wife, Adele Fleet Bacow, were married in 1975 and have two adult sons.

Linda Henry is the Managing Director of the Boston Globe and STAT. She is a co-founder and chair of HUBweek, a civic collaboration between the Boston Globe, Harvard University, Massachusetts General Hospital, and MIT that explores the future being built at the intersection of art, science and technology. Linda is also a limited partner in Fenway Sports Group, an Emmy-award winning television producer, and a community activist.

Linda serves as a director of the Red Sox Foundation, a Trustee of the Liverpool Football Club Foundation, Chair of the Boston Globe Foundation, and Chairman of the John W. Henry Family Foundation. In addition, she is a founder of the Boston Public Market, serves on the Advisory Board of MassChallenge, and is on the board of The Engine at MIT.

Linda received her Bachelor of Science Degree from Babson College and her Masters Degree from MIT.

Scientific Advisory Committee 2019

David Altshuler, MD, PhD
Executive Vice President, Global Research
Chief Scientific Officer
Vertex Pharmaceuticals
SAC 2019 through SAC 2023 (1st term)

Mark C. Fishman, MD
Professor, Stem Cell and Regenerative Biology
Harvard University
Chief, Pathways Clinical Service
Massachusetts General Hospital
SAC 2016 through SAC 2020 (1st term)

Constance L. Cepko, PhD
Professor, Genetics and Ophthalmology
Investigator, Howard Hughes Medical Institute
Harvard Medical School
SAC 2015 through SAC 2019 (1st term)

Elaine Fuchs, PhD
Rebecca C. Lancefield Professor of Mammalian Cell Biology and Development
Investigator, Howard Hughes Medical Institute
The Rockefeller University
SAC 2018 through SAC 2022 (1st term)

Elazer R. Edelman, MD, PhD
Professor, Medical Engineering and Science
Director, Institute for Medical Engineering and Science (IMES)
Massachusetts Institute of Technology
SAC 2019 through SAC 2023 (1st term)

Richard O. Hynes, PhD
Daniel K. Ludwig Professor for Cancer Research
Investigator, Howard Hughes Medical Institute
Massachusetts Institute of Technology
SAC 2018 through SAC 2022 (2nd term)

Scientific Advisory Committee 2019

Talmadge E. King, Jr., MD
Dean, School of Medicine
Vice Chancellor, Medical Affairs
University of California, San Francisco
SAC 2019 through SAC 2023 (1st term)

Daniel Podolsky, MD
President
University of Texas Southwestern Medical Center
SAC 2019 through SAC 2023 (2nd term)

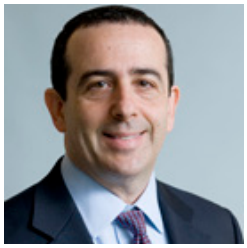
Vivian S. Lee, MD, PhD, MBA
President, Health Platforms
Verily Life Sciences
SAC 2015 through SAC 2019 (1st term)

Selwyn M. Vickers, MD, FACS
Senior Vice President, Medicine
Dean, School of Medicine
University of Alabama at Birmingham
SAC 2019 through SAC 2023 (1st term)

Douglas A. Melton, PhD
Xander University Professor
Co-Director, Harvard Stem Cell Institute
Investigator, Howard Hughes Medical Institute
Harvard University
SAC 2018 through SAC 2022 (1st term)

Ex Officio
George Daley, MD, PhD
Dean, Faculty of Medicine
Harvard Medical School
Ex Officio

Executive Committee on Research
Officers and Members 2019



ECOR CHAIR
April 2018 - March 2021
David E. Fisher, MD, PhD
Chief, Dermatology

ECOR VICE CHAIR
April 2018 - March 2021
Merit E. Cudkowicz, MD, MSc
Chief, Neurology

ECOR IMMEDIATE PAST CHAIR
April 2018 - March 2021
David N. Louis, MD
Chief, Pathology

ECOR DIRECTOR
Maire C. Leyne, MS, MBA
Ex-officio

Galit Alter, PhD
Ragon Institute
Alternative representative

R. Rox Anderson, MD
Director, Wellman Center for Photomedicine
Ex-officio

Katrina A. Armstrong, MD
Physician-in-Chief, Medicine
Ex-officio

Dennis A. Ausiello, MD*
Medicine
April 2013 - March 2019

W. Gerald Austen, MD
Chair, Chief's Council
Ex-officio

Jodie L. Babitt, MD
Nephrology
Elected Representative
January 2018 - December 2020

Gaurdia Banister, RN, PhD*
Executive Director, Institute for Patient Care
May 2017 - April 2021

Stephen J. Bartels, MD, MS
Director, The Mongan Institute
Committee on Clinical Research (CCR) Representative
Ex-officio

Sally Mason Boemer, MHSA
Chief Financial Officer, MGH
Ex-officio

Genevieve Boland, MD, PhD
Surgery
Elected Representative
January 2019 - December 2021

Miriam Bredella, MD
Radiology
Elected Representative
January 2019 - December 2021

James A. Brink, MD*
Chief, Radiology
April 2013 - March 2019

Dennis Brown, PhD
Director, Office for Research Career Development
Ex-officio

Emery N. Brown, MD, PhD*
Anesthesia
April 2015 - March 2021

Bob S. Carter, MD‡
Chief, Neurosurgery
April 2018 - March 2024

Patricia A. D'Amore, PhD, MBA
Ophthalmology, MEEI
Ex-officio

Iain A. Drummond, PhD
Nephrology
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

Jeffrey Ecker, MD‡
Chief, Obstetrics & Gynecology
April 2016 - March 2022

Maurizio Fava, MD
Director, Division of Clinical Research
Ex-officio

Timothy G. Ferris, MD
Chairman and CEO, Massachusetts General Physicians Organization (MGPO)
Ex-officio

Marcia B. Goldberg, MD*
Infectious Diseases
April 2018 - March 2024

Daniel A. Haber, MD, PhD
Director, Cancer Center
Ex-officio

Kurt J. Isselbacher, MD
Honorary Member

*Chair Appointment, ‡ Chiefs Council

Executive Committee on Research
Officers and Members 2019

Sekar Kathiresan, MD
Director, Center for Genomic Medicine
Ex-officio

Robert E. Kingston, PhD*
Chief, Molecular Biology
April 2018 - March 2024

Anne Klibanski, MD
Chief Academic Officer, Partners Healthcare
Director, Center for Faculty Development
Ex-officio

David M. Langenau, PhD
Pathology
Committee on Fundamental Research (CFR) Representative
October 2017 - September 2020

Keith D. Lillemoe, MD
Surgeon-in-Chief, Surgery
Ex-officio

Andrew O. Luster, MD, PhD
Chief, Rheumatology, Allergy and Immunology
Chair, Subcommittee on Animal Resources (SAR)
Ex-officio

Joren C. Madsen, MD, DPhil*
Director, MGH Transplant Center
April 2018 - March 2024

Karen K. Miller, MD
Neuroendocrine
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

David M. Nathan, MD
MGH Institutional Representative
Harvard Catalyst CTSC
Ex-officio

Harry W. Orf, PhD
Sr. Vice President for Research
Ex-officio

Roy H. Perlis, MD, MSc*
Psychiatry
August 2016 - April 2021

Jonathan Rosand, MD, MSc
Neurology/Center for Genomic Medicine
Elected Representative
January 2018 - December 2020

Bruce Rosen, MD, PhD
Director, MGH Martinos Center
Ex-officio

Jerrold F. Rosenbaum, MD*
Chief, Psychiatry
April 2018 - March 2024

Anthony Rosenzweig, MD*
Chief, Cardiology
April 2015 - March 2021

Paul S. Russell, MD
Honorary Member

Edward T. Ryan, MD
Infectious Diseases
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

David T. Scadden, MD
Director, Center for Regenerative Medicine
Ex-officio

Susan A. Slaugenhaupt, PhD
Scientific Director,
MGH Research Institute
Ex-officio

Peter L. Slavin, MD
President, MGH
Ex-officio

Elsie M. Taveras, MD, MPH
Population Health Management/Pediatrics
Elected Representative
January 2017 - December 2019

Guillermo J. Tearney, MD, PhD
Wellman Center for Photomedicine
Alternative Representative

Maria Troulis, DDS, MSc‡
Chief, Oral and Maxillofacial Surgery
May 2017 - April 2023

Korkut Uygun, PhD
Center for Engineering in Medicine/ Surgery
Elected Representative
January 2017 - December 2019

Bruce D. Walker, MD
Director, Ragon Institute
Ex-officio

Ralph Weissleder, MD, PhD
Director, Center for Systems Biology
Ex-officio

Kristin White, PhD
Dermatology, CBRC
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

Ramnik J. Xavier, MD, PhD
Director, Center for Computational & Integrative Biology
Ex-officio

Warren M. Zapol, MD
Anesthesia
Chair, Institutional Animal Care and Use Committee (IACUC)
Ex-officio

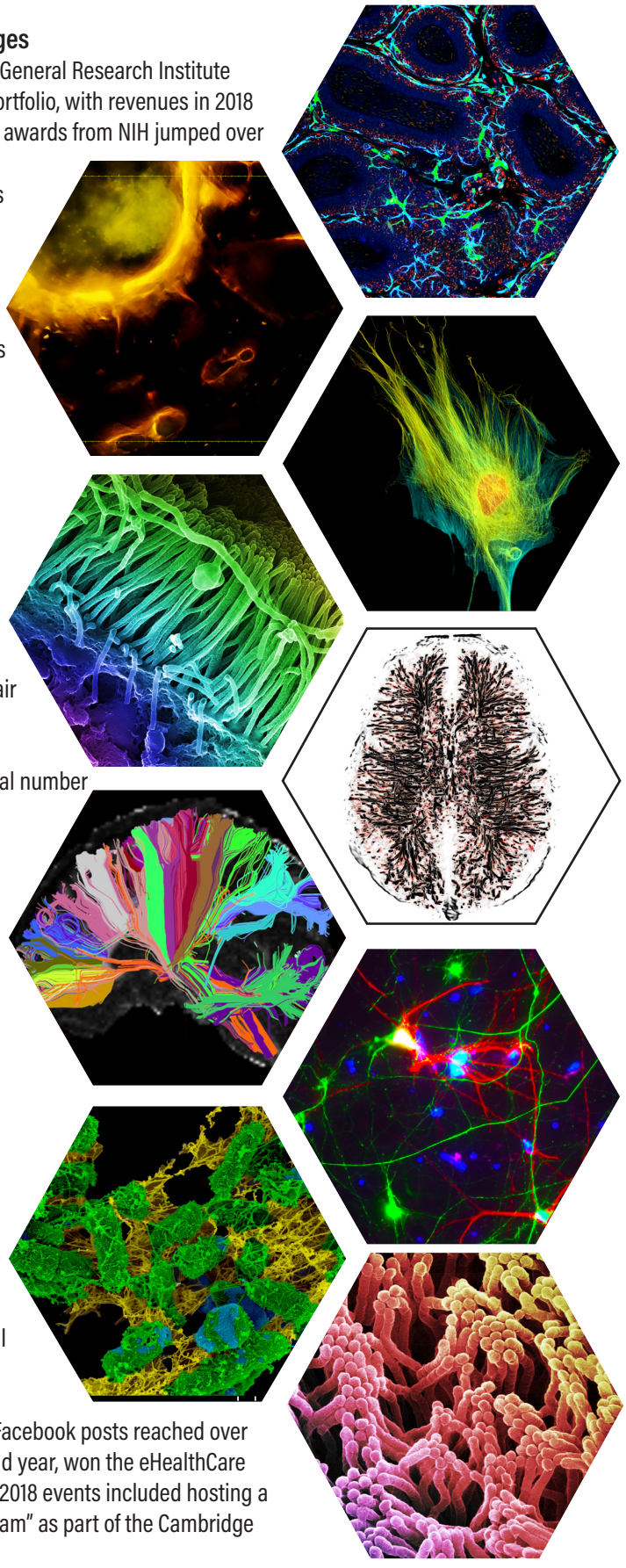
*Chair Appointment, ‡ Chiefs Council

Mass General Research Institute

Executive Report

Record Research Revenue Brings Opportunities and Challenges

Continued progress in strategic initiatives underway within the Mass General Research Institute (RI) has yielded another year of exceptional growth in our research portfolio, with revenues in 2018 increasing $16M to $928M, another all-time high. And, amazingly, new awards from NIH jumped over $70M this past year to $466M, forecasting continued strong research revenue growth for the coming years. Unfortunately, the opportunities this increased funding can bring - to develop new programs, recruit new faculty, and retain our current faculty – may not be realized because our continued growth in research revenue over the last decade has not been accompanied by concurrent growth in research space. This has resulted in overcrowding in many research labs and is now becoming the rate-limiting factor to sustaining our leading role in biomedical innovation. I will devote a major portion of the "Looking at the Year Ahead" section of my report to discussing this challenge, but, first, let's look at the progress and developments across the research enterprise this past year.



Highlights of RI accomplishments/milestones in 2018 include:

- The appointment of the 55th MGH Research Scholar (five new ones in 2018) and the installation of Dr. David Altshuler, Executive VP and Chief Scientific Officer of Vertex Pharmaceuticals and former MGH physician, as the new Chair of our Research Institute Advisory Committee.
- An increase of eight industry-sponsored clinical trials in the Translational and Clinical Research Centers, bringing the total number of studies in 2018 to 32.
- The addition of a sixth Strategic Alliance (SA) thematic program in rare diseases, bringing the total number of investigators now participating in SA initiatives to 126.
- Creation of a new research center – CARE (Community Access, Recruitment, and Engagement) that uses a community-led, collaborative model of partnership and engagement to conduct groundbreaking research on poor accrual rates to clinical trials, with a focus on disparities for racial and ethnic minorities.
- The development of an innovative translational training program for our researchers consisting of a 14-week course on research strategy and tactics and a solution-driven project competition.
- The creation of the Charlestown Navy Yard Quality of Life Committee to improve the work environment of our largest research community. The Committee has already made noticeable improvements in shuttle bus transportation, meal offerings, social/community-building events, and upgrades in WiFi and video streaming capabilities.
- Expansion of our RI communication and marketing efforts. Facebook posts reached over 320,000 people this past year and our blog, in only its second year, won the eHealthCare Leadership Award for Best Social Networking in 2018. Other 2018 events included hosting a table at the MGH Science Carnival, conducting a "Science Slam" as part of the Cambridge

Science Festival, and holding our third annual "Art of Talking Science Competition" as part of the city-wide HUBweek festival.

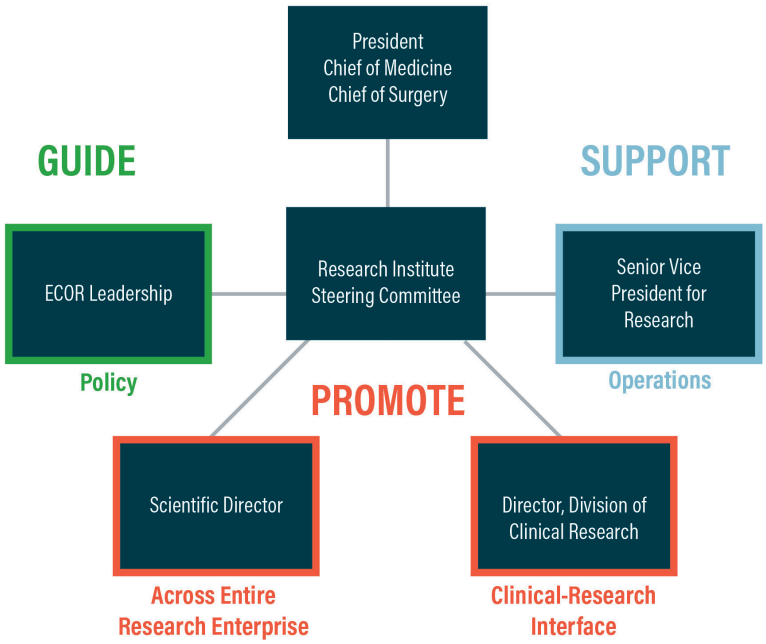
- Steady growth in the Partners Biobank at MGH, with consented patient recruitment now over 95,000 and genotyped samples exceeding 30,000. Due in part to the Biobank's notable growth and prestige, MGH received a major NIH grant to become a regional medical center supporting enrollment into the Precision Medicine Initiative's All of Us Research Program.
- A 50% increase in MGH patents filed in FY18 to 1643, up from 1091 the previous year. Royalty and licensing revenue also grew from $87.7M in FY17 to $94.6M in FY18.
- Continued researcher participation in the Isuggest program, with the number of suggestions to improve research services at the end of 2018 exceeding 1,200 and the number implemented exceeding 600.
- Completion of major process and organizational improvements to our animal care and IACUC programs. Highlights include: 1) implementation of an entirely new protocol submission process that dramatically simplifies and reduces the amount of work required by PIs; 2) installation of new rodent cage racks that increase capacity by 15% without any increase in housing square footage; 3) development of a first-ever retirement option and policy for non-human primates; 4) receipt in March 2018 of continued full accreditation from AAALAC with a report that, for the first time, had no mandatory findings.

These and other important developments from the past year are reported below, in a sectional format that aligns with the organizational components (Guide, Promote, Support) of the RI governance structure. As I did for the first time last year, I conclude the report by "Looking at the Year Ahead", where I discuss the most notable opportunities and challenges facing the research enterprise in 2019.

The Research Institute Steering Committee (RISC)

The MGH Research Institute is led by a Steering Committee whose structure is shown in the diagram below. The hospital President, Chief of Medicine, and Chief of Surgery sit ex-officio on the committee, and the President may, at his/her discretion, appoint an additional ad hoc member. The Executive Committee on Research (ECOR), which is the body chartered by the hospital's General Executive Committee to set science policy (i.e., GUIDE the research enterprise), is represented on RISC by the ECOR Chair, Vice Chair, and Immediate Past Chair. ECOR administers the hospital's internal research grant programs, awarding over $10M annually to MGH investigators, and effectively serves as the legislative branch of the Research Institute. The MGH Research Management Department serves as the executive branch of the Institute, directing all SUPPORT departments and managing the administrative and financial components of the entire research enterprise. It is represented on RISC by the Senior Vice President for Research. Finally, the newest elements of Research Institute leadership were born out of the MGH Research Strategic Plan and created to PROMOTE the research enterprise. They are the Scientific Director of the Research Institute and the Director of the Division of Clinical Research whose offices, respectively, PROMOTE science across the entire research enterprise and at the clinical-research interface.

Leadership Structure of Research at MGH



GUIDE

The Executive Committee on Research — Maire C. Leyne, MS, MBA, Director

The MGH Executive Committee on Research (ECOR) has existed since 1947 with responsibility for strategic planning and policy-making for the hospital's research enterprise. It is a standing subcommittee of the General Executive Committee (GEC). A major strength of ECOR is its diverse and regularly-rotating membership which includes more than 50 senior research faculty, chiefs, and hospital executives. Meeting twice-monthly, this committee is the central body for research governance, bringing together a broad representation of internal stakeholders to provide strategic guidance to the hospital's leadership regarding research priorities.

Leadership of ECOR

The ECOR Chair is selected from among the Chiefs of MGH Services and Departments. The current Chair is David E. Fisher, MD, PhD (Chief, Dermatology); the Vice Chair is Merit E. Cudkowicz, MD, MSc (Chief, Neurology); and the Immediate Past Chair is David N. Louis, MD (Chief, Pathology). Each position is a three-year term, with the Vice Chair succeeding to the role of Chair and the previous Chair remaining a part of the ECOR leadership team after their Chair term, thereby assuring continuity over a nine-year period.

ECOR Membership

In addition to the ECOR chairs, all members of the Research Institute Steering Committee serve as members of ECOR. Further ECOR membership includes two elected representatives from each of the three HMS faculty ranks (Assistant Professor, Associate Professor, and Professor), as well as representatives elected from the Chiefs' Council and faculty appointed by the Chair of ECOR. Senior MGH and MGPO leadership, including the MGH President and the MGPO President, are also members.

There is a total of 6 elected representatives to ECOR, two from each faculty rank. Elected representatives serve a 3-year term and represent faculty concerns and issues. To ensure a balance of continuity and renewal, terms are staggered so that two seats are up for election every year. Please see pages 10-11 to view the entire committee membership.

ECOR's broad areas of focus include:

Meetings and Events

ECOR hosts roughly 100 meetings, conferences and events annually, including monthly Research Council meetings, the annual Scientific Advisory Committee (SAC) Meeting and the Warren Triennial Prize and Symposium.

Research Council

Research Council meetings take place on the first Monday of the month at noon in the Simches auditorium. The meetings are open to the entire research community, and it is one of the primary means of communicating scientific and administrative issues relevant to the research community.

Scientific Advisory Committee

The MGH Scientific Advisory Committee (SAC) is a group of distinguished scientists who advise the hospital's leadership on issues related to its research mission. For over 70 years the committee members have served as a sounding board for the hospital's leadership, helping us evaluate our research mission and address challenges we are facing. SAC membership has included Nobel laureates and leaders in science and medicine from academia, industry and government. Current membership is listed on pages 8 & 9.

Warren Triennial Prize and Symposium

The Warren Triennial Prize was first given in 1871 in honor of Dr. John Collins Warren, a dedicated teacher, researcher and a founding member of the Massachusetts General Hospital (MGH). Dr. Collins played a key role in establishing the journal now known as the New England Journal of Medicine, which was first published in 1812, and took part in the first public demonstration of ether anesthesia in what is now known as the Ether Dome at the MGH in 1846.

A medallion of Dr. Warren, presented to recipients

The Warren Triennial Prize is awarded every three years to recognize the work of up to two outstanding scientists. The goal of the Warren Prize is to recognize pre-eminent leaders of science whose work is expected to have a major impact on the future of medicine. Our past Warren Prize winners' contributions stand as a testament to the power of scientific discovery to shape the future of medicine. Between 1871 and 2018, the Warren Prize has been awarded on 42 occasions to 73 recipients. Twenty-four of these individuals have also received the Nobel Prize, which was first presented in 1901. Each Prize recipient presents his or her scientific work in a symposium at MGH and receives a $50,000 cash award.

Committees, Subcommittees and Initiatives
Various initiatives and relevant committees/subcommittees have been established through ECOR to enact and support the research enterprise at Massachusetts General Hospital. Some of these include:

The **Research Space Advisory Committee (RSAC)** makes recommendations on the allocation and management of research space.

The **Committee on Fundamental Research (CFR)** was created out of the former PhD Steering Committee to provide a forum for fundamental research investigators to actively engage in developing solutions to improve MGH/Partners policies, infrastructure, and environment to benefit the fundamental research community. The CFR membership is made up of faculty selected by their Chiefs to represent their Department/Unit/Center. The CFR membership elects a representative to serve on ECOR.

The **Subcommittee on Animal Resources (SAR)**, which meets quarterly, makes recommendations on the allocation and management of animal research space and provides guidance to the Center for Comparative Medicine (CCM) and Institutional Animal Care and Use Committee (IACUC). Additionally, this committee is charged with ensuring that the Animal Space Policy is working smoothly. For more information on our animal program, see page 33.

The **Subcommittee on Review of Research Proposals (SRRP)** provides an essential service to the MGH Research Community. The SRRP reviews all funding applications that are submitted to ECOR. They also conduct preliminary reviews for limited institutional nominations to external sponsors. In evaluating applications, SRRP considers the candidate and the quality and relevance of the proposed study. Each review panel is led by one of the four SRRP co-chairs. The SRRP is composed of a diverse set of reviewers from across the institution, currently consisting of 169 members - 53 Professors, 71 Associate Professors, and 45 Assistant Professors. Approximately 52 SRRP members are eligible to review Deliberative Interim Support Fund (ISF) applications, as we require prior study section experience to participate in the panel.

Post Doctoral Division (PDD)
At the recommendation of SAC in 2015, ECOR began the process of creating a Division to serve the postdoctoral community. The Post Doctoral Division (PDD), located within the Office for Research Career Development (ORCD), was officially implemented in 2016 with Marcia Goldberg, MD, serving as the inaugural Director of the Division. The goals of the PDD include: serving the career advancement needs of postdoctoral fellows in all research settings, providing professional development programs, services, counseling and resources - while enhancing the existing sense of community, as well as the overall experience of postdoctoral fellows affiliated with MGH. For more information on the work being done by the PDD, see page 60.

Thematic Center Review Process
Our SAC 2016 meeting focused on the Thematic Centers at MGH 10 years after their inception. The response from the SAC members was generally very positive – they were impressed with the quality of the science at MGH and in the five Centers.

The SAC members encouraged ECOR to engage in a deeper discussion of the Thematic Centers and to do this on a regular basis, including how we approach the idea of new centers going forward. Additionally, the members recommended that ECOR formulize and revitalize the current review process and begin to create a strategic process for thinking of new Centers.

Currently, the Thematic Center Directors meet annually with the ECOR Chair and SVP for Research; going forward, summaries of these meetings will be provided to the Research Institute Steering Committee annually. Additionally, in-depth reviews of the Centers will

occur every five years; the review committees will be comprised of three external faculty members, two internal faculty members, ECOR leadership and one member from MGH administration. Summary of these reviews will be reported into both the Research Institute Steering Committee and SAC every five years.

To learn more about the science currently being done in the Thematic Centers in 2018, see pages 64-77.

Charlestown Navy Yard (CNY) Quality of Life Committee
One of ECOR's 2018 initiatives included the formation of a committee to focus on our research community located in the Navy Yard in Charlestown. The committee is co-chaired by Dr. David Langenau and Susan Cronin-Jenkins with executive oversight from research administration and faculty including Michael Fisher, Patricia Frederico, Maire Leyne, Dr. Iain Drummond, Dr. Kristin White, Dr. Mo Motamedi, Dr. Shannon Stott, and Susan Smith.

To be able to ascertain the needs of the community, the Committee sponsored a survey to better understand the challenges of working in the Navy Yard for students, post-doctoral fellows, staff and faculty. Members of the CNY research community were surveyed to determine how the quality of life for those working in the Navy Yard could be improved. Respondents had the opportunity to give suggestions for improving the quality of life and work environment in the Navy Yard.

In June of 2018, we received 453 responses that identified the following for areas of improvement:

1. Better transportation between campuses (42% noted this was an area to work on)
2. Increased food options (22%)
3. Community building and need to enhance scientific interactions (20%)
4. Improving facilities and technology (16%)

The committee has already made a significant impact in the short time it has been active. The CNY QoL committee was able to:

- Obtain funding and successfully petitioned research leadership for financial support to enhance community building
- Improve transportation between campuses by working with the city and Partners Transportation to implement changes to the shuttle route to reduce travel time from Charlestown to the main campus
- Add and improve meal options by
    - inviting food trucks to offer lunch options on Thursdays and Fridays in the summer and fall
    - sponsoring Pop-up food options 5 days a week, 3 days in Building 149 and two days a week in Building 114;
    - working with MGH Catering to advertise and enhance the 149 Eat Street Cafe
- Build community and enhance interactions by
    - holding Town Hall meetings to allow open discussions and feedback
    - launching a monthly Lunch Scientific Seminar Series
    - offering Ice Cream Socials in the summer (Over 600 people attended each one!)

The committee remains focused on a vision for the future that would require additional involvement and financial support to:

- Increase cafeteria hours
- Renovate the building including Coffee Central and the First-Floor space
- Add additional TV monitors at all three elevators as well as the cafeteria in CNY149
- Upgrade video conferencing and AV in conference rooms

Communication
ECOR also plays a vital role in facilitating communication within the MGH research community via its website (http://ecor.mgh.harvard.edu), e-newsletters (weekly Research News) and targeted mailing campaigns.

Awards and Grants
ECOR manages a multi-million-dollar grant program, virtually a mini-foundation, which annually reviews over 800 applications from MGH investigators and fellows, and awards approximately 120 internal grants. Over the past several years, ECOR has experienced a significant increase in the number of grant mechanisms administered by ECOR, along with an increase in applications to these opportunities. To meet the needs of an increasing application pool, we established an online grant management system where we manage the entire life-cycle of an ECOR application from the start of an application, through the review process, and to the notification of funding.

In FY18, we awarded $10.6M to 114 investigators.

Grant	$	PIs	Target Group
Interim Support Funds (ISF) Formulaic/Deliberative)	$4.5M	56	All faculty
Tosteson /Fund for Medical Discovery (FMD)	$1.6M	22	Research fellows/trainees
MGH Research Scholars	$2.5M	5	Junior & Mid-career faculty
Claflin Distinguished Scholar Awards	$690,000	6	Junior faculty (Female)
Howard M. Goodman Fellowship	$345,000	1	Junior faculty
CDI Physician-Scientist Development Award	$276,000	2	Junior faculty (URM)
Martin Prize	$200,000	2	All faculty
MGH-MIT Grand Challenges	$250,000	5	All faculty
Shared Instrumentation Grants	$225,000	3	All faculty
SAC Abstracts	$13,800	12	Junior faculty, Fellows and Students

Interim Support Program
ECOR launched a major grants program in 2006 to provide interim/bridge support to faculty whose NIH or other federal funding was delayed or otherwise interrupted. The Interim Support Program is intended to preserve valuable research programs at MGH that are suffering due to the harsh funding climate, giving investigators a chance to retool their applications for resubmission. This program serves a vital role in supporting researchers at MGH: 86% of investigators who received funding from the Interim Support Program from 2006-2018 are still working within the institution. Since the program's inception in 2006, ECOR has awarded over $54.6M of interim support funding. Our investigators have gone on to leverage these funds ten-fold, bringing in over $613M of federal funding to the institution. Within this program are two grant mechanisms, Formulaic Bridge Support and Deliberative Interim Support Funding, which provide similar funding under different guidelines.

- Formulaic Bridge Support (FBS) applications are accepted monthly from investigators whose R01 or R21 NIH grant received a percentile equal to or better than a 20th percentile (1-20%).

- Deliberative Interim Support Funding (ISF) applications are accepted three times a year to investigators who have a lapse or delay in their research funding from the NIH or another federal agency (i.e. National Science Foundation, Department of Defense, etc.). This grant mechanism is open to investigators whose federal grant application received a score higher than a 20th percentile (21-99%) or were not scored.

In order to help as many people as possible, we ask investigators who receive their NIH funding during the ISF award to return the remaining funds to ECOR. This helps ECOR support more awards in the future. In FY18, ECOR recovered $1M in unspent funds and a total of $8.8M has been recovered to date.

Tosteson & Fund for Medical Discovery Fellowship Awards
The Tosteson & Fund for Medical Discovery (FMD) Fellowship Awards are intended to support junior investigators (MD and PhD fellows/postdocs) at MGH pursuing clinical or fundamental research. The award is offered three times per year, with one cycle dedicated solely to clinical research. Each award includes a salary stipend of $48,500. In FY18, 22 fellows received fellowship awards through this program.

Claflin Distinguished Scholar Awards

Although women scientists are recruited to MGH programs, their advancement to senior faculty positions is still far less frequent than that of their male counterparts. In 1993, The Women in Academic Medicine Committee, originally chaired by Mrs. R. Morton Claflin, Honorary Trustee, was established to facilitate the academic careers of women in science at MGH. Recognizing that a significant obstacle to career advancement is the difficulty of maintaining research productivity during the child-rearing years, this committee, with the sponsorship of ECOR, established the Claflin Distinguished Scholar Awards. It is intended that this funding will increase opportunities for women to advance to senior positions in academic medicine.Among those who received the award between 1997-2017 and are still at MGH, 73% have been promoted and 89% received ~$397 million in total external grant funding.

In FY18, six women received the Claflin Award.

Kimberly Blumenthal, MD (Assistant Professor, Medicine/Rheumatology, Allergy, and Immunology)

Laura Dichtel, MD, MHS (Instructor, Medicine/Neuroendocrine)

Jenna Galloway, PhD (Assistant Professor, Orthopedics)

Emily Hyle, MD (Instructor, Medicine/ Infectious Disease)

Karen Nanji, MD, MPH (Assistant Professor, Anesthesia)

Korilyn Zachrison, MD (Assistant Professor, Emergency Service)

MGH Physician-Scientist Development Award

J. Sawalla Guseh, MD

The MGH Physician/Scientist Development Award (PSDA) is designed for MD and/or PhD investigators at MGH to support the development of research investigators who are considered underrepresented in medicine (URM), and thereby increase opportunities for URM researchers to advance to senior positions in academic medicine at MGH. In FY18, two investigators received this award:

- J. Sawalla Guseh, MD (Clinical Research Fellow, Medicine/Cardiology)
- Camille Powe, MD (Instructor, Medicine/Diabetes Unit)

Camille Powe, MD

MGH-MIT Grand Challenges

The MGH-MIT Grand Challenges initiative was developed to increase collaboration between the two institutions in the hopes of bringing together approaches from engineering and basic science with clinical medicine. To do this, the program sought to focus the research agenda on the rapid translation from bedside to bench and back to bedside.

Grand Challenge 1: Diagnostics - This challenge was launched with the goal of developing cost-effective and accurate diagnostics to guide individual clinical decisions based on real-time monitoring and massive patient data sets. Through this challenge, we gave $850,000 to thirteen teams of investigators through two cycles of grants. Year 4 projects of Grand Challenge 1 launched during the spring of 2018 and a workshop

was held in October to highlight each team's progress. Projects are expected to end in the spring of 2019.

Grand Challenge 3: Neurosciences - This challenge was launched with the goal of developing joint ventures which link basic and clinical research to accelerate progress towards more effective diagnostic approaches and therapies in clinical neuroscience. Through this challenge, we provided $750,000 to six teams of investigators. Out of the 6 projects, 5 of them were awarded a third year of funding in 2017. These remaining projects concluded their work at the end of August 2018. The GC3 teams presented their research several times throughout the project period.

These various collaborations resulted in multiple patent applications; multiple published papers; grants from federal, foundation, and industry sources; and additional spin-off projects.

MGH Research Scholars

In January 2011, ECOR launched the MGH Research Scholars Program, a major initiative to award research funding to outstanding faculty in our community in support of innovative, cutting-edge research. As of 2018, 55 Scholars have been appointed, each receiving research funding of $100,000 a year for five years.

The 2018 Class of Mass General Research Scholars

Ingrid Bassett, MD, MPH
Associate Professor
Medicine/Infectious Disease

Daphne Holt, MD, PhD
Associate Professor
Psychiatry

Eric Liao MD, PhD
Associate Professor
Surgery

Karen K. Miller, MD
Professor
Medicine/Neuroendocrine

Alexander Soukas, MD, PhD
Assistant Professor
Medicine/Diabetes Unit/
Endocrine/CGM

Other ECOR Awards

The **Howard M. Goodman Fellowship** honors Howard M. Goodman, PhD, founder of the MGH Department of Molecular Biology in 1982 and Chief of that Department until 2004. Dr. Goodman's guiding principle was that great science should not be encumbered by the continual need to convince the world concerning the merit of an individual scientific vision. He believed in choosing scientists of demonstrated excellence and giving them the resources to pursue their goals with vigor, a model that was resoundingly successful. Each year, a Goodman Fellow is chosen from the MGH community to honor that legacy and to support the pursuit of excellence by young scientists of uncommon passion and ability. The award is for two years at $150,000 per year. Please see page 6 for more information on the 2019 recipient.

The **Martin Research Prizes** are awarded annually in honor of Harvard Medical School (HMS) Dean Emeritus Joseph Martin, MD, PhD. Dr. Martin served as Dean of Harvard Medical School from July 1997 to July 2007. Each year, ECOR awards two $100,000 Martin Research Prizes to recognize outstanding research papers published by MGH investigators in Fundamental research and Clinical research. Please see page 5 for more on the 2019 recipients.

Awards and Honors
The summer of 2014 saw the creation of the MGH Committee on Awards and Honors, chaired by Dr. Samuel Thier, president of MGH from 1994-1997. The committee ensures that there is an MGH nominee for over 40 major national and international scientific awards and prizes, and provides hospital endorsements for faculty member admission to distinguished honorific societies. The committee is comprised of 16 esteemed leaders from throughout our institution who meet regularly. In 2018, the committee championed the nominations of more than 30 outstanding MGH investigators for major awards and society memberships and national and international awards.

Some of the major awards and prizes received by MGH investigators in 2018 include the following:

Albert Einstein College of Medicine Lifetime Achievement Award
Julie R. Ingelfinger, MD (Pediatrics, Pediatric Nephrology)

American Academy of Arts and Sciences
Patricia A. D'Amore, PhD, MBA (Schepens Eye Research Institute, Mass Eye and Ear)

American Academy of Dermatology Honorary Membership
Ernesto Gonzalez, MD (Dermatology)

American Academy of Neurology Neuro-Oncology Scientific Award
Scott Plotkin, MD, PhD (Neurology, Cancer Center)

American Association of Indian Scientists in Cancer Research (AAISCR) Outstanding Scientist Award
Shyamala Maheswaran, PhD (Cancer Center, Surgery)

American Association of Physicists in Medicine (AAPM) Fellow
David P. Gierga, PhD (Radiation Oncology)

American Cancer Society Research Scholar Award
Mo Motamedi, PhD (Cancer Center)

American College of Laboratory Animal Medicine (ACLAM) Vice President
Donna Jarrell, DVM (Center for Comparative Medicine)

American Group Psychotherapy Association (AGPA) Distinguished Fellow
Kathleen H. Ulman, PhD, CGP, DFAGPA (Psychiatry)

American Heart Association 2018 Distinguished Scientist Award
Robert A. Levine, MD (Cardiology)

American Orthopaedic Association 2018 Distinguished Contributions to Orthopaedics Award
William H. Harris, MD (Orthopaedics)

American Pediatric Surgical Association President
Joseph P. Vacanti, MD (Surgery, Pediatric Surgery, Center for Regenerative Medicine)

American Society for Photobiology (ASP) Lifetime Achievement Award
Tayyaba Hasan, PhD (Dermatology, Wellman Center)

American Society of Clinical Investigation (ASCI)
Jodie Babitt, MD (Medicine, Nephrology)
Murat Bastepe, MD, PhD (Medicine, Endocrine)

American Society of Gene and Cell Therapy Outstanding New Investigator Award
Luk Vandenberghe, PhD (Mass Eye and Ear)

American Society of Human Genetics 2018 Curt Stern Award
Sek Kathiresan, MD (Center for Genomic Medicine)

American Society of Nephrology (ASN) 2018 Homer W. Smith Award
M. Amin Arnaout, MD (Medicine, Nephrology)

American Society of Neuroradiology Vice President
Joshua A. Hirsch, MD, FACR, FSIR, FSNIS (Radiology)

Anxiety and Depression Association of America (ADAA) Board of Directors, President-elect
Luana Marques, PhD (Psychiatry)

Association for Research in Vision and Ophthalmology (ARVO) Foundation 2018 Dr. David L. Epstein Award
Janey L. Wiggs, MD, PhD (Mass Eye and Ear)

Banting Postdoctoral Fellowship
Cameron McAlpine, PhD (Radiology)

Bright Focus Helen Keller Prize for Vision Research
Thaddeus P. Dryja, MD (Mass Eye and Ear)

Britton Chance Biomedical Optics Award - 2018
Tayyaba Hasan, PhD (Dermatology, Wellman Center)

Carnegie Mellon University Dickson Prize in Science
Emery N. Brown, MD, PhD (Anesthesia)

Charles L. Schepens, MD /American Academy of Ophthalmology (AAO) Award - 2018
Joan W. Miller, MD (Mass Eye and Ear Ophthalmology)

Clinical Research (CR) Forum Herbert Pardes Clinical Research Excellence Award
Florian Eichler, MD (Neurology)

Doris Duke Charitable Foundation 2018 Clinical Scientist Development Award
Karen Nanji, MD, MPH (Anesthesia)

Douglass Foundation Prize for Excellence in Hematology-Oncology Laboratory Research
Leif Ellisen, MD, PhD (Cancer Center)
Srinivas Vinod Saladi, PhD (Cancer Center)

Ellis Island Medal of Honor
Jerrold "Jerry" F. Rosenbaum, MD (Psychiatry)

Florida Inventors Hall of Fame
Emery N. Brown, MD, PhD (Anesthesia)

German Medical Physics Society (DGMP) Glocker Medal
Thomas Bortfeld, PhD (Radiation Oncology)

German Society of Anesthesiology and Intensive Care Medicine (Deutsche Gesellschaft fuer Anaesthesiologie und Intensivmedizin) DGAI Corresponding Member
Marcos Vidal Melo, MD, PhD (Anesthesia)

Harrington Discovery Institute 2018 Harrington Scholar-Innovator Award
Marc Wein, MD, PhD (Medicine, Endocrine)
David Sykes, MD, PhD (Medicine, Cancer Center, Center for Regenerative Medicine)

Harrington Rare Disease Award - 2018
Jeannie Lee, PhD (Molecular Biology, Pathology)

International Academy of Cardiology Walter Bleifeld Memorial Award
Robert A. Levine, MD (Cardiology)

M.D. Anderson Cancer Center Margaret L. Kripke Legend Award
Nancy J. Tarbell, MD, FASTRO (Radiation Oncology)

Massachusetts Medical Society 2018 Men's Health Award
Curtis L. Cetrulo, Jr., MD (Surgery)
Dicken S.C. Ko, MD (Surgery)
Thomas Manning (Patient)

Massachusetts Medical Society Information Technology Award - 2018
Stephanie Rutledge, MD (Medicine)

McGivney Global Advisors and The Lynx Group 40 Under 40 in Cancer Rising Stars and Emerging Leaders for 2018
Areej El-Jawahri, MD (Cancer Center)
Sophia C. Kamran, MD (Cancer Center)
Zofia Piotrowska, MD (Cancer Center)

Ministry of Science and Technology in Argentina Premio Raices (Roots Prize)
Raul Mostoslavsky, MD, PhD (Cancer Center)

National Academy of Inventors
Tayyaba Hasan, PhD, (Dermatology, Wellman Center)

National Academy of Medicine (NAM)
Robert E. Kingston, PhD (Molecular Biology)
Keith Lillemoe, MD (Surgery)
Janey L. Wiggs, MD, PhD (Mass Eye and Ear)

National Academy of Sciences (NAS)
Daniel Haber, MD, PhD (Cancer Center)

National Association for Proton Therapy Lifetime Achievement Award
Herman D. Suit, MD, PhD (Radiation Oncology)

National Cancer Institute (NCI) Outstanding Investigator Award
Xandra Breakefield, PhD (Neurology)

The Obesity Society (TOS) Vice President
Lee Kaplan, MD, PhD (Medicine, Gastroenterology, Weight Center)

Pierre Fabre Foundation 2018 Global Observatory eHealth Award
Farrah J. Mateen, MD, PhD (Neurology)

Pinnacle Award from the Greater Boston Chamber of Commerce
Merit Cudkowicz, MD (Neurology)

Postpartum Support International (PSI) 2018 Susan A. Hickman Memorial Research Award
Sharon Dekel, PhD (Psychiatry)

Radiological Society of North America Trainee Research Prize
Dania Daye, MD, PhD (Radiology)

Research to Prevent Blindness (RPB) Stein Innovation Award
Reza Dana, MD, MSc, MPH (Mass Eye and Ear)

Retina Research Foundation Gertrude D. Pyron Award
Joan W. Miller, MD (Mass Eye and Ear Ophthalmology)

Society of Nuclear Medicine and Molecular Imaging (SNMMI) Fellow
Georges El Fakhri, PhD (Radiology, Gordon Center)

Thieme Medical Publishers 2018 Thieme Chemistry Journals Award
Steven H. Liang, PhD (Radiology)

For more information on the Executive Committee on Research, please visit our website at http://ecor.mgh.harvard.edu/.

PROMOTE

Office of the Scientific Director (OSD) - Susan A. Slaugenhaupt, PhD

The Office of the Scientific Director is primarily charged with promoting science at Massachusetts General Hospital through three initiatives:

- Marketing and Communications
- Philanthropic outreach
- Building new partnerships with industry

Our marketing efforts are focused on increasing awareness of research at Mass General, both to our own community and to audiences outside our walls. We work with the Development Office to increase philanthropic giving for research through programs such as the MGH Research Scholars and Research Institute chairs. Finally, we are building new relationships with industry through our Strategic Alliance initiative and by working in close partnership with the Partners HealthCare Innovation office.
Below, we expand on each of these initiatives and give a few highlights from the past year.

Marketing and Communications

Internal communications: We continue to create and distribute our newsletter communications to help promote the remarkable work of our research community. Our most popular, Snapshot of Science, is a monthly newsletter that includes a listing of publications from high impact scientific and medical journals in which Mass General researchers are lead authors with accompanying lay summaries. The goal of this newsletter is to promote awareness of new Mass General research studies within our community, help the Research Institute establish relationships with individual researchers, and encourage researchers to think critically about translating their science for a broad audience. We use the format of this newsletter to help us think about marketing to the external community, especially through social media.

Additionally, we continued publishing monthly issues of our From the Lab Bench email newsletter, which typically features two or three articles about research at the hospital as well as news and updates from the Office of the Scientific Director.

The Research Institute Blog: Our Blog is in its second year and has become a major vehicle for sharing research news and updates both within the Mass General community and to the world at large. The blog typically features three new postings each week and includes original content, recaps of news articles, awards and honors announcements, infographics, tips for communicating science and much more. Our blog won the eHealthCare Leadership Award for Best Social Networking in 2018.

Since launching the blog, we've had: 450 published blog posts, 350 new followers, 51,922 page views, and over 38,000 visitors.

Social Media: We have also increased the impact of our research marketing via targeted Facebook posts, which enables us to strategically place updates about research breakthroughs at Mass General in the news feeds of individuals who are most likely to be interested in the results. For example, we can target a study about heart health to individuals who follow heart-related causes and organizations on Facebook, and a study about new treatment strategies for depression to individuals who follow organizations that promote mental health awareness.

In 2018, we used promoted posts to reach 324,325 people on Facebook, and those posts generated approximately 7,000 engagements (likes, shares, comments, reactions, link clicks, etc.). In addition, we doubled our number of Facebook followers from 784 to 1,559 in 2018, and added 1480 followers on Twitter, for a total of 2,528 followers.

Communicating Science: The Research Institute launched a series of initiatives designed to help our scientists better communicate the importance of their research to the general public.

In April, we teamed up with Mass General investigators to host a table at the Science Carnival and to host a Science Slam as part of the Cambridge Science Festival. In October, we held our third annual "Art of Talking Science Competition" as part of the city-wide HUBweek festival, this year hosting student competitors from the Boston Public Schools. These events gave researchers an opportunity to talk about science in front of a lay audience, and for us to partner with the Boston Public Schools to help foster the development of future scientists.

Internship Program: We also continued our communications internship program, which is designed to give aspiring science writers from local colleges—and from within our own postdoctoral community—an opportunity to write stories and social media posts about Mass General research. We hosted 3 interns in 2018.

Collaborative Efforts: We continue to work closely with our colleagues in Public Affairs, Development, and Central Marketing to coordinate the promotion of our research stories across various communication outlets (including MGH Hotline, Development's Giving website, and the main Mass General website and Facebook page). Initially a challenge, the sharing of content and ideas across these departments improved significantly over the past year and the result is better awareness of the depth and breadth of the research enterprise at Mass General, which is our ultimate goal.

Advancement

We work closely with our colleagues in the Development Office to inspire philanthropists and potential donors about the important role research plays in driving new discoveries in medicine. We had a very successful year of fundraising, and our ability to raise unrestricted support for research continues to grow. In 2018, we selected five new MGH Research Scholars, bringing the total number of Scholars awarded unrestricted funding over the past seven years to 55. This remarkable donor-supported program has had a substantial impact on the careers of the awardees and the advancement of research at Mass General. In addition, we named four Endowed MGH Research Institute Chairs. We continue to work towards our goal of supporting more members of our research community with MGH Research Scholar Awards and Endowed MGH Research Institute Chairs.

Our Communicating Science initiative is supported through a gift from Fred and Donna Seigel, and our activities in this initiative are highlighted in the marketing section above. Our research community has directly benefited from their gift through our Cambridge Science Festival and HUBweek competitions- the Art of Talking Science, through workshops led by science communication leaders, and through our Science Slams.

Our Research Institute Development team – including Drs. Slaugenhaupt, Orf, Kingston, Fisher and others in research leadership - held numerous meetings, lunches, and lab tours with individual donors and prospects in 2018, including the wildly popular Lab Day hosted in May. In addition, we were able to hold donor events in Beijing, China and Florida.

In 2018, Dr. David Altshuler was selected as chair of the Research Institute Advisory Council (RIAC). Dr. Altshuler, a former Mass General physician himself, is currently the Executive Vice President, Global Research and Chief Scientific Officer at Vertex Pharmaceuticals. With his help, and the council's, we hope to raise awareness for the Mass General research community. Overall, the success of our collaboration with the Development Office can be seen in their willingness to make research a philanthropic priority and in the growing portfolio of support for our investigators.

Strategic Alliances

We developed the Strategic Alliance Initiative with the objective of helping our investigators establish productive collaborations with industry, biotech and venture communities at all stages of their work; from fundamental research and proof of concept (early translation), to development and transfer to market and patient care (late translation). With the incredible support of the Strategic Alliance (SA) Committee of the Research Institute Advisory Council (RIAC), composed of key leaders in the field of biomedical research from industry and venture capital, we were able to push many of our programs forward in 2018. The Strategic Alliance Initiative focused on three key areas: building the research portfolio, assembling thematic programs and creating a unique translational training program.

Research Portfolio: In 2016, we initiated the Mass General research portfolio initiative as a key mechanism to build common understanding of the scope of research at Mass General. This portfolio serves as a comprehensive scientific foundation for promoting our research, enables programmatic efforts across departments and centers and establishes a sound mechanism to define well-informed strategies and tactics for engaging with industry across different themes. In 2018, we continued using collected research outlines to invite researchers to present their work for colleagues from Mass General Development and Partners Healthcare Innovation at our monthly Research Portfolio Wrap Sessions. Over the past two years, 40 investigators presented at 13 sessions. In addition, researchers who engaged with the Research Institute by submitting scientific outlines were often selected to have their work highlighted by our marketing team.

Thematic Programs: The RIAC Strategic Alliance Programs (RIAC-SA) come from research "themes" that were collected from departments, centers and institutes across campus. In total, we built six SA programs around Epigenetics, Cancer Immunotherapy, Neuroinflammation in Neurodegeneration, the Microbiome, Cardiometabolics, and Rare Diseases that bring together 126 investigators from many departments and thematic centers across the institution. In total, we organized 13 industry-focused sessions during which our investigators presented to invited industry executives. Our goal is to build collaborations that benefit both the program investigators and the industry partner.

In 2019, we plan to launch at least one new program, potentially in the area of infectious diseases.

Bridging Academic with Industry Course: Given the vital importance of the academic-industry bond in transforming discoveries into new and affordable cures and medical solutions for patients in need, we developed and launched an innovative translational training program co-directed by Gabriela Apiou, PhD, Director, Strategic Alliances, and Robert Tepper, MD, Partner, Third Rock Venture. The program will teach Mass General faculty (MD and/or PhD) and aims to teach them:

- Why and how to think about the potential applications of their research early in the discovery process
- How to develop a translational plan that includes research, intellectual property, and business perspectives
- How to build and manage a translation team
- How to interact with industry

The program involves a 14-week course on research strategy and tactics and a solution-driven project competition. We successfully identified 20 academic and 17 industry faculty who have agreed to participate as lecturers or as mentors. We received funding for the project award for the inaugural class and will host 21 students in the inaugural class that will take place from January – April 2019.

Supporting the Mass General Research Community: We supported our research community by meeting regularly with Partners Healthcare Innovation to ensure that our goals are aligned. We hosted over 125 meetings with companies interested in working with Mass General investigators and streamlined introductions where needed. We also worked with Mass General investigators on proposals to companies and/or other academic institutions. Lastly, we supported and coordinated the Partners Healthcare Innovation programs at Mass General including the Sanofi iAwards, Pfizer Centers for Therapeutic Innovation, Industry Fellowships, and World Medical Innovation Forums.

Division of Clinical Research (DCR) — Maurizio Fava, MD, Director

To view a complete version of DCR 2018 Progress Report, please visit: www.massgeneral.org/research/DCR

Founded in 1996, the Division of Clinical Research (DCR) of the Mass General Research Institute, formerly known as the MGH Clinical Research Program (CRP), is now entering its 23d year. Since its inception, the DCR has had a simple and constant mission: to increase the quality, quantity, and efficiency of translating basic science advances into improved care for our patients. More recently, DCR has become the hub for all PHS services (CTO, IRB, QI, Innovation), as well as the Harvard Catalyst.

Following DCR's Mission as well as MGH Strategic Plan recommendations, the following DCR Centers, Units and "Think Tanks" are providing support to MGH Clinical Research Investigators and staff:

DCR Centers

Bioinformatics Consortium, Ruslan Sadreyev, PhD

Computational data management, analysis, and interpretation are both a major driver and major bottleneck in many areas of biomedical research. The goal of the Bioinformatics Consortium is to provide bioinformatics and wider genomics service, consulting, education, and training for biological, pre-clinical, and clinical investigators at MGH and in the broader research community.

Biostatistics Center, Dianne Finkelstein, PhD & Hang Lee, PhD

Senior members of the Biostatistics Center collaborate with MGH clinical research investigators in various areas of statistical methods research that cover many topics in clinical trials and epidemiology, including study design (sample size), analysis of survival and longitudinal data, handling missing observational data, and high dimensional data.

Center for Clinical Research Education, Karen K. Miller, MD & Andrew Nierenberg, MD
The goal of the Center for Clinical Research Education is to improve the quality and quantity of clinical research within MGH by providing educational opportunities (live and online) for clinical investigators and study staff. The Center provides educational programs for physician scientists, PhD scientists, research nurses, project managers, coordinators and assistants. These programs are created to address the needs of the MGH clinical research community and are responsive to the ever-changing clinical research landscape.

Center for Quantitative Health (CQH), Roy Perlis, MD, MS
The Center for Quantitative Health (CQH) in the MGH DCR focuses on utilizing large data sets to develop strategies for probabilistic medicine and quantitative health. The CQH has four main areas of focus: developing ways to better match patients with effective treatments; developing tools to allow clinicians to quantify short- and long-term risks for individual patients; identifying promising treatments already approved by the FDA that can be repurposed for other applications; and monitoring treatment outcomes.

Clinical Research Center (CRC), David Nathan, MD
The goal of the Clinical Research Center (CRC), partly supported by the Harvard Catalyst, is to provide a research infrastructure for clinical investigators who conduct patient-oriented research. The CRC can be used by investigators who are supported by the National Institutes of Health, other federal, state and local agencies, foundations, individual departments or by the private sector. The CRC also supports pilot studies that may lead to future NIH or other support.

Community Access, Recruitment, and Engagement (CARE) Research Center, Jonathan Jackson, PhD
The new CARE Research Center uses a community-led, collaborative model of partnership and engagement to conduct groundbreaking research on poor accrual rates to clinical trials, with a focus on disparities for racial and ethnic minorities. This new center streamlines and institutionalizes the clinical trial recruitment process, leveraging a community-led collective impact model, while facilitating collaboration within academic medical centers as well as with other community health centers across greater Boston. This community-based model of engagement aims at helping develop community-wide resources that empower patients and their families to access cutting-edge medical treatment, also reducing the significant risk of clinical trial failure due to low or non-diverse enrollment. CARE aims to bring clinical research into underserved and marginalized communities in a way that engages and empowers the community to co-lead and contribute to these research endeavors.

Pediatric Translational Research Center (PTRC), Alessio Fasano, MD
With the appreciation that the biological events in childhood can strongly influence disease onset in both childhood and adulthood, this center applies a much stronger and integrated model by formally establishing the PTRC to facilitate Industry-Academia partnerships so that specific projects can be shaped together from their inception rather than along the way. The creation of a PTRC within the DCR allows us to expand our current research portfolio to become a unique asset complementary to the overall mission of the MGH Research Institute.

Trial Innovation Unit (TIU), Judy Hung, MD
Trial Innovation Unit (TIU) aims to improve efficiency and quality of the implementation of outpatient clinical trials. TIU targets junior faculty and fellows, or senior faculty with no access to infrastructure support. TIU is based on Simches 2 and is set up to leverage existing space and resources of the DCR, Harvard Catalyst, and contiguous programs. TIU offers free consultations and training for clinical research workforce. TIU services include: study design and planning support; study start-up and implementation support; patient involvement and recruitment strategies and tools.

Yvonne L. Munn Center for Nursing Research, Gaurdia Banister, RN, PhD
The official dedication of the Munn Center in May 2008 acknowledged the hospital's commitment to nursing and interdisciplinary research collaborations that foster high quality, cost-effective, patient and family-centric care. Some of the Center's goals include: accelerate research in core areas of focus: care of the elderly, ethics, symptom management, workforce evaluation, and complementary interventions to enhance healing and recovery; design strategies to promote the development, use, and translation of evidence into practice and enhance visibility of research conducted by nurses at MGH through dissemination in high-impact journals and presentation at internal and external scientific meetings.

DCR Units

Comparative Effectiveness Research Unit (CERU), James Meigs, MD

The Comparative Effectiveness Research Unit (CERU) has two main objectives: to support clinical research aimed to improve the clinical practice of medicine and population health and to provide mentorship and advice to those seeking academic research careers in clinical epidemiology and effectiveness research. The CERU focuses specifically on the "Second Translational Block" that exists between clinical trial and other research results and the implementation of their advances to improve clinical practice and public health. The principal activity of the CERU is research mentoring for MGH trainees and faculty at all levels, as well as providing free consultations. The CERU provides advice and support for research that addresses a spectrum of approaches and topics from disease pathogenesis to the effectiveness, efficiency, and equity of health care delivery and delivery systems.

Drug Discovery Rounds Unit, David Barlow, Mark Fishman, MD & Steven Paul

The Drug Discovery Rounds Unit provides opportunity for meetings between MGH investigators and leaders in the pharma and biotech world. During these face-to-face meetings, a clinical investigator and/or a basic science investigator from MGH can brainstorm about drug discovery opportunities in their field of interest with key advisors in pharma and biotech. Topics may include how to approach biotech and pharma companies, what companies are looking for, and conceptual advice about working with pharma and biotech.

Global Health Research Unit (GHRU), Jessica Haberer, MD

The Global Health Research Unit (GHRU) offers free consultations on the conduct of global health research, as well as sponsors campus-wide seminars on general principles for global health research. The GHRU research is generally cross-disciplinary and reflects several clinical fields, such as internal medicine, infectious diseases, psychiatry, and behavioral science. Research methods are both quantitative and qualitative. Funding experience includes the US National Institutes of Health, the Bill and Melinda Gates Foundation, other foundations, USAID, and philanthropic support. The GHRU also includes experts in grants administration and management of global health research projects.

Imaging Biomarkers Unit, Bradford Dickerson, MD & G. Scott Gazelle, MD

The Imaging Biomarkers Unit provides free consultations to help investigators identify questions in their research that can be answered using imaging technologies, and then helps to connect investigators to resources (personnel and technological) within MGH and the Partners HealthCare System.

Information Technology Unit, Henry Chueh, MD & Carl Blesius, MD

The broad goal of the Information Technology Unit (ITU) is to support the increasing information technology needs of the MGH clinical research community. The Unit's specific approaches to meeting this goal are: improving existing information management resources, while creating a broad, new information management infrastructure to support the work of the clinical research community at MGH and Partners HealthCare; providing IT management support for MGH clinical investigators, including assisting in the recruitment of study subjects and supporting the DCR's educational initiatives; envisioning and creating transformative informatics and IT solutions for the clinical research community and beyond.

OMICS Unit, Jordan Smoller, MD, ScD

The missions of the DCR Omics Unit are threefold: provide free consultative support to clinical investigators initiating or planning genetic and genomic studies at MGH; support clinical investigators already performing such studies through educational programs and process improvements; and serve as a link between the MGH clinical research community and the educational and technological platforms in Omics research of the Partners HealthCare System and the greater Harvard Medical School community. As genomic medicine becomes a reality, the Omics Unit continues to make significant progress in arming MGH clinical research teams with the knowledge and tools needed to incorporate or expand genomic and other omics in their clinical research studies. Omics consultations are designed to assist investigators in genetic study design and execution, human subject protection, career advice and resource identification.

Patient-Centered Outcomes Research (PCOR) Unit, Andrew Nierenberg, MD

The Patient-Centered Outcomes Research (PCOR) Unit was established to address the research needs and funding opportunities provided by the creation of the Patient-Centered Outcomes Research Institute (PCORI). The PCOR Unit seeks to facilitate research by providing

support in each of these domains. Specifically, the PCOR Unit advances work through four complimentary strategies: working with the DCR Center for Clinical Research Education to host a series of educational seminars and workshops to prepare investigators to submit PCORI applications; providing project specific consultative services through review of investigator-initiated proposals in the pre-award phase; supporting the expansion and evaluation of methods for collecting patient-reported outcome measures, specifically as routine components in clinical care settings; establishing best practices for patient and community engagement strategies and disseminating these resources to investigators.

Philanthropy Education Unit, Lee Cohen, MD & Roman DeSanctis, MD
The Philanthropy Education Unit coordinates meetings between past and present investigators at MGH to brainstorm on the best ways to raise philanthropic support for clinical and translational research projects. During these face-to-face meetings, investigators brainstorm about how to raise philanthropic support for their research with key advisors in the field.

Qualitative Research Unit, Elyse Park, PhD, MPH, Christina Psaros, PhD & Lara Traeger, PhD
The Qualitative Research Unit helps researchers investigate the "why" and "how" of questions related to healthcare and biomedicine. The Qualitative Research Unit provides free consultations in qualitative and mixed methods study design and execution. The Unit's consultations advise investigators on all aspects of qualitative study design, data collection, interpretation and publication of study findings, feedback on draft research proposals and identification of potential collaborators.

Survey Research Unit, Karen Donelan, ScD, EdM
The Survey Research Unit provides expertise in the development of survey tools for clinical investigators. The Unit provides consultations to investigators on designing and planning surveys and provides survey consultations and advice for all aspects of study design, execution and interpretation of survey data.

Think Tanks
"Think Tanks" are recurrent meetings with representatives from academia, pharma/biotech etc. to discuss programmatic collaborations. Current Think Tanks include:

- Think Tank on Rare Diseases (chaired by Florian Eichler, MD)
- Think Tank on Neuroinflammation (chaired by Rudy Tanzi, PhD and Chris McDougle, MD)
- Think Tank on Microbiome (chaired by Alessio Fasano, MD and Ashwin Ananthakrishnan, MD)
- Think Tanks on Early Detection of Sepsis (chaired by Marcia Goldberg, MD and Mike Filbin, MD)

Below is the expanded report on two cornerstone initiatives: The Partners Biobank at MGH and the Translational Research Center (TRC).

The Partners Biobank at MGH — Susan A. Slaugenhaupt, PhD & Jordan Smoller, MD, ScD

The Partners Biobank at MGH was devised to be a collaborative effort among patients, clinicians, and scientists to better understand disease, identify novel targets for therapy, and enable personalized medicine, by collecting and storing fully consented blood, serum, and plasma samples, linked to electronic medical records and lifestyle and family history survey data, from patients across the institution. Through the Mass General Research Institute, resources were committed to add personnel, space, and equipment to jumpstart the consent and collection program at Mass General. In its first five years of operation, the Biobank collected only 8,500 samples across all of Partners. With the additional resources contributed over the past four years, we have seen a dramatic increase in patient recruitment to over 95,000 consented patients. Through the dedicated efforts of the team, including site-Principal Investigators Drs. Kerry Ressler and Ross Zafonte, and Mass General-based managers Nicole Allen and Joe Coletti, the Biobank program at Mass General, McLean, and Spaulding have enjoyed great success since the implementation of the strategic plan. From a recruitment standpoint, the Mass General program met and exceeded recruitment metrics in 2018 thanks to the sustained growth of our team and successful partnerships with high volume clinical departments and research teams including Pathology; the Cancer Center; Neurology; Urology; Center for Perioperative Care; the Emergency Department research team; and collaborating biorepositories including the Cardiovascular Biorepository; the Biorepository for Neurological Injury; the MGH Department of Neurology Biobank; the Biorepository for Thyroid, Parathyroid, and Adrenal Disease Biorepository; the SNP study; and the Partners Calciphylaxis Biorepository. Over the past year, the Biobank partnered with the Mass General Departments of Medicine, General Medicine, Oncology, and Surgery on expansion efforts to inpatient settings. Inpatient recruitment in these units is now one of the Mass

General Biobank's most successful recruitment sites and a testament to the synergistic collaboration between our clinical and research teams at Mass General.

Due in part to the Biobank's notable growth and prestige, Mass General received an NIH-funded grant to be a regional medical center supporting enrollment into the Precision Medicine Initiative's All of Us Research Program. The All of Us Research Program is a large research study that is enrolling 1+ million individuals reflecting the diversity of the United States and collecting a broad range of phenotypic data linked to bio specimens to facilitate advances in precision medicine. As the Biobank and All of Us share similar missions and values, we are collaborating heavily on these efforts, and are dually enrolling interested patients in both programs as appropriate.

The Mass General Research Institute continues to be committed to increasing awareness of the Biobank, and now All of Us, to patients and investigators. Our investment in the creation of two dedicated consent and collection rooms on Wang 2 and Yawkey 3, as well as the interactive electronic "kiosks" in the Wang and Yawkey lobbies, greatly expanded visibility of these programs in the MGH community, and drawn publicity and recognition by local media (NPR). It has also solidified the link between research and clinical care, as patients who come to the Biobank labs can contribute both research and clinical samples at the same time. The Community Advisory Panel (CAP) that launched in 2015 has expanded its membership and has added All of Us to its purview. The CAP continues to be a tremendous success with members contributing valuable input on patient engagement efforts. Biobank sample collection has been accelerated by the integration of Sunquest sample collection orders into Epic, which has made contributing a sample to the Biobank significantly easier for our patients. The Biobank has also expanded its services to investigators and enhanced the profile of research activities at Partners sites both at an institutional and national level. Partners efforts to genotype 40,000 Biobank samples continues to generate research requests with data for over 30,000 genotyped patients to date freely available to investigators via the Biobank Portal. In parallel to the genotyping work, the Biobank continues to return medically actionable genetic results for pathogenic variants within 59 genes (as recommended by the American College of Medical Genetics and Genomics) to Biobank participants. The Biobank provides genetic counseling services to return these results and assist with clinical confirmation.

Because of the success of the Biobank, our co-directors have successfully competed for other national grants that have brought important resources to the Institution. These include our participation in the eMERGE network, a national network funded by the National Human Genome Research Institute that combines genetic data with electronic medical record systems for large scale, high-throughput genetic research. Expanding precision medicine research efforts such as eMERGE and All of Us, together with the extraordinary work of the Biobank staff, have resulted in a major increase in participants recruited and sample and data utilization from Mass General investigators.

Goals for this coming year include close integration of Biobank and All of Us with clinical teams throughout Mass General to promote recruitment efforts, increased visibility of both Biobank and All of Us within and outside of our institution and expanding research use of the Biobank data and sample resources.

Translational Research Center (TRC) — Mason Freeman, MD

Goals

The TRC's overall goal is to facilitate the movement of basic science and new technology discoveries, both at the MGH and in the biopharma community, toward the clinic in order to improve diagnostic capabilities and therapeutic interventions. Specifically, the TRC works with investigators to advance projects from pre-clinical findings that suggest clinical benefit through the required stages of development necessary to test the concepts in human trials. This work involves:

- Clarifying the development pathway necessary for a given idea to be taken forward;
- Providing an assessment of the feasibility and cost of pre-clinical studies, including pharmacology, manufacturing, and toxicology;
- Preparing the electronic submission and obtaining an Investigation of a New Drug (IND) designation from the FDA;
- Conducting meetings with relevant regulators at the FDA;
- Assisting in the writing of clinical protocols for submission to the Partners IRB; and
- Partnering with MGH investigators and local biotech companies to conduct early patient-based clinical trials in the Translational and Clinical Research Centers facility on White 12.

These activities are typically time-intensive projects and require significant commitments on the part of the TRC staff. The TRC must become

familiar with the details of individual investigator's projects to facilitate meaningful interactions with the FDA, external contract research organizations, or third-party vendors whose expertise is needed to enable a translational project to advance.

Accomplishments

1. During the calendar year of 2018, the TCRC conducted 32 industry sponsored clinical trials. That represents an increase from 24 in calendar 2017. The trials were distributed among the Departments of Anesthesia, Dermatology, Medicine, Neurology, Pediatrics, Psychiatry, and Surgery. 40% of the PI's were based in the Department of Medicine, 25% in Neurology, and 22% in Pediatrics. While a lot of exciting work was conducted by investigators in 2018, none was more compelling than the trial of Axexis, Inc.'s gene therapy for children with spinal muscular atrophy, led by Kathy Swoboda, M.D of Pediatric Neurology. Two such patients have been treated in the TCRC under the formal study protocol and a third was treated with the assistance of the TCRC staff on a compassionate use basis. While it is still earlier days, the first child treated, a neonate, has reportedly met all developmental milestones through approximately one year of life. This outcome would be unprecedented in an untreated child and thus holds the promise of being a spectacularly valuable therapeutic advance in the treatment of this devastating disease. This work has energized the entire research staff on White 12, reinforcing the vision behind the TRC's creation, which was to improve patient lives through partnering with companies that have created novel, potentially life-saving therapies.

2. A second major focus of the TRC in 2018 was the outreach efforts of Rajesh Ranganathan, PhD, the head of business development for the TRC. Rajesh devotes two-thirds of his effort to this program and one-third to the Department of Medicine Pathways program. Through a combination of networking at external meetings and direct outreach to individual companies, Rajesh had conversations about clinical trial work with over 43 companies in 2018. 20 of these companies proceeded to sign CDA's to discuss their development needs and, of those, 8 remain in active discussion, 5 led to trial contracts, and 3 resulted in hand offs to PI's when it was clear that the proposed trials could be conducted in investigators' own clinical trial space, rather than in the TCRC. Contracts that were signed for trials to be conducted in the TCRD were with Novartis (for NASH with Dr. Kathleen Corey), COUR (Celiac disease, with Dr. John Garber), Rebiotix (C. difficile enteropathy with Dr. Hamed Kalili), AveXis (Spinal Muscular Atrophy with Dr. Kathy Swoboda), and Tissuegene (Osteoarthritis with Dr. Minna Kohler). While the outreach effort has generated a lot of interaction between the MGH and the biopharma community, the execution of these trials has highlighted some deficiencies in our system for ensuring success. Several important lessons were learned from this work that will be discussed in the appropriate lessons learned section below.

3. Improvements in administrative processes have continued. Lynelle Cortellini, who previously served as the TRC administrative director, assumed the role of the administrative director for the combined TRC/CRC programs in mid-year. She now manages both the industry trial work and the NIH-funded (or departmentally funded) investigator portfolio of the CRC that is overseen via the Harvard Catalyst grant. Lynelle has brought new administrative methods to the overall TCRC operation and is working hard to streamline the burdens of study initiation that continue to frustrate busy PI's. Many of the computer tools used to improve efficiency were originally developed in the Translational Medicine Group/Translational Research Center and were ported over to support CRC investigators as well.

4. The TRC study staff has continued to advance programs and build new relationships that are designed to enhance the trial work conducted in the TCRC. The staff supported a NIH grant award for John Stone, M.D. of Rheumatology who applied to have the MGH host one of NIAID's major Autoimmunity Centers of Excellence (ACE). The grant was scored very highly, and Dr. Stone has indicated that he expects award funding to start in in mid-2019. The TRC submitted a companion grant proposal with Dr. Stone that would fund the TRC to administer the clinical trials for all of the ACE centers. A decision on that grant is expected in mid-2019. The TRC continues to work with a large number of MGH investigators on therapeutic or diagnostics efforts of their own. A few notable examples of this are the work with Drs. Robert Levine and Jacob Dal-Bianco who were provided study design and protocol planning help for a project to determine the value of using losartan to improve outcomes in children with rheumatic heart disease. The TRC also provided support letters for grants related to this proposal. Ed Ryan's work also progressed, with extensive drug product modeling performed so that the Gates Foundation might understand the cost of a combined shigella/cholera vaccine. The Foundation continues to deliberate on funding Dr. Ryan's project. The TRC director and Dr. Ranganathan met with Dr. Rochelle Walensky, chief of Infectious Disease, about strategies we could develop together to help her create an active clinical trials

program in ID. Subsequent discussions with two of her faculty members about specific trials they are interested in conducting have been held and we are working to find ways we can support the ID faculty in an ongoing way in the TCRC facility. Over the course of the year, the TRC director met with about a dozen young faculty members and trainees individually to discuss careers in translational medicine both in academia and in industry. The director also served as a faculty mentor for two fellows training at companies who are participating in the Innovation Office fellowship with industry program.

5. The TRC has undertaken a new model of therapeutic development in which the TRC team will serve as the clinical trial manager for an industry sponsor of a trial done at MGH. The first trial, on which the TRC director served as the PI, was a study of an oral anti-diabetes drug in patients with hepatic impairment. The study required 3 consecutive overnight stays in the TCRC and required the TCRC staff to assume new roles as active study investigators. The study was successfully completed. A second study utilizing this same model was approved for initiation by the FDA and Dr. Fava will serve as the PI. Its goal is to determine the safety and PK of transdermal ketamine in patients with resistant depression. The TRC has worked closely with Dr. Fava and his colleagues to design the study, achieve FDA IND approval, and then coordinate the conduct of the trial at the MGH and two external sites. These two trials provide a template for how the TRC can work with local PI's to conduct trials at MGH, but also serve as the coordinating center for multi-center trials.

6. The long-standing TMG/TRC oral diabetes drug development program, sponsored by Theracos, enrolled its last patient for its phase 3 program in 2018. The clinical outcomes study is expected to be completed in 2019, enabling the filing of an NDA. The TMG/TRC team will have overseen the entire drug development program from candidate selection to NDA filing for a major market, diabetes drug that has entailed the treatment of over 6000 patients on five continents. We believe this effort is unprecedented in the history of an academic drug development group. The TRC program manager, Dr. Yuan-Di Halvorsen, is primarily responsible for this achievement.

Adaptation Planned

In late 2018, we developed a partnership with Boston Biopharmaceuticals that was initiated in a dialog between the director of the DCR and the TRC director and the company's CEO. The concept was to identify faculty who would derive substantial salary support from a grant from the company in return for helping with the design and conduct of clinical trials in an area of keen interest to Boston Biopharmaceuticals. We selected dermatology as the initial clinical disease area of interest, and we anticipate that this program will be in full swing in 2019. The program should provide ample financial resources to support both the investigators and their time commitments to successfully recruit for the trials they help design, as well as provide support for team members from dermatology and the TRC in support of the PI's efforts.

The trials led by the DCR Director and the TRC Director provide a template for a model of interaction with industry that looks promising. Dr. Ranganathan's outreach efforts in 2019 are going to focus on identifying more of these kinds of relationships. He plans to first identify specific company needs, using a comprehensive industry database, that align with known areas of MGH expertise and experience. He will then approach MGH PI's with that expertise to verify that they have a willingness to take on the challenges of designing, recruiting and conducting trials of novel therapeutics. We hope this much more targeted approach will yield studies of real interest to the faculty that are better recruited.

SUPPORT

By the Number$ - Another All-Time High – Again! — Gary J. Smith, MPA, Senior Administrative Director, MGH Research Management

(Supporting figures and charts for this section are included at the end of the report.)

Research revenues for FY18 again reached another all-time high of $928M ($714M direct costs and $214M indirect), a $16M increase from FY17. Our awarded dollars from the National Institutes of Health (NIH) in FY18 increased from $394M to $466M (18% increase). In FY18, MGH jumped from the #15 to #9 spot in NIH funding for all institutions and continues as the #1 ranked independent hospital, a spot we have held for the past 20+ years. The percentage of funding awarded to MGH from the entire NIH extramural grant pool (market share) grew slightly to 1.6%, up from 1.5% the previous fiscal year.

Overall, MGH submitted 4,442 research proposals to all sponsors in FY18, down 3.7% from the prior fiscal year. DHHS applications were down 5% compared to FY17. This may be due to the dramatic increase in NIH dollars awarded to MGH this past year. We did, however, see increases compared to the previous fiscal year in the volume of proposals submitted to the Federal Other (24%) and Foundations (3%) categories. DHHS success rates for MGH proposals are approximately 25%, six points higher than the NIH national average of 19%.

Research expenditures from direct DHHS funding (which consists mostly of NIH funding), now accounts for 43% of MGH research, up 2% from last year's 41%. DHHS-sponsored research expenditures increased from $371M in FY17 to $386M in FY18. In addition, Federal Subcontract (predominately NIH) expenditures were $95M in FY18, increasing from $84M in the previous year. This is an indication that our collaborations with NIH funded investigators at other academic institutions is strong and increasing.

Research expenditures for all of our other non-NIH sponsor types continued to remain strong in FY18 and totaled $440M. The overall growth rate was 1.8% over FY17. The All Other Sponsor category, which is predominately sundry funds, saw a -20% expenditure decrease in FY18 compared to the prior year. We speculate that our strong NIH financial picture is resulting in less spending of sundry and gift funds. Since 2003 (15 years), MGH research expenditures across all sponsor types has grown 127%.

In aggregate, research activity (direct + indirect dollars) continues to comprise slightly under one quarter (23%) of the total MGH annual operating budget and is distributed across more than 40 departments and centers.

Space – The Final Frontier! — Michael L. Fisher, LPD, Director, Research Space Management Group

The Research Space Management Group (RSMG) functions under the organizational sponsorship of the Research Institute and is responsible to the Executive Committee on Research (ECOR) and the Research Space Advisory Committee (RSAC). RSMG manages all aspects of research space including space requests and allocations, proper space utilization, and renovations, which can range from minor site reconfigurations to major building/floor construction projects. Partnering with RSAC and MGH leadership, RSMG assists in developing space strategies, providing recommendations to fulfill space requests, optimizing space use, and supporting the overall Institutional research space objectives.

One of the department's primary goals is to support the Research Institute's Prime Directive by creating an environment in which scientists can concentrate on their research without having to worry about their physical environment. This goal is achieved by working closely with the hospital's ancillary and support services to ensure that research facilities are maintained to the highest possible standards. In addition, the department takes seriously its responsibility to analyze research space utilization using sophisticated metrics to ensure that all research space is used in the most effective manner possible.

MGH currently owns or leases approximately 1.32M net assignable square feet (nasf) of space, essentially the same amount as last year, but nearly double the amount of research space that existed in 2000. Research sites now exist in forty-four buildings across seven campuses in six cities. The percent allocations amongst the campuses are also similar to last year with 42% in the Charlestown Navy Yard campus, 21% on the Main Campus, 21% in Charles River Park, 6% on the Boston Campus, and the remainder in various metro Boston and Cambridge locations.

This year the Indirect Cost (IDC) density (defined as the recovered indirect costs per square foot) decreased somewhat from an average $185 per square foot in Fiscal Year 2017 to $183 per square foot. The main causative factor for this decrease was changes in funder mix; i.e., a greater number of grants from non-profit organizations and foundations. Of the major campuses listed above, the Boston Campus has the highest IDC density, $255. Major research groups contributing to the high IDC density have research sites at 5 Longfellow, 100 Cambridge St., 165 Cambridge St., 175 Cambridge St., 101 Merrimac St., 125 Nashua St., and 25 New Chardon.

Fulfilling outstanding space requests remains one of RSMG's most difficult challenges, particularly when there are few if any opportunities to add new space to our current inventory; thus, the only option available is to renovate existing space to make it more efficient. RSMG works with RSAC and the research community to better understand the true space requirements and promote space adjacencies amongst collaborative groups. Outstanding space requests from departments with valid funded grants averaged 87,343 nasf over the past five years. In September of this year space requests increased to 46,700 nasf for wet space and 42,325 nasf for dry space, a total of 89,000 nasf. Never static, the current space request total in December 2018 is approximately 119,925 nasf, reflecting new Institution and Department initiatives.

Constantly updating and analyzing data in the Research Space Management System (RSMS), RSMG utilizes this one-of-a-kind relational database to identify opportunities where space use can be optimized, and densities improved. Coupling RSMS data analysis with site surveys, analysts identify under-utilized space which often provides the basis for satisfying many space requests and justifying new Institutional initiatives. Successful densification projects can often result in increased MTDC and IDC densities transforming very valuable and much needed underutilized space into active revenue-generating research space.

In Fiscal Year 2018, thirteen renovation projects, whose costs totaled approximately $8M, were completed. These projects included CBRC Lab renovations on B149-03, Nuclear Medicine Lab renovations, on EDR-0, Cardiology Research Lab renovations on EDR 1 and 3, and the completion of the Simches Market Place. Twenty-five projects, totaling $36.5M in project costs, are in process. Major ongoing projects include the Surgery/CCM vivarium on B149-9, CVRC Zebrafish facility upgrade on B149-4, Radiology 7T in B149-1, and I3/IBC projects on the second and tenth floors of B149. Depending on the outcome of Capital Requests for Fiscal 2019, there could be as many as twenty additional projects totaling $13M initiated over the next few months.

RSMG continues to work with the Partners' Research Applications and Analytics team to update and improve the functionality of the Research Space Management System and the Microstrategy Reporting module. Work will begin in the new year on implementing new staff and performance metrics which are designed to more accurately capture seat occupancy and more finite research space utilization at any designated research site. This detail is invaluable for senior management when assessing space requests and planning for new program initiatives and Institutional expansion needs.

In addition to space-related responsibilities, RSMG also operates special Cores which support 75 research laboratories, coordination of the annual "Laboratory Cleanup Event", and research equipment tracking and auditing. In addition, RSMG is responsible for updating all floorplans for research space and designing and approving furniture purchases for research areas. As part of the IDC annual negotiation process, RSMG, in conjunction with Research Management, documents site locations for all research grants, helping to ensure the correct IDC rate is applied. This year RSMG, in collaboration with BWH, initiated a new time line for data review and annual reporting to ensure that the database is accurate and that all data is verified in an orderly fashion prior to the end of the calendar year. In additional to Departmental reporting, RSMG is in process of creating new reports and "Heat Maps" that accurately represent how well research space is being utilized.

Animal Care and Compliance — Donna Jarrell, DVM, Director, Center for Comparative Medicine (CCM) & Anne Clancy, PhD, Director, Animal Welfare Assurance

On any given day, approximately 105,000 mice, rats, guinea pigs, rabbits, sheep, pigs, non-human primates, and amphibians plus more than 35,000 zebrafish are housed and used within 95,000 square feet dedicated for such purposes on all 3 MGRI campuses. In addition, the MGRI operates two off-site facilities including a BL-2/BL-3 rodent facility that supports the Ragon Institute in Cambridge, MA, and a rodent facility at 65 Landsdowne Street. In anticipation of increasing non-human primate housing needs in 2018, a contractual agreement with Biomere (Worcester, MA) was established that expands census capacity by an additional 40-50 housing units. MGH is also establishing a collaboration with Accuro Farms, Inc in Southbridge, MA to offer relief to our heavily-utilized in-house livestock housing space.

Mass General Research Institute

Executive Report

The Center for Comparative Medicine (CCM) is the central laboratory animal care service for MGRI investigators and is led by Donna Matthews Jarrell, DVM, DACLAM, who also serves as the MGH Attending Veterinarian. CCM facilities are located on the Charles River Plaza campus, the Charlestown Navy Yard Campus and the Cambridge Campus. Its activities include husbandry, animal procurement, importing and exporting mouse lines from other academic institutions, inter-institutional transportation, preventive and clinical veterinary care, training in animal manipulative techniques, surgery and post-operative support, mouse breeding and colony preservation, and consultation in animal modeling and protocol design. There are approximately 130 employees, including seven staff veterinarians (six of whom are board-certified in laboratory animal medicine) and a leadership team of 25 mid- and director-level managers, who provide these services throughout the MGRI. In 2018, CCM successfully recruited their first veterinary resident in Laboratory Animal Medicine and Management (LAMM), the first residency with an equal focus on clinical medicine and program management in the country. This residency is recognized by the American College of Laboratory Animal Medicine (ACLAM) as well as MGH's Graduate Medical Education (GME) Program.

Specific efforts were taken in 2018 to:

- Improve animal welfare in partnership with the MGH IACUC. Innovative educational materials, including video demonstrations and visual or pictorial-based descriptions were developed for laboratory leadership to utilize in laboratory-based procedural areas. This will help to assure best practices and protocol compliance especially related to rodent experimental surgery and anesthesia monitoring.
- Lead the implementation of key capital projects on both the Charles River Plaza campus as well as the Charlestown Navy Yard to increase rodent caging capacity by 15-20% with no increase in overall animal facility square footage as well as address on-going HVAC environmental deficiencies.
- Control operational costs through continued elimination of non-valued added activities and process improvements resulting in a positive operating margin (OM) for FY18.
- Actively participated in several PHS-wide animal program initiatives including 1) legislative advocacy by PHS Govt Relations for petitioning the DOT to investigate discriminatory practices by the airline industry creating significant costs challenges for importing/exporting critical research models (10-fold increase in costs for ground versus air), 2) establishment of comparable (per other Boston and Partners-based lab animal programs) compensation packages for front-line care staff; 3) comparable cost setting initiatives for per diem rates across all PHS entities, and 4) Insight 4.0 forms standardization to assist researchers in understanding animal care and use best practices and regulatory-driven animal welfare expectations.

CCM supported several key research conduct support initiatives that are noteworthy. These include: 1) Facilitation of key research program improvements that address regulatory agency focused animal welfare concerns while ensuring that the research can be accomplished successful; 2) The establishment of a NHP Retirement Program as the first phase of a MGH Animal Adoption/Retirement program for all species; 3) Provision of sustained-released buprenorphine administration to support appropriate pain management of USDA-regulated species associated with surgical models, 4) expanded breeding program oversight for the Ragon Institute (> 30 lines) and 5) increased study conduct for short-term experiments which mimics our competitors (CROs) business model and is an avenue for increased revenue generation outside of per diems (limited by capacity restraints). We expanded research support services (beyond husbandry) by more than 25% compared to previous years utilizing current front-line technical personnel.

Lastly, CCM continued to host site visits in 2018 from manufacturing, healthcare, research and laboratory animal leaders who expressed interest in adopting a lean operations model in their facilities and programs. Seminars and webinars on this subject were presented at annual conferences of the American College of Laboratory Animal Medicine, the American Association of Laboratory Animal Science and the Public Responsibility in Medicine and Research and through our on-going affiliation with the Vivarium Operations Excellence Network (http://www.voenetwork.com).

The Institutional Animal Care and Use Committee (IACUC) governs the use of research animals at MGH. The Committee is fully constituted in accordance with regulatory requirements and is comprised of 30 members including veterinary staff, IACUC administrators, research investigators from many departments and research centers throughout the MGH Research Institute, and two community representatives. The IACUC Chair is Dr. Warren Zapol, Reginald Jenney Professor of Anesthesia and (HMS) Chief Emeritus, Department of Anesthesiology and Critical Care Medicine (MGH). Dr. Zapol is supported by Dr. James Allan, Assistant Professor of Surgery and Associate Vice Chair-IACUC and Mark Randolph ,M.A.Sc., Director, Plastic Surgery Research Laboratory, and Assistant Vice Chair-IACUC. The IACUC professional staff office supporting the IACUC is led by Anne Clancy, PhD.

MGH is registered with the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS), holds an Assurance with the NIH Office of Laboratory Animal Welfare (OLAW) and is licensed with the Massachusetts Department of Public Health and City of Cambridge. The hospital has been accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALACi) since July 30, 1993. Currently, there are more than 900 active protocols being performed by over 370 Principal Investigators.

A primary role of the IACUC is the review and approval of IACUC applications. Approximately 2,500 transactions were processed by the MGH IACUC in the past year, comprised of new protocols, triennial reviews and study amendments. Complete metrics data for the MGH IACUC are available on the Partners Research Navigator website, Research-Analytics-Reporting.

A primary focus for the IACUC office this past year was to work with Partner's Research Applications and Analytics, and the other Partner's IACUC offices, to develop and release the new Animals Module in Insight 4.0. This release represented a complete overhaul of how IACUC protocols are prepared and reviewed within Insight and introduced several business practice changes to remove unnecessary administrative burden for investigators and the staff office, and to ease the workload of the IACUC membership. Of note: (1) In collaboration with the MGH Committee on Fundamental Research, the IACUC offices created a new, streamlined IACUC Form set with more pre-approved checkbox options, less redundant, free text, and the option to include IACUC-approved procedure forms in protocol submissions; (2) MGH IACUC partnered with CCM veterinary services to formally incorporate veterinary review and consultation as part of the protocol pre-review and review processes; (3) The new commenting feature and meeting management module better support protocol review and allowed the office to implement weekly protocol review agendas (previously monthly), reducing the wait time for protocol review. The work to streamline the Animals Module and IACUC protocol review practices and procedures will continue through 2019.

Other significant events in the past year:

- On March 16, 2018 MGH received notice from AAALAC International that the program received a status of Full Accreditation in follow-up to their site visit in November 2017. This recognition by AAALACi reflects the excellent standards for animal care and use maintained at MGH thanks to the collaborative effort of the IACUC, CCM, Safety, RSMG and the research community.
- The IACUC office underwent staffing changes with the retirement of Diane McCabe and Laurie Harhen who made invaluable contributions to MGH for more than 20 and 40 years, respectively, many of which were in the IACUC office. The IACUC office welcomed Rosemary Foster, PhD as the new IACUC Manager; Rosemary is well known and respected by her fellow IACUC members and research personnel, having led several animal research projects in the Cancer Center, Harvard Stem Cell Institute and the Vincent Center for Reproductive Biology at MGH.
- MGH was assigned a new USDA Veterinary Medical Officer (VMO) who conducted an unannounced inspection of the MGH animal research facilities and a second focused inspection to review reported compliance concerns. The VMO commended MGH on our animal care and use program including the IACUC's practices and procedures for protocol review and animal welfare concern investigations. Our senior research investigators were provided special mention for their active engagement in upholding the high standards for care and use of animals in their laboratories at MGH.
- The City of Cambridge conducted its annual inspection of the MGH animal research facilities in Cambridge; no deficiencies were identified in the program.

Research Support IS Committee — Carl Blesius, MD and Deverie Bongard, MBA, Co-Chairs

The Research Support IS Committee (RSIS) was created to serve as a more formal interface for project teams across Partners to help coordinate technical efforts within the MGH research community. The committee works regularly on numerous tactical projects (e.g., Web support, software selection, software development, policy/procedural issues, etc.) and is also involved in major strategic initiatives. The overarching focus is to help identify and implement solutions and infrastructure to best support the cutting edge and dynamic technical needs of the research community.

Major Accomplishments in 2018

- Improved WIFI in Research areas: working closely with the MGH CIO, MGH network engineers and RSMG we increased WIFI coverage at the CNY campus from 10% to 80%, with remaining space to be covered in 2019.
- New Realtime Streaming and Teleconferencing Options: installed real time streaming system in 4 major Research Conf rooms.

Started using these systems to routinely stream events to the desktop as well as record presentations for later viewing. Implemented a self-service model for expanded use and started training various groups on the use of the system
- MGH Find a Researcher: replaced "Find a Researcher" link in the banner of https://massgeneral.org with a new application that provides real time access to researcher information at MGH from data feeds and researcher input.
- Applications for Research Administration: (a) HR: expanded roll out of an online Performance Evaluation for non-professional staff. Defined requirements to convert existing professional-staff evaluations to online, (b) Safety: released of new safety inspection application for use during monthly safety inspections, (c) Animals: worked with CCM to determine application needs for animal inspections, (d) developed specs for phone app to facilitate access to safety information and reporting, (e) Training: refined training compliance app and developed plans for expansion of scope for coverage beyond new hires.
- Information Security Committee Work: continued active involvement in IS committees providing input on data classification, data management and data collaboration policies. Our goal has been to ensure Research needs are addressed and are viable under new and existing policy constraints.

In addition to these major accomplishments we continue to support and refine applications developed and/or deployed in previous years.

Strategic Priorities in 2019
- Applications for Research Administration: (a) streamline Research Staff Cohort Identification System for further automation and delegation, (b) refine Lab Safety Survey App and add escalation module, (b) add features to the research training survey application for broader rollout, (c) expand HR online evaluations across MGH, (d) develop animal inspections pilot system based on safety survey system
- Work on Applications for Research Training and Education: (a) Continue work on LEARN to better support the research community's education and research training needs, (b) Generalize educational event attendance tracking application to track general research events using badge readers and iOS devices.
- Infrastructure Improvements: (a) 100% WIFI coverage of research space at CNY and improvement of coverage at MGH research areas, (b) facilitate network upgrades to bring 10 Gigabit to desktops, (c) add encrypted storage option to internal cloud platform for use with projects that need to store sensitive research data in an encrypted format.
- Committee Work: (a) Establish a user group for telecommunication and video conferencing, (b) explore technology upgrades for shared conference rooms, (c) leverage local expertise to solve problems and identify areas where consolidation of resources, services, and procedures can help leverage limited research resources, (d) work with in-house departmental technical support groups to outline strategic needs for the coming years.

We will continue to educate, encourage innovation, and foster scientific opportunities enabled by technology, pushing the organization towards technology adoption that will reduce administrative and workflow burdens.

Research Institute Training and Education Committee — Andrew A. Nierenberg, MD, Chair

The Research Institute Training and Education Committee (RITE), in collaboration with the Laboratory of Computer Science and the Center for Clinical Research Education of the Division of Clinical Research, maintains the LEARN platform (https://learn.partners.org) as a searchable comprehensive catalogue of courses for investigators for compliance training modules and research professional development. LEARN lists online and face-to-face courses and allows researchers to sign up for them efficiently. Additionally, new research hires are required to complete a survey which then lets them know their required training courses.

The RITE committee continues to work to identify gaps in compliance related trainings which lead to researchers getting into difficulties with regulations and fines to the hospital.

MGH Research Policy Updates and Initiatives – Harry W. Orf, PhD

Update – Isuggest Surpasses 1,200 Suggestions

Isuggest was rolled out in March 2016 as a Partners-wide expanded version of the Continuous Research Operations Improvement (CROI) Program launched in 2012 at MGH. This program provides straightforward ways for members of our research community to offer ideas that

will help us improve our support of the research enterprise.

In 2018, Isuggest received 200 new suggestions, bringing its total to over 1,200. Of these, over half have been implemented. Since its renewed launch in 2016, Isuggest has been receiving 3-5 new suggestions a week, indicating that the program has effectively reached a steady state where it is known and used routinely across the research enterprise. This success has in large part been due to the continual upgrades to the program to make it more intuitive and user friendly, and to the continued promotion of the "Suggestion of the Month" campaign, where a slide describing a successfully-implemented suggestion along with a photo of the suggestor is shown at the beginning of every research meeting (ECOR, Research Council, RADG, etc.).

While many of the working groups within the Isuggest structure are functioning well and addressing their suggestions in a timely manner, some are lagging in their responses. To address this issue, new metrics were developed to show both working group leaders and the Isuggest administrative management group which working groups are not operating effectively. Use of these metrics began at the end of 2018 and are already starting to result in increased attention being paid to previously neglected suggestions.

Update – Research Safety Committee Completes Its Sixth Year

Meeting #24 of the Research Safety Committee (RSC) took place in December, marking the end of six full years of the committee's existence. Formed in late 2012 and meeting quarterly since its inception, the RSC has a membership of over 70 people, including departmental safety coordinators from every research department and center in the hospital, as well as representatives from Compliance, Environmental Health & Safety (EH&S), Police and Security, and the Research Space Management Group. Task forces are formed on an as-needed basis to work on major safety projects. The committee meetings consist of an incident update from the MGH Director of EH&S, reports from active safety task forces, and presentations on various topics of safety and security of interest to the research community.

Accomplishments of the Committee this past year include: 1) A review, update, and hospital-wise distribution (with Police and Security) of the safety and emergency information on the orange badges that accompany issuance of the MGH ID Badge; 2) Development of a safety tip handout sheet for new research employees; 3) Review and update of the MGH Research Safety website and safety orientation information; 4) Working with the MGH Compliance Office, formalized a new controlled substances compliance reporting process.

Goals for 2019 include: 1) Development of a hospital-wide template for managing chemical inventories in research labs; 2) Completion of a successful Comprehensive Compliance Inspection of research labs by the state Department of Environmental Protection; 3) refinement and expansion of the piloted "Help and Safety" app to include problem reporting and general information sources; 4) Re-establishment of the MGH Laser Safety Committee with Dr. Rox Anderson as Chair; 5) Development of a Lab Orientation Checklist for safety coordinators to use when introducing new researchers to the safety elements within the lab environment.

Update – MGH Onsite Indirect Cost Rate Goes Down

In 2017, the federal government changed the indirect cost (IDC) negotiation schedule for MGH from a 3-5-year fixed rate basis to an annual rate negotiation with carry-forward adjustments. While this process is more labor intensive, it does provide the hospital with a more accurate annual picture of the cost of our research support elements and allows adjustments to be made to streamline them more quickly and reflect them in the published overhead rate. As a result of this new process, the government onsite IDC rate was reduced in 2017 from its previous fixed rate of 71% down to 68.5% and the offsite rate was increased from 27% to 32% for FY18. The primary reason for this reduction was the hospital's purchase of the Charlestown Research Facility, Building 149. When the hospital was leasing this facility, the entire cost of the lease could be charged to the indirect rate. Once the building was purchased, only the annual building depreciation cost could be applied to the IDC rate.

The FY18 rate of 68.5% was set from information sent by MGH to the federal negotiators with the understanding that a site visit would occur in 2018 in order to review the FY18 rate and set a new rate for FY19. The site visit took place in August 2018 and lasted for three days. Following the visit and review, the FY18 rate was confirmed and the FY19 rate was set at 68% with the offsite component set at 34%. Overall, we were pleased that the FY19 rate only dropped a half of a point given that our research revenues grew while our space and associated indirect costs remained relatively static.

Update – Research Orientation

The restructuring and addition of new support components that led to the formation of the Research Institute were substantial and somewhat complex. These changes left many members of our research community without a good understanding of the new organizational structure or new services created to improve the enterprise. Accordingly, Research Management developed a comprehensive one-hour "Research Road Show" to explain the new structure and services available. The show consists of a slide presentation featuring an overview of organization and services and is followed by a live demo of the "Top Ten Things Every MGH Researcher Should Know" using links on the MGH research intranet page. To date, 40 road shows have been given at various departments and centers to audiences ranging from 20 to over 200.

While the road shows successfully reach large groups of existing research employees, new weekly paid (non-professional) employees joining MGH receive during their day-and-a-half hospital orientation only a cursory introduction to a few of the many innovative breakthroughs created/discovered at the hospital. And new professional staff (faculty, postdocs, etc.), receive only a benefits orientation and no information about the Research Institute or the hospital itself. Accordingly, in 2018, Research Management developed a thirty-minute, condensed version of the Research Road Show that is now presented to new research employees during the weekly employee day-and-a-half orientation and the professional staff benefits orientation. The orientations began in Spring 2018 and are given by a rotating group of young research administrative and scientific leaders. The orientations have been very well received and have now become integral parts of the overall orientation process for all research employees. For 2019, we plan to produce a thirty-minute video of the orientation that can be shown to the small cohort of new research employees (such as some transferred faculty and graduate students) who are not able to attend the in-person orientations.

Policy Change in Royalty Distribution

An examination of the royalty/licensing distribution policies at over 20 major academic medical centers and research institutions showed that the Partners distribution policy (25% inventor, 25% inventor lab, 25% department, and 25% institution) returned a significantly lower percentage to the institution than the 40+% average from other institutions. With the institutions bearing the full (and rapidly increasing!) cost of patent filing and maintenance, it was deemed appropriate to revise the distribution formula to increase the institutional share. Similarly, our policy returned a slightly lower percentage to inventors (30% average elsewhere), although only eight of the other institutions gave any income to the inventor's lab.

In order to bring our royalty distribution policy more in line with other institutions, MGH and Partners leadership adopted a new formula giving the institution a 35% share by reducing the departmental share to 20% and reducing the combined sum of the inventor and lab shares by 5%. At the time a patent is filed, the inventor may elect to have the default distribution of 25% to the inventor and 20% to their lab, or they may select any alternate distribution in 5% increments provided that neither the inventor nor lab share is less than 15%. This new policy gives the institution more revenue to cover their increasing patent costs and while allowing the inventors more flexibility in determining the relative revenue distribution between themselves and their labs.

New Initiative – CARE

As a contributor to the MGH Diversity and Inclusion strategic plan, the Research Institute created and helped launch the CARE (Community Access, Recruitment, and Engagement) Center. Led by its Director, Jonathan Jackson, PhD, and as described previously in the Division of Clinical Research section of this report, CARE uses a community-led, collaborative model of partnership and engagement to conduct groundbreaking research on poor accrual rates to clinical trials, with a focus on disparities for racial and ethnic minorities. Specifically, CARE aims to bring clinical research into underserved and marginalized communities in a way that engages and empowers the community to co-lead and contribute to these research endeavors.

Starting the year with a staff of three, CARE has already obtained outside funding and has grown to seven members, with two more expected to join later in 2019. The CARE staff will also be assisting the MGH All of Us regional center in recruiting racial and ethnic minorities to this national Precision Medicine initiative. Additionally, CARE members will work with staff at our MGH community health centers to serve as a resource for patient recruitment there.

Partners Research Departments

Office of the Chief Academic Officer (CAO) - Anne Klibanski, MD

Anne Klibanski, MD, the Chief Academic Officer (CAO) for Partners HealthCare, works closely with senior research leadership across the Partners system – including Harry Orf, PhD, Senior Vice President of Research at MGH, Paul Anderson, MD, PhD, Chief Academic Officer and Senior Vice President of Research at BWH, Kerry Ressler, MD, PhD, Chief Scientific Officer at McLean, and Ross Zafonte, DO Senior Vice President Medical Affairs Research and Education at Spaulding –to create a collaborative and compliant research culture that directly supports the research community and provides key infrastructures to enable advances in basic and clinical research. At MGH, the CAO works closely with the MGHRI and its scientific director, Sue Slaugenhaupt, PhD and ECOR leadership.

The office of the Partners CAO directly oversees several departments that support a $1.7 Billion research enterprise ($906M MGH research) including the IRB, Research IS & Computing, the Clinical Trials Office, Innovation, Personalized Medicine (Partners Biobank and associated research cores). Together, these offices provide critical infrastructure that enable an efficient and innovative research enterprise. Research infrastructure at Partners also includes Research Management, Research Compliance, the Biosafety Office and the Office of Industry Interactions to ensure that all aspects of MGH's research as well as industry engagements are supported.

Human Research Affairs – P. Pearl O'Rourke, MD, Director

The Human Research Affairs (HRA) Office includes three components: (1) The Partners Human Research Committees (Institutional Review Boards or IRBs); (2) the Quality Improvement Program (QI) and (3) the Human Embryonic Stem Cell Research Oversight Committee (ESCRO).

The IRBs and QI Program in combination are responsible for the ethical and regulatory oversight of all research involving humans at MGH, BWH, McLean, North Shore, Spaulding, Newton Wellesley and, most recently, Mass Eye & Ear.

IRBs: Research that is not exempt from the regulations must be initially approved by an IRB before any subject is recruited or enrolled. During the life of the protocol, the IRBs are then responsible for continuing review, review of any change to the protocol (amendments), adverse events, unanticipated problems, and deviations from the approved protocol. Details of each these reviews are mandated and informed by federal and state laws as well as myriad conditions of grant award. IRB review requires close coordination and communication with Research Management, Clinical Trials Office, Office of General Counsel and Office of Interaction with Industry as well as institution-level sign-offs and reviews.

IRB Activity (PHS)

FY17 (10/1/17 - 9/30/18)	Full	Expedited
Initial protocol review	320	2053
Continuing review	805	5848
Staff amendments	-	14771
Other amendments	286	6251
Other (e.g., adverse events)	46	1299
Total transactions	**1457**	**31022**

QI Program: The QI Program provides resources for investigators as well as the IRB with the primary goal of supporting research that is compliant with ethical standards and regulatory requirements. The QI program works one-on-one and generally face-to-face with Investigators and study teams to conduct for-cause and not-for-cause on-site audits of study files; supports sites through external audits (e.g., FDA inspection); provides specific training for holders of investigational drug and device applications from the FDA; supports study teams with educational activities including study specific consultations, provides Regulatory Binder consultations, and presents at numerous department and institution educational sessions. In addition, the QI Program administrates the PHS ClincalTrials.gov program required for compliance with federal law.

QI Program Activity (PHS)

Activity 10/1/17-9/30/18	Number
On-site reviews	99
Consultations	118
Presentations/education	66

ESCRO Committee: The ESCRO Committee is responsible for the oversight of research involving the generation of human embryonic stem cells (hESC) as well as select uses of hESCs and induced human pluripotent stem cells. This requires close monitoring of relevant local and federal laws and policies as well as conditions of grant award.

As HRA supports the large and complex PHS research portfolio, it constantly encounters advances in science and research that present new ethical and regulatory challenges. Research has changed dramatically in the past several years. The single-site study has given way to multi-site (often multi-national) studies. New challenges of risk/benefit analysis that must be addressed include research in genetics, Big Data, data sharing, mobile apps, gene therapy and perhaps soon CRISPR. The HRA must be able to effectively deal with these changes as they come.

In addition, changes in federal regulations and in conditions of grant award require constant attention. Examples include:

- Mandated use of a single IRB for domestic multi-site research included in NIH policy (1/25/2018) requires significant changes in HRA operations and coordination as PHS increasingly provides single IRB review, relies on external IRBs at other academic institutions and expands the use of commercial IRBs.
- The Common Rule (the main federal regulation regarding the oversight of human subjects' research) has undergone a major revision, with an implementation and compliance date of January 21, 2019 for the new Rule. HRA processes and procedures are being modified to accommodate to changes in the categories of research that require IRB review; the review of ongoing research; the informed consent form, among others.

In summary, the health of the PHS research enterprise relies on our ability to conduct safe, ethical and compliant research. The programs within the HRA are critical to this task.

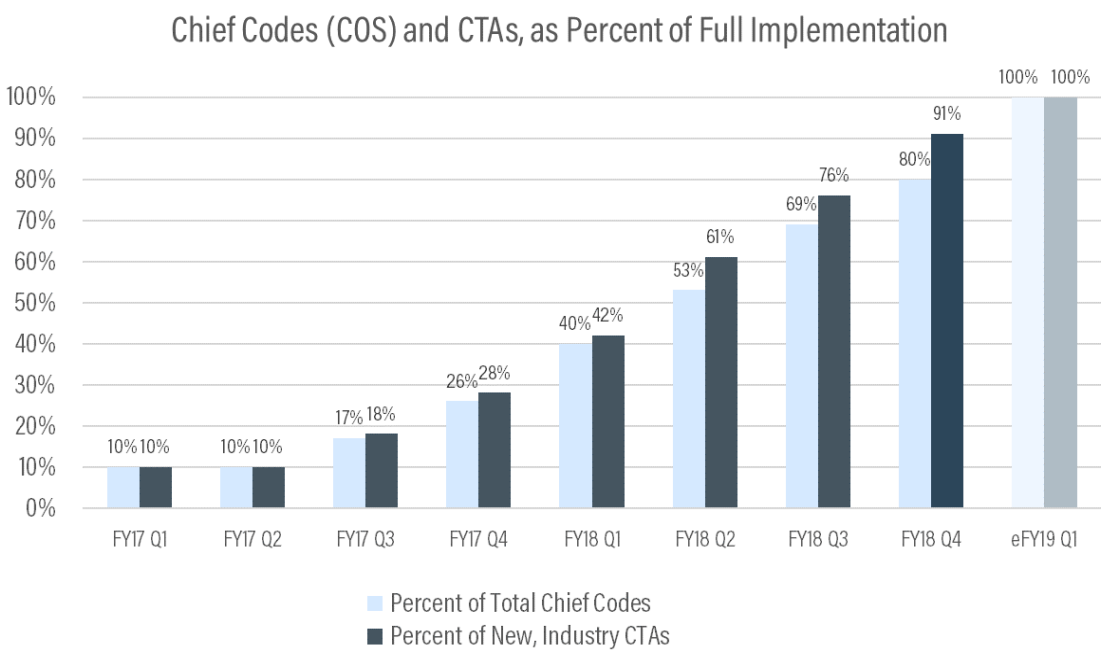
Clinical Trials Office – Stephen D. Wiviott, MD, Executive Director

The Partners Clinical Trials Office (CTO) serves to facilitate, support and expand the conduct of clinical trials at PHS through service excellence and effective collaboration between investigators and industry sponsors. The CTO is responsible for services to the MGH research community including contracting, budgetary development/negotiation and electronic resources for clinical trials management. These service areas are designed to provide clinical researchers with resources to engage in local, national and international clinical trials initiated by both industry and our investigators. Through participation in these trials, MGH is able to provide its patients with the most innovative and state of the art treatments for a variety of disease states and contribute to medical knowledge in support of the Hospital's scientific mission.

The Clinical Trials Office achieved a number of important goals in support of MGH investigators and leadership this year. These include a sustained 45% reduction in contracting and budgeting turnaround times since 2016, meeting institutional goals. This has in part been related to an increased number of master clinical trials agreements with more than 50 industry sponsors, and an additional 40 department or investigator specific master agreements. These master agreements allow for efficient start-up of new clinical trials. Overall volume of executed agreements was steady between FY17 and 18, with new clinical trials agreements increasing by 17% at MGH from 183 to 214, with a corresponding similar increase in trial budget approvals.
Significant advances in FY 18 have been achieved in the area of electronic clinical trial support services. First, the CTO has completed the roll-out of the OnCore Clinical Trials Management System (CTMS) to all departments and divisions at MGH, allowing for accurate tracking of industry sponsored research activity and invoices.

CTO Executed Agreements Volume (all-PHS)

Agreement Type	FY18	% change FY18-17	FY17	% change FY17-16	FY16
Clinical Trial Agreements	370	15%	323	-7%	349
Amendments	387	-20%	481	24%	389
Support & Other* Agreements	210	15%	182	5%	174
Confidentiality Disclosure Agreements	581	13%	512	12%	458
Subcontracts	75	-49%	147	99%	74
Total	**1623**	-1%	**1645**	14%	**1444**



Since initiation of the CTMS at MGH, more than 180 clinical trials by more than 80 unique investigators have utilized this system. In addition, in FY18, the CTO launched the Forte Payments system, a streamlined, real-time subject payment system to all users of the OnCore CTMS, providing an efficient solution to a labor-intensive area of clinical trials research. The CTO is currently piloting use of Forte Payments among non-industry-sponsored clinical trials in response to a strong interest from the broader research community.

To increase the utility of the OnCore CTMS for investigators and administrators, the CTO is piloting two major initiatives for FY19. The first is the development and use of advanced dashboards to provide up to date institution, department, division and investigator level information about clinical trial activity and invoicing progress. The second is to create direct connections between the CTMS and enterprise financial reporting systems to reduce the need for manual information input and allow for the CTO to take on additional roles in supporting MGH to maximize research revenue collection. In addition to these new initiatives, CTO strives to continue to work with industry sponsors to bring new clinical trials opportunities to the outstanding investigators at MGH through direct outreach and building on existing relationships between sponsors and CTO and to provide continued efficiency in in core contracting and budgetary services.

Partners Research Compliance Office – Mary Mitchell, Chief Research Compliance Officer

Mary Mitchell leads the Partners Research Compliance Office (RCO) which was established in 2007 to provide system-wide leadership and coordination of research compliance activities for consistency in interpretation, application and monitoring of regulations, sponsor policies, and Partners research policies. The RCO works collaboratively with Partners Research Management/Finance, hospital-based Research Compliance or Corporate Compliance offices, the hospital Sr. Vice Presidents for Research, and the hospital or Partners offices that manage the human subjects, animal research, and biosafety compliance programs.

Data Integrity: As data management and data integrity continue to be an important aspect of the Partners and MGH research enterprise, in 2018 the RCO continued its partnership with Partners Information Security and Privacy (IS) and MGH to improve investigator awareness of data/information security regulatory and institutional policies and to address new regulatory requirements. For example, in February 2018, the RCO published the Partners Research Data Management Requirements, a 30-page booklet (and interactive web site) that brings together institutional and regulatory requirements in one-location and establishes requirements for investigators to develop formal data management plans (DMP) and transition to electronic laboratory notebooks (ELN) and data collection systems. To meet the 10/1/19 compliance date for these requirements, the RCO is working with Partners Research Computing, and with MGH investigators and research staff, to develop a DMP template on Insight (the Partners system of record for grants management) to reduce regulatory burden when investigators establish their data management plans, in addition to working on ELN policy and process development.
In response to a new European Union (EU) regulation effective in May 2018, a major aspect of the data integrity/management program during 2018 has been (and continues to be) the development of an EU General Data Protection Regulation (GDPR) compliance program. The GDPR regulates acquisition, sharing and use of personal data of individuals residing in the European Union. Many MGH PIs have active

collaborations with EU colleagues that involve collection or transfer of personal data making these projects subject to GDPR. Industry sponsors routinely include GDPR requirements in MGH clinical trial agreements. Thus, it is essential that MGH have a robust GDPR compliance program. We anticipate that in-depth guidance will be available to the research community by early spring to supplement educational materials that have been available since May.

Training and Education: A key component of the RCO's role in supporting the research hospitals is maintenance of a training and education program for investigators, postdoctoral fellows, and research administrators. RCO educational activities in 2018 consisted of:

- Managing and delivering three Partners Responsible Conduct of Research (RCR) seminars for the 300+ trainees and career awardees across the Partners system required to complete this training.
- Offering three RCR seminars each at MGH on:
  - Animal Research Compliance
  - Biological Materials Research Compliance
  - Rigor and Reproducibility
- Information seminars at MGH on:
  - General Data Protection Regulation (GDPR)
  - Data Management Template (DMP)
  - Electronic Lab Notebooks (ELNs)
- Continued oversight of the PI Research Education series to ensure completion of required education by new MGH PIs.

Research Information Science and Computing (RISC) – Shawn Murphy, MD, PhD, Chief Research Information Officer

The division of Research Information Science and Computing (RISC) is the cornerstone of the scientific utilization of Information Technology at Partners. It provides the bridge for scientists who work in big data to access the electronic health record (EHR), imaging repositories, genomics repositories, and healthcare registries, and it provides the power for scientists to perform computation upon Partners-supported, privacy-aware, processing platforms at-scale.

Queries against integrated healthcare data can be initiated through the Research Patient Data Registry (RPDR), a centralized clinical data registry that gathers Electronic Healthcare Data from across all Partners institutions. With a self-serve query tool, researchers can define patient cohorts of interest for further study and, with proper Institutional Review Board (IRB) approval, obtain detailed clinical data on these patients within the guidelines of the IRB. The RPDR is utilized by over 1400 scientists every year, obtaining over 3,100 sets of EHR data supporting over $1.2 billion in healthcare research. The RPDR has been actively improving the quality of diagnostic data for the EHR, providing better phenotypes in the hands of researchers. Researchers can now start with over 65 high quality phenotypes as the basis of their queries.

The Partners Big Data Commons enables Big Data to be integrated with the RPDR and enables tighter integration of the RPDR with Epic. It allows more types of data to be integrated and become discoverable by researchers in a format that is easily consumable by researchers. For example, the Partners Biobank Portal is a web-based application that contains EHR and genomic data that can be queried online for over 95,000 consented Biobank subjects. The Clinical Image Bank is a web-based application that contains integrated disease registry data, EHR data, and imaging studies. There are currently over 600 investigators using these portals.

RISC's patient recruitment strategy encompasses several pathways to optimize the number of patients involved in research. People can volunteer through the Research Portal for Patients (rally.partners.org), signing up for studies by searching through areas of interest presented in an attractive and informative format. At registration, patients can opt into being contacted for studies that researchers determine may be a good fit for the patient; consented patients can be messaged directly using outreach tools built into Epic. For patients that have not opted in to be contacted directly by researchers, a workflow to contact patients through their providers is provided by the RPDR.

The RISC Health Innovation Platform (HIP) allows the efficient development and deployment of secure, Epic-linked apps into our clinical environment. Using HIP, sophisticated clinical decision support (CDS) apps can be built leveraging RISC capabilities for machine learning and providing high quality data. These apps can then be used to alter clinical workflows and/or improve decision making as well as

allowing unique clinical data elements collected through the apps to flow back into research.

Enterprise Research Infrastructure & Services (ERIS) supports research platforms, tools, applications and Information Technology consulting. It services 25,000 staff members and their projects, supporting High Performance Clusters for Computing and Hosted Cloud Services. Research data capture services are enabled through a suite of secure HIPAA-compliant data collection and survey tools such as Research Electronic Data Capture (REDCap) and Electronic Lab Notebooks (ELN) with in-depth consulting, training and Research IT contracting through the ERIS Core facility. REDCap is utilized by over 1200 scientists every year who construct over 5000 registries to support their research. The ERIS computational systems support over 1000 scientists running clustered applications averaging 60 thousand CPU days per quarter on 2 million gigabytes of storage.

Partners Personalized Medicine (PPM) – Scott Weiss, MD, MS Scientific Director

The goal of Partners Personalized Medicine is to enhance research and patient care at Partners' Hospitals through a series of services that can be utilized by individuals and institutions. These services provide a platform for personalized medicine at the Partners' Hospitals. The platforms are in the following 4 areas:

1. Partners Biobank
2. Partners Translational Genomic Core (TGC)
3. Laboratory for Molecular Medicine (LMM)
4. Personalized Medicine IT and Bioinformatics

Centralization of these platforms provides cost savings across the system, efficiency gains, and increased flexibility in building each hospital's own programs and in serving individual investigators.

Partners Biobank: The Biobank is a data and sample repository that contains DNA, serum, and plasma of consented patients linked to clinical and research data. The Biobank includes samples and data from across Partners HealthCare hospitals and community sites and enables individual investigators at MGH to access this resource for research with IRB approval. It leverages a common electronic health record which spans PHS. As of December 2018, 94,000+ participants consented and 68,000+ samples have been collected. In addition, the Biobank has supported over $315M in research activities through the distribution of Biobank samples and data as well as through the sample management services, such as DNA Extraction services, cell lines, and discarded samples distribution.
The key value/services provided to Partners HealthCare investigators are:

- Access to serum, DNA, or plasma
- Access to a large cohort of patients who are consented for broad-based research and recontact
- Powerful tools that query across previously disconnected data (e.g. clinical data, research data, and specimen data)
- Rich, curated phenotype data (validated disease populations and calculated healthy controls) as well as additional research data (e.g. self-reported surveys)
- Sample management services
- GWAS Data and Imputed Genomic Data
- Participation in a NIH-funded longitudinal research program, All of Us, which aims to consent over 90,000 participants in New England (as part of the larger goal of 1M+ participants over next 5 years) via a $53M grant at MGH that includes BWH and Boston Medical Center.

Partners Translational Genomics Core: The Partners Translational Genomics Core (TGC) supports research groups ($105M in grants annually) as well as system-wide Partners initiatives such as the Partners Biobank with the following cost-effective services:

- Genotyping and Next Gen Sequencing
- DNA analysis and serum/plasma miRNA analysis platforms optimized for sample types collected/extracted from Biobank patients
- Sequencing (Next Gen and Sanger) to support the Partners Biobank
- Novel sequencing workflows developed in partnership with Partners investigators (e.g. Parkinson's biomarkers study using a 7Mb sequencing panel)
- Identification of novel methodologies that can be used for Partners Biobank samples. On-going or recent development efforts include: miRNA from serum/plasma (supports use of Biobank samples), targeted methyl-seq capture (supports use of Biobank

samples), and 16s microbial sequencing in whole blood (supports use of Biobank samples)
- Basic and advanced analysis options for genomic and expression analysis, in partnership with the PMM Bioinformatics department.

Laboratory for Molecular Medicine (LMM): The LMM is a CLIA-certified molecular diagnostic lab that concentrates on advanced techniques for germline testing. It was created to bridge the gap between research and clinical medicine by focusing on:
- Supporting NIH-funded genomic medicine programs requiring cutting edge clinical genetic and genomic testing

Personalized Medicine IT and Bioinformatics: The Partners Personalized Medicine IT and Bioinformatics teams supplies IT support for the Biobank, LMM, TGC Core as well as assisting on numerous grant-based projects. The team's key functions are to:
- Support operations and maintain application infrastructure for the Biobank, LMM and TGC
- Develop functionality required to maintain near real-time programmatic access to patient genetic data for the LMM and Biobank
- Offer custom analysis for NGS data to Partners Investigators thru the TGC, such as: Genome/Exome/Panel variant calling and filtration
- Support data processing, analysis, and storage of Genotyping results for Biobank participants' samples
- Assist in the development of the Health Innovation Platform (HIP) and associated apps to improve clinical workflows
- Support eMERGE from both lab processing and clinical results delivery perspectives

Partners Innovation – Chris Coburn, Chief Innovation Officer, President, Partners HealthCare International

Partners Innovation monetizes the unique assets of MGH and its Harvard faculty. Its business development responsibilities include company creation, license transactions, international consulting, securing research collaborations, technology development funding and managing intellectual property including filing for patents. Partners Innovation is the largest academic organization of its kind with 125 staff that includes 32 PhDs, 32 MBA/MAs, 16 JDs, and 8 MDs. Industry backgrounds include the former head of research at Baxter, numerous entrepreneurs, investment executives as well multiple degree recipients from Harvard, MIT, Brown, Columbia, Cornell, Penn, Yale, University of Chicago, Georgetown and Northwestern. Total FY18 revenue was $138.6 million, a 6% increase from the prior year with more than three quarters associated with MGH.

Over 280 companies have been established based in whole or in part on the work of Partners HealthCare investigators with 2/3 of those being tied to MGH. The Partners Innovation Fund I and II has $171 million in capital under management that includes strategic investors such as Astellas Pharma, Eli Lilly, ShangPharma, and Simcere Pharmaceutical Group. It has invested in more than 35 companies, nearly a dozen of which have gone public or been acquired. Its net internal rate of return is nearly 20% which equates to top quartile performance in the venture industry and is largely unrivaled in the academic realm. Plans are underway for launching PIF III in FY19. A translational innovation fund and artificial intelligence and digital innovation fund are under consideration. Innovation is also spearheading several large scale strategic MGH-industry collaborations that should public by the time of the SAC meeting.

MGH Outcomes	FY14	FY15	FY16	FY17	FY18
Licensing Activity	113	127	130	133	198
Material Transfer Agreements	1,073	987	1067	1360	1374
New Disclosures	408	318	365	311	366
Patents Filed (US)	253	228	910	1091	1643
Patents Filed (Int'l)	644	399			
Patents Issued (US)	86	89	109	108	144
Patents Issued (Int'l)	172	120	190	267	212
Royalty and Licensing Income	$68.9M	$80M	$77M	$87.7M	$94.6M

The World Medical Innovation Forum will be held April 8-10, 2019 in Boston. It will feature the growing impact on artificial intelligence and machine learning throughout healthcare – in research, diagnosis, therapy, management and operations. More than 2000 registrants from around the globe representing more than 600 organizations are expected with nearly a third being PHS faculty and trainees who will experience first-hand how commercial innovation priorities are set.

Partners Research Management — Andrew Chase, Vice President of Research Management and Research Finance

Andrew Chase, Vice President of Research Management and Research Finance, who reports to Peter Markell, Executive Vice President of Administration and Finance, CFO, and Treasurer of Partners HealthCare, leads the Partners Research Management team working closely with

Harry Orf, PhD, Senior Vice President of Research, at MGH, Paul Anderson, MD, Chief Academic Officer and Senior Vice President of Research at BWH, and Anne Klibanski, MD, Chief Academic Officer of Partners HealthCare.

It was another record-breaking year for research across Partners with over $1.7B in activity. MGH led the way with this success, again exceeding the $900M threshold. Being in Assembly Row with the other Partners research support teams, including the Industry Clinical Trials Office and Innovation, has allowed us to better manage research activities that are increasingly becoming more complicated and span government, industry and non-profit sponsors.

To support the continued success of the MGH research community, Research Management continues to make improvements to systems and the support infrastructure for the MGH investigators. Last year significant time and effort was put into the rollout of the new and improved version of the INSIGHT grants management system. The updated system includes improvements to the user experience with automation in workflows, enhancements to the layout, and additional functionality. Research Management also continues to develop and improve upon its training curriculum for Hospital Grants Administrators, Research Staff, and Investigators. There are currently 30 trainings offered tri-annually to the MGH community via online courses or in person sessions. Additionally, training and competency-based learning for Grants Administrators was identified as an area of focus as part of the Partners 2.0 Research Workstream. Preliminary discussions and scoping have been undertaken with Hospital Administrators and the team from the Center for Continuing Professional Development to further enhance the positive impact of the Research Management trainings.

With the growing volume and complexity of the Research Portfolio and the overall pressure to contain costs, Research Management continues to improve upon the reporting tools that compliment INSIGHT to improve transparency into research support operations. Enhancements were made to the research dashboard that provides information on research activity; proposal submissions, expenses, and financial activity. The dashboard can be filtered from a department view down to the individual PI level. The goal over the next year is to provide the dashboard on a routine quarterly basis to an increased audience at MGH.

We continue to work with sponsors to find common ground and on behalf of our investigators push back on unnecessary administrative requirements. As in years past, the increasing administrative and regulatory burdens from the government and funding sponsors partially offset the improvements made internally. Over the past year we have seen increased scrutiny of progress reports and award activity from the NIH. Also, many foundation sponsors continue to include terms and conditions in their awards requiring administrative oversight that require substantial negotiations.

Partners Office for Interactions with Industry — Chris Clark, Esq., Director

The Office for Interactions with Industry (OII) oversees, administers, and continually works to refine and improve Partners policies and processes relating to the complex relationship between academic medicine and the for-profit biomedical sector. Our focus continues to be on fostering such relationships as essential to Partners in the fulfillment of its missions while ensuring that the relationships do not bias the way that Partners carries out its charitable activities.

The work of OII is overseen by the following committees, which have overall responsibility for Partners policies on interactions with industry:

- The Professional and Institutional Conflicts Committee (PICC), a subcommittee of the Partners Board of Directors, has overall responsibility for all institutional policies and activities relating to interactions with industry.
- The Committee of Outside Activities (COA) is responsible for reviewing and approving live cases that raise conflict of interest issues for Partners HealthCare staff and employees, and for interpreting and implementing policies relating to conflicts of interest. COA is chaired by two department chiefs, one from MGH and one from BWH, and its other membership consists entirely of Partners professional staff members, several of whom also have senior management positions.
- The Education Review Board (ERB) is responsible for approval and oversight of all industry support of fellowship programs and other educational activities at Partners HealthCare. The ERB is chaired by two senior professional staff members and its other membership consists entirely of professional staff members all of whom are involved either in Partners fellowship programs or other Partners educational activities.

OII staffs the above three committees. In order to fulfill its responsibility, OII organizes its work into four areas:

- The Research Activities section review investigators' financial interests in connection with hospital research activities for potential conflicts of interest. This group is responsible, among other things, for ensuring compliance with Public Health Service regulations on PHS-funded research.
- The Outside Activities section reviews the outside activities (personal consulting arrangements and the like) of physicians and staff to ensure they are consistent with Partners policy and is responsible for obtaining COA and PICC review of outside activities of senior institutional officials.
- The Educational Grants section oversees the receipt of industry funding in support of Partners educational activities, to ensure compliance with Partners policy. This section also handles conflicts arising in purchasing and similar types of transactions and has responsibility for handling gifts from industry to support research activities.
- The Systems and Education section works with Partners Research Applications Group to design the online conflict of interest disclosure system; administers the Annual Disclosure process to physicians and staff; provides online and in-person training to the Partners community; maintains the OII web site; and coordinates the distribution of educational materials to the Partners community.

Significant accomplishments in each of the OII sections during FY18 included the following:

1. Research Activities – in addition to handling, as part of the normal workflow, the processing of over 20,000 financial interest disclosures needed for compliance with PHS regulations and HMS and Partners COI policies:

- Achieved significant improvements, both in efficiency and the turn-around time required, for the COI review process of research grants by working with Research Applications and Analytics to design and implement new functionality in the Insight Disclosures Module.
- Continued to work extensively with the staff of HMS and affiliated hospitals to develop and refine the process for the intake, preparation, and consideration by COA and the HMS Standing Committee of investigators' petitions for exceptions to the HMS and Partners Clinical Research Rule (HMS 1a) and the Research Support Rule (HMS 1b). These rules were revised several years ago to allow for investigators to participate in research notwithstanding having a conflicting financial interest by requesting an exception to the rules which previously had prohibited holding certain types of financial interests while participating in specific types of research activities. Refining and making this petition process more efficient have been a major focus of the Research Activities section over the last few years.

2. Outside Activities – In addition to handling, as part of normal workflow, over 1800 consulting and related agreements:

- Continued streamlining processes for handling consulting and other outside activity agreements, in part by developing more coordinated approaches across OII to outside activities that have implications for Partners research, with particular emphasis on discussions with investigators interested in forming start-up companies;
- Maintained approach of constantly revisiting policies for course-correction, leading to revisions in several Partners policies, specifically:
    i. Guidelines for participation of Partners individuals in company videos;
    ii. Gift Policy application to companies paying for device training;
    iii. Guidelines and process for addressing supervisory conflicts of interest in research scenarios and institutional service agreements.
- Revised the intake process for outside activities, refining the questionnaire that provides information to enable the identification of potential conflicts of interest in outside activities.

3. Educational Grants – in addition to handling, as part of the normal workflow, over 250 educational grants bringing in about $5.5M in funding:

- Built an entirely new Ed Grants team;
- Leveraged the perspective of the new team to launch a comprehensive Process Improvement initiative, focusing on clarifications and revisions to numerous policy and process standards, including:
- Guidelines for Industry Attendance at Partners Educational Activities;
- Guidelines for Promotional Opportunities in Conjunction with Partners Educational Activities; and

- Updated Budget Guidelines for Partners Educational Activities.
- Worked with the ERB to establish Educational Training Centers as Partners Educational Activities and created relevant guidelines;
- Established a reliable process for the review and approval of industry gifts for research, coordinating with the hospital Development Offices, Partners Innovation, Partners Clinical Trials Office, and the Office of the General Counsel. During the year, OII finalized 36 industry gifts for research, totaling over $6.9M.

4. Systems and Education – in addition to handling, as part of the normal workflow, the distribution and completion of annual disclosure forms to nearly 11,000 Partners staff:

- As part of Partners Research Applications & Analytics' initiative to implement major usability upgrades to Insight modules, worked with RAA and an end-user group of faculty, investigators and Compliance Officers to continue to refine and enhance the functionality of the Insight Disclosures Module. This past year, the focus was on the integration between the Disclosures module and the new Agreements and Humans 4.0 modules.
- Prepared training materials and held user training sessions for the new Disclosures module and assisted users in completing their Annual Disclosure and Financial Interest Disclosure Forms.
- Facilitated the Conflicts of Interest in Research online training course for over 700 faculty.

Looking at the Year Ahead – Challenges and Opportunities – Harry W. Orf, PhD

As the previous sections of this report document, significant progress has been made in 2018 implementing the strategic plan for research and improving the services that support the Research Institute. Looking ahead to 2019, there are many opportunities for strengthening the research enterprise as well as challenges to be met to sustain our standing as a leader in academic medicine and biomedical research. The most challenging of these is the need for additional research space, as discussed in the final segment of this section, The Case for Space.

New Science Initiatives. Recent leadership changes and new science programs forecast an exciting year for the Research Institute. In 2018, Dr. Ramnik Xavier succeeded Dr. Brian Seed as Director of our Center for Computational and Integrative Biology (CCIB), with plans to expand its faculty and presence in Simches. Concurrent with assuming the CCIB Directorship, the Department of Medicine also established a new Center for Experimental Medicine under Dr. Xavier. Initially, the Center will focus on the integration of the role of the microbiome in autoimmune disease and cancer, the use of systems immunology for dissecting the autoantibody repertoire and cytokine responses in specific tissue compartments, and qualitative science (e.g. bioinformatics and big data science) to integrate multiple data types to decipher these processes in the pathogenesis of disease.

Appointments of unit chiefs made at the end of 2018 also bring with them exciting research programs new to MGH. Dr. Wolfram Goessling, MD, PhD, new Chief of the Division of Gastroenterology, uses zebrafish as the primary model to study the liver and explore the regulation of endodermal progenitor cell specification, organ differentiation and growth. Dr. Yolonda L. Colson, MD, PhD, new Chief of Thoracic Surgery, brings her research program focused on sentinel lymph node mapping and prevention of cancer recurrence through polymer-mediated drug delivery and nanotechnology. Dr. Eugene Rhee, MD, newly named chief of the Renal Division, is interested in several aspects of renal metabolism, with the goal to understand how alterations in energy metabolism contribute to kidney disease pathogenesis and its complications and to discover metabolite markers of CKD and its progression. Dr. Rhee has also recently secured capital funding to consolidate research within the Renal Unit in Charlestown and planning is currently underway.

Perhaps the largest science initiative undertaken in 2018 at MGH and Partners involves digital health. At MGH, leadership has provided resources to stand up the Center for Innovation in Digital Healthcare (CIDH). The Center is co-led by Dr. David Ting, MD, Chief Medical Information Officer of the MGPO, and Dr. Shawn Murphy, MD, PhD, Chief Research Information Officer at Partners. Dr. David Louis, MD, MGH Chief of Pathology, serves as Executive Sponsor for the Center and Ms. Sara Silacci serves as its Director for Strategic Alliances. CIDH plans to work closely with its counterpart at BWH, the iHUB directed by Dr. Adam Landman, MD, to create common processes and tools for managing digital health programs across both institutions. This cooperative effort will be coordinated through a new digital healthcare department within Partners Healthcare, created this year and led by Dr. Alistair, MD, who recently joined Partners at its Chief Research Information Officer. Partners will provide the infrastructure and data resources to support digital health initiatives across the enterprise with the understanding that digital science programs and innovation will be centered at the academic medical centers.

Internal Grant Support. The ability of ECOR to sustain its Interim Support Funding program and to sponsor internal awards and prizes, which collectively provided over $13M in funding in 2018, is threatened by the projected depletion of its current-use funds within the next two years. With the hospital operating budget being increasingly strained by changes in healthcare reimbursement policies, new revenues sources from Development (philanthropy) and, hopefully, licensing/royalty revenue streams will be needed to fill the gap. Hospital leadership understands the importance of this funding to our research enterprise and has vowed to work with ECOR leadership to identify funding sources to sustain the Interim Support Funding program.

Philanthropy and the Capital Campaign. In 2018, MGH embarked on the "silent phase" of a new, multi-year capital campaign. The exact duration and financial goal of the campaign are in the process of being finalized, but it will be in the $2-3B range, and the Research Institute will be among the 4-5 major campaign themes being promoted. This campaign will provide the hospital with an unprecedented opportunity to solidify the financial support base of the Research Institute. Research leadership has suggested "Lead Healthcare Transformation through Research (MGH Research Institute)" as the flagship research theme.

In addition to the campaign, the Research Institute development team continues its diligent work to raise support for the Research Scholars program and RI Endowed Chairs. In January, we celebrated the third and fourth RI Endowed Chairs, and, working with Dr. David Altshuler (new Chair of the RI Advisory Committee), the team is focusing on efforts to secure the next class of Research Scholars.

Another important recent development regarding philanthropy involves the Ragon Institute of MGH, MIT, and Harvard. Terry and Susan Ragon, whose generous support established and has sustained the Institute for the past 10 years, have stated their intention to permanently endow the Institute with an additional major gift. As of January 2019, the draft agreement has been completed and will hopefully be signed by the 2019 SAC meeting.

The Case for Space – Sustained Growth Leads to Overcrowding

Over the last 16 years, research revenues at MGH have grown from $400M to $928M annually. This unprecedented growth has occurred in literally every department across the hospital, making MGH not only the largest, but also the most diverse biomedical research enterprise in the country. But this growth has come at a price. In the last decade, research space at MGH has grown 18.9%, while the number of research employees has grown at twice that rate, and research revenues have grown at three times that rate, even when adjusted for inflation. Consequently, overcrowding in research spaces is approaching a critical level. This crowding is further evidenced by the significant increase in the density of research conducted per square foot. The MTDC (modified total direct cost) density (MTDC/SF), which is a direct measure of the quantity of research taking place per unit area, has risen to $537/SF, 20% higher than comparable medical center and research institutions.

Looking ahead, overcrowding will become critical very soon. The recent dramatic (18%) increase in the amount of long-term NIH grant funding awarded to our investigators combined with significant increases in the number of collaborations with pharma/biotech companies project that strong growth in research revenues will continue at an even greater pace in the future. This will bring our space shortage to a critical stage within the coming year. The emergence of new research activity (the difference between new awards starting and old ones ending) tells us that an additional $55M per year will be available to spend in the coming years. But to spend this new funding will require us to hire over 280 research FTEs. "Where will we put them?" is a question becoming increasingly difficult to answer.

Unfortunately, overcrowding impacts more than just the space occupied by our research employees. Animal housing across the hospital has also reached critical crowding levels, resulting in important, well-funded research programs being delayed or put on hold. Most rodent rooms in Simches are at capacity and continuously on "red" status, meaning no new cages may be placed in the rooms. Work is underway to renovate every available support room into additional animal housing space, but this process is slow and expensive and, even when completed, will provide relief for only a year or two at best given the backlog of housing requests already on file. And crowding in large animal housing is just as critical. Recently, we have had to rent expensive, offsite non-human primate space at a local company (Biomere) to accommodate the needs of new recruits in transplant sciences and neurosurgery.

Doing the Best We Can for Now. Of course, not all labs are overcrowded. At the extremes, we have PIs with lab MTDC densities over $1700/SF and some under $100/SF. So there are pockets of space where opportunities exist to reallocate space to those overcrowded by taking

from those with more than they are using. These underutilized spaces, however, are scattered across our 1.2M SF of research space and, taken individually, are not very large. This often requires us to locate new investigators or investigators with growing labs wherever we can find space, sometimes placing them away from their base lab and collaborating colleagues.

In a vibrant research community such as ours, people come and go all the time, promises are made as part of chief recruitment packages, new scientific programs emerge, and we continuously need space for faculty recruits and growing PI programs. The new metrics and management processes we are putting in place all help us reallocate underutilized space in a fair, equitable manner. However, they can no longer compensate for the critical space shortage we are now facing. RSMG, our Research Space Management Group, has outstanding requests for space totaling over 117,000 SF (60,000 SF wet and 57,000 SF dry). Most requests have been received within the last two years but some that are several years old still represent active needs. Included in the request list are chief recruitment packages and other, large square footage projects for new scientific programs. The highly dense use of active research space, coupled with the complete lack of swing space, makes it difficult, if not impossible, to piece together sizable areas from the available, scattered underutilized research spaces. And when a plan for significant consolidated research space is developed, it inevitably involves displacing numerous existing programs at considerable expense while delaying the progress of the researchers being relocated.

Where Do We Go from Here? There is a paucity of space available in the vicinity of the hospital that can be used or converted to use for research. And the huge and growing pharma/biotech/academic research ecosystem in Boston ensures that any space that becomes available will be purchased quickly and at a premium. With the only main-campus hospital space slated for development as clinical towers (parcel 4B on Cambridge Street), we need to look at other nearby spaces controlled by or available to the hospital. Given the capital required for the new clinical towers, we will also need to garner new fiscal resources from a combination of philanthropy and creative financing.

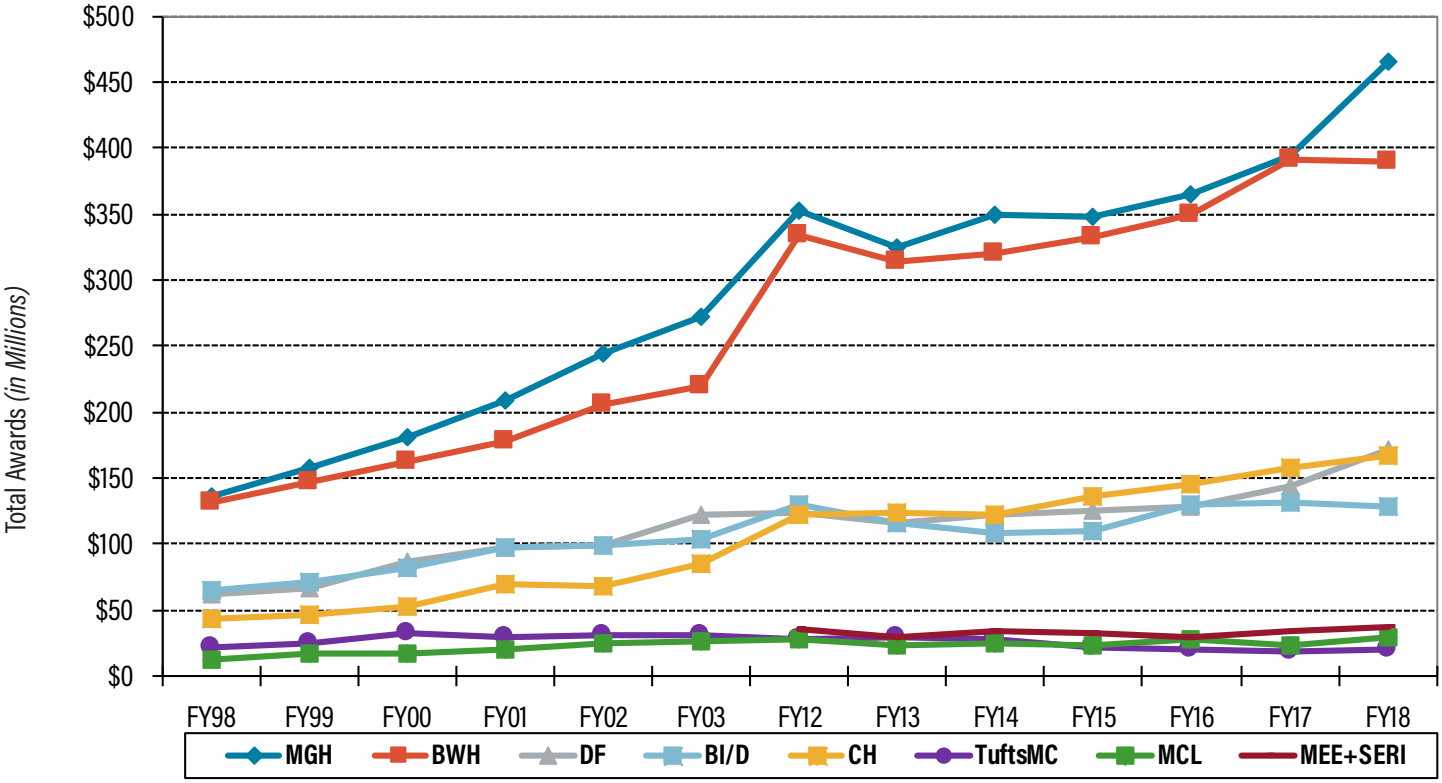
Regarding nearby options for a new research building, the hospital owns or has access to several spaces. Each space comes with its own unique capacities and constraints (vibrations from trains at 125 Nashua, expensive clean-up and permitting at CNY, etc.), but their proximity to current MGH locations and the lack of other options demands that we explore every possible near-term opportunity.

How much research space should we build, what mix of space types (wet, dry, 'damp') are needed, and which programs should relocate to the new space? A comprehensive study must be undertaken to properly answer these questions. The study should include: a complete inventory of current research space usage; a review of emerging and projected scientific programs/fields (digital health, microbiome, cancer immunology, epigenetics, etc.); a study of financing options; and a comprehensive search of existing nearby buildings/spaces available for development. This study will take time, and for our Research Institute, time is of the essence. We have come to an inflection point where we will either sustain and grow our research enterprise or watch it diminish. The dedication and vision of our extraordinary community of researchers have us poised for success, but only by acting now to provide much-needed space and support will our continued preeminence in biomedical innovation be ensured.

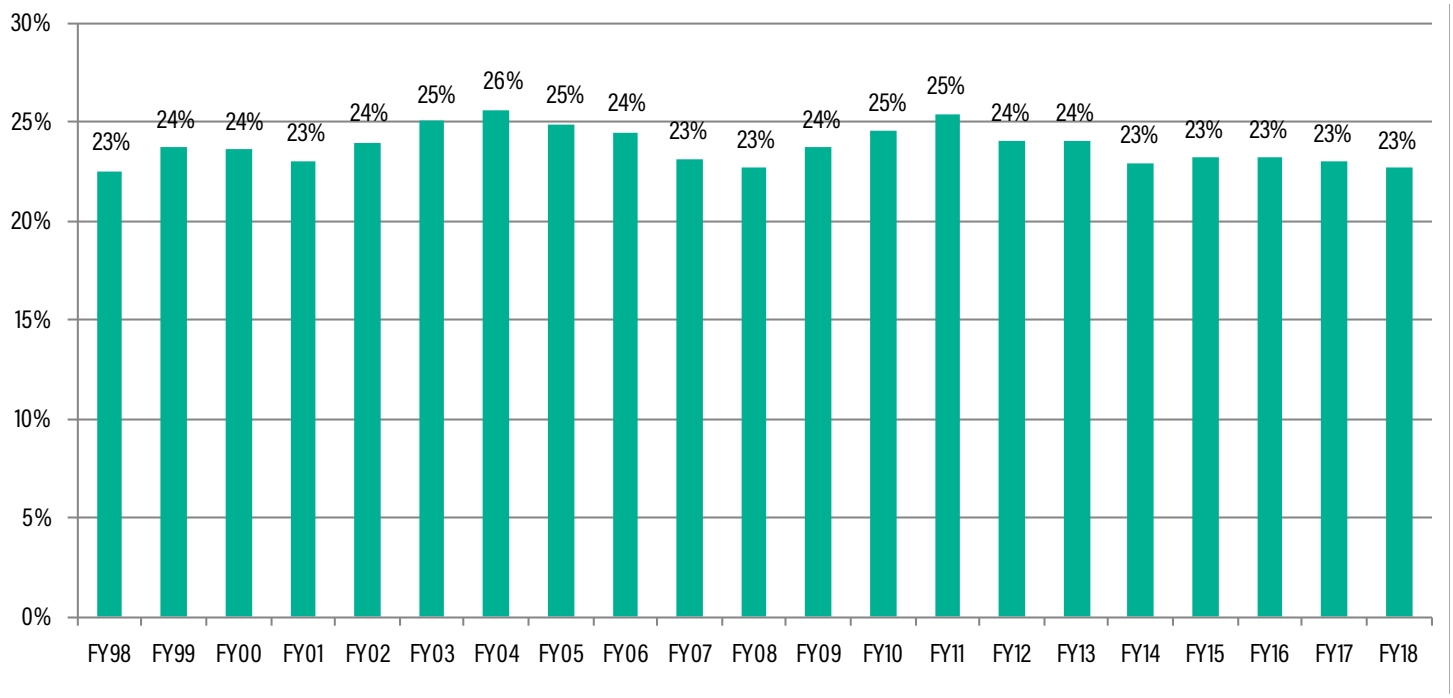
The significant progress realized in 2018 to promote innovation and improve the services so vital to maintaining our position as a preeminent biomedical research institution have been made by an extraordinary group of hospital and Partners leaders, faculty, and staff. On behalf of the entire Mass General Research Institute, I offer our thanks and appreciation for their dedication to constantly improve and strengthen our research enterprise.

Harry W. Orf, PhD
Senior Vice President for Research
Massachusetts General Hospital

NIH Extramural Awards - Top Local Hospitals FY98-FY18



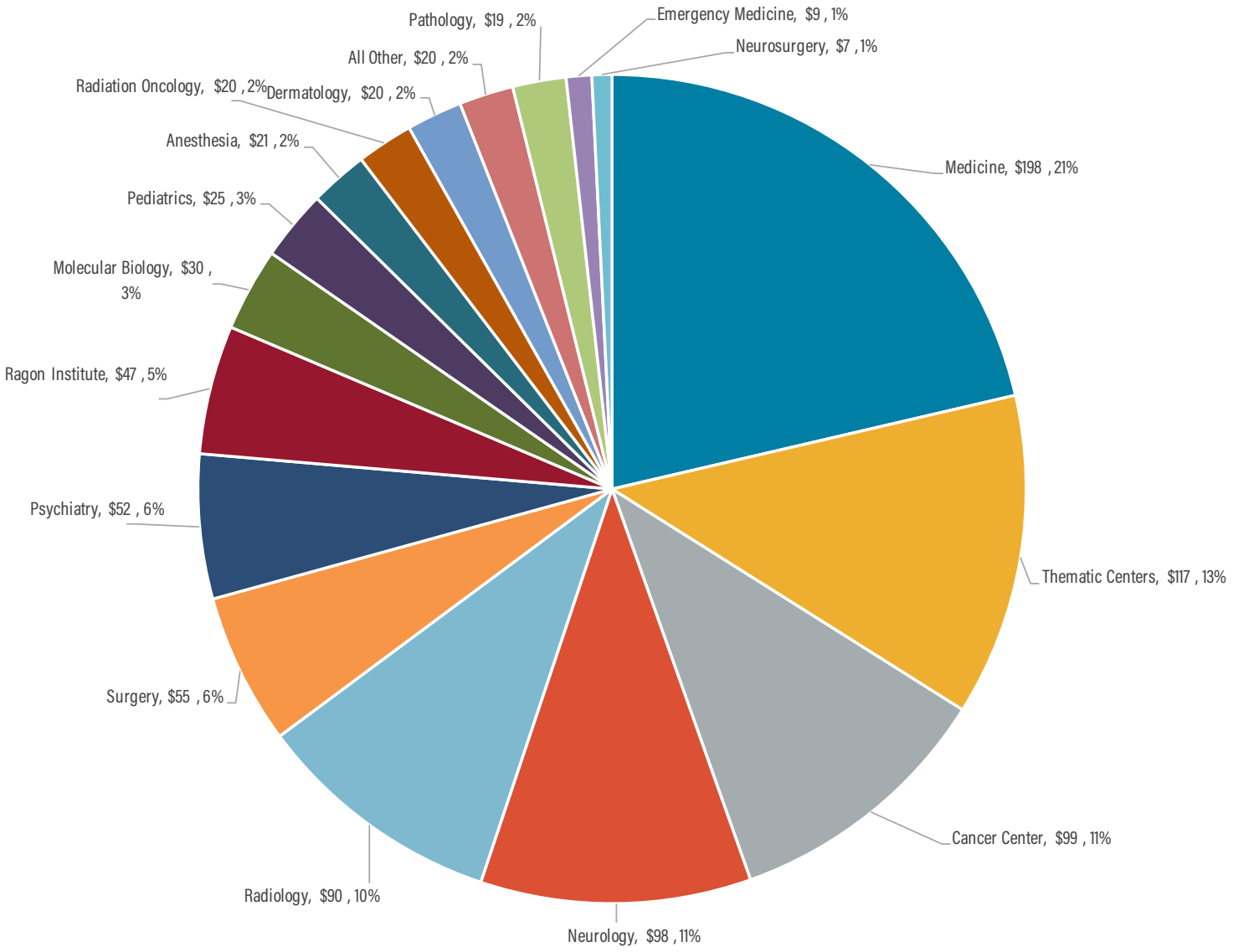
MGH Research Revenue as a Percentage of Total MGH Operating Revenue FY98-FY18



MGH Research Expenditures by Department

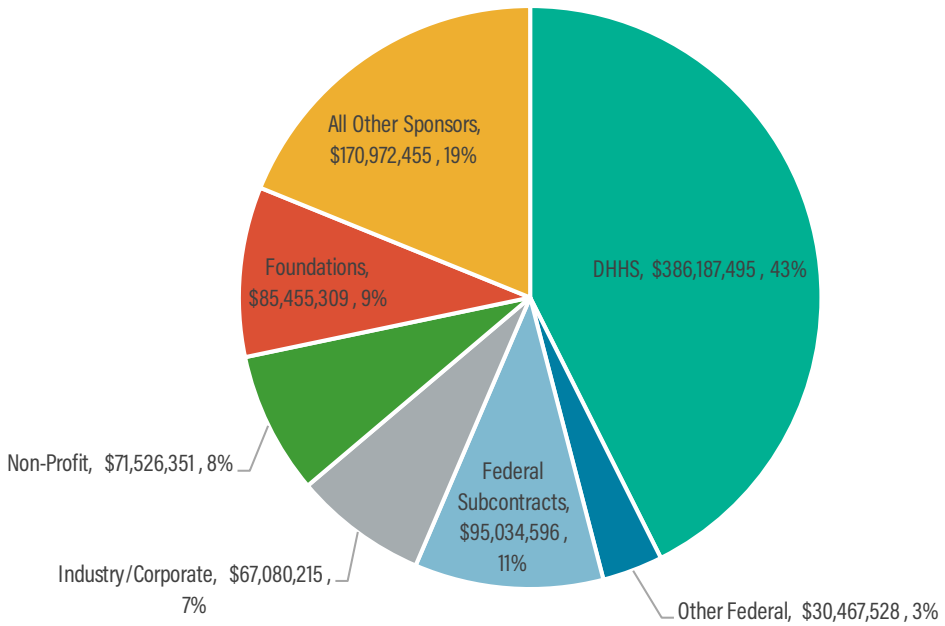
FY18 Direct & Indirect Expenditures - $928M

(shown in Millions)



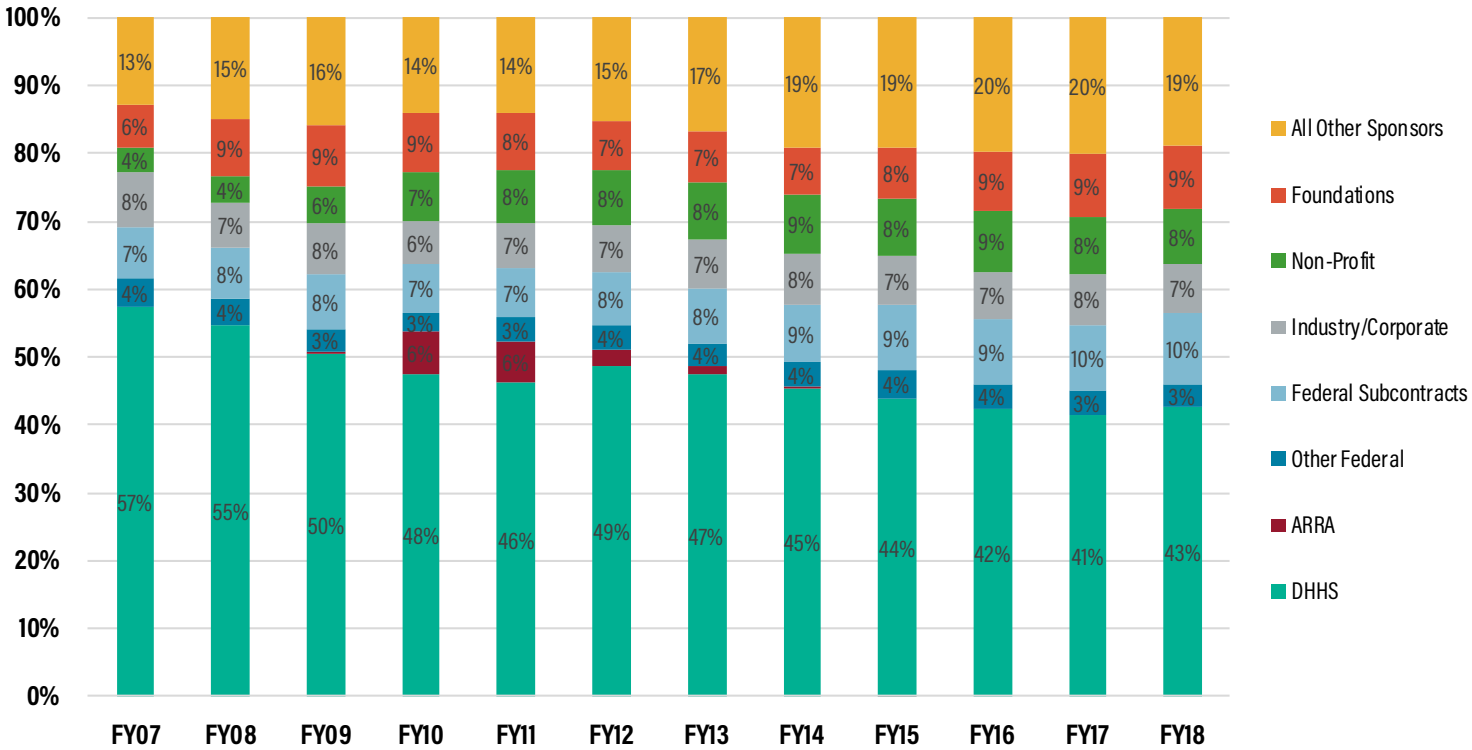
MGH Research Expenditure by Sponsor

FY18 Direct & Indirect Expenditures - $928M



MGH Research Expenditure by Sponsor

FY08-FY18



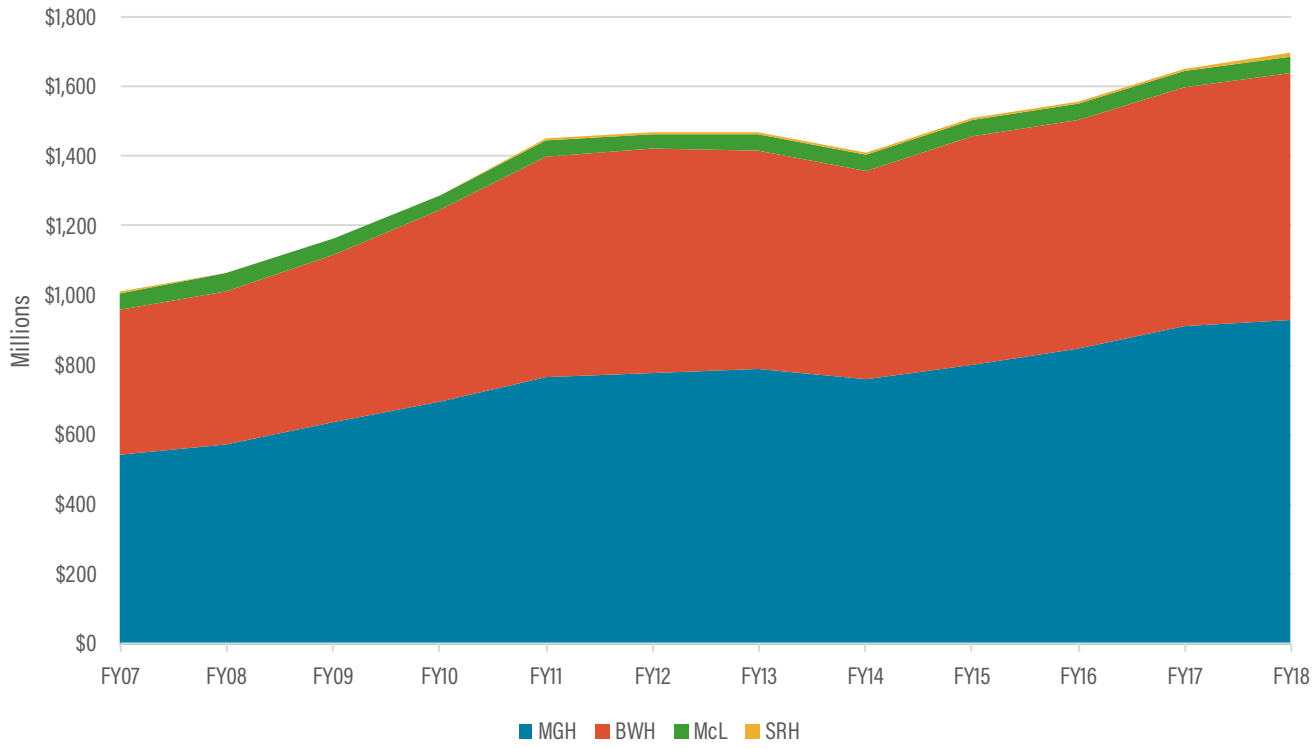
MGH Science Activity by Sponsor

FY18 - 10/1/17 - 9/30/18

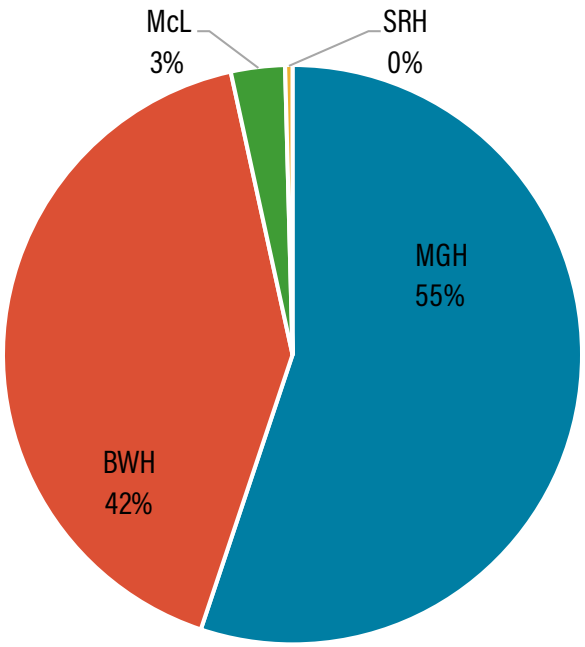
Type of Activity	Direct	Indirect	Total
Federal & State	$ 300,826,488	$ 122,408,383	$ 423,234,871
Non-Federal	$ 414,550,363	$ 89,832,675	$ 504,383,038
Total Expenses FY 18	$ 715,376,851	$ 212,241,058	$ 927,617,909
Federal Activity by Sponsor			
NIH	$ 274,886,138	$ 112,036,433	$ 386,922,571
DOD	$ 14,283,705	$ 7,220,606	$ 21,504,311
DARPA	$ 3,836,236	$ 1,067,417	$ 4,903,653
NASA	$ 269,210	$ 185,097	$ 454,307
NSF	$ 977,423	$ 621,220	$ 1,598,643
Other Federal	$ 1,637,942	$ 455,337	$ 2,093,279
Total Other Federal Activity	$ 21,004,516	$ 9,549,677	$ 30,554,193
Subtotal Federal	$ 295,890,654	$ 121,586,110	$ 417,476,764
State	$ 4,935,834	$ 822,273	$ 5,758,107
Total State Activity	$ 4,935,834	$ 822,273	$ 5,758,107
Total Federal and State	**$ 300,826,488**	**$ 122,408,383**	**$ 423,234,871**
Non-Federal Activity by Sponsor			
Industry	$ 53,529,745	$ 21,638,308	$ 75,168,053
Foundations	$ 76,962,379	$ 9,047,706	$ 86,010,085
Subcontracts/Other Nonprofit	$ 122,024,510	$ 37,315,232	$ 159,339,742
MGH Endowment & Gifts	$ 160,249,184	$ 21,614,360	$ 181,863,544
Total Non-Federal Activity	$ 412,765,818	$ 89,615,606	$ 502,381,424
Total Expenses	$ 713,592,306	$ 212,023,989	$ 925,616,295
Harvard Medical School	$ 1,784,545	$ 217,069	$ 2,001,614
Grand Total	**$ 715,376,851**	**$ 212,241,058**	**$ 927,617,909**

Partners Healthcare Total Research Activity

PHS Total Research Activity has grown to more than $1.65B, up $650M (64%) since 2007



Partners Healthcare Total Research Activity by Institution



Elena B. Olson, JD, Executive Director

MISSION

The Center for Diversity and Inclusion (CDI) promotes the recruitment and advancement of physicians and scientists underrepresented in medicine (URM) and seeks to develop a culturally competent and engaged workforce at Mass General where all can experience a true sense of belonging. CDI is one of the first academic hospital-based centers in the country dedicated to helping build a diverse and inclusive community of physicians and scientists.

FOCUS

CDI accomplishes its mission through three focus areas:

- Professional leadership development and workforce recruitment at all stages of a URM physician's and scientist's career: student, trainee, and faculty
- Cross-cultural education of staff and physicians to enhance the quality of care of patients and employee engagement
- Advancing the science of diversity and inclusion by measuring outcomes of our programs and interventions

STRATEGIC PRIORITES

CDI accomplishes its mission working with hospital and department leadership, as well as many local and national strategic partners, focusing on four strategic priority areas:

- Expose students underrepresented in medicine (URM) to academic research and clinical careers;
- Advance URM trainees and faculty through recruitment, career development, networking, mentorship and funding;
- Champion health equity, community outreach and social justice through advocacy and education;
- Drive organizational change by helping embed diversity and inclusion into the fabric of Mass General.

NOTABLE ACHIEVEMENTS FOR THE 2018 YEAR

1. Creation and development of CDI's first Annual Report

2. Recognition for mentorship in the Summer Research Trainee Program (SRTP).

For 26 years, SRTP has brought together talented college and medical students from across the country to engage in a novel research project with an MGH investigator. We expanded this program to 20 students in 2016, and the program was honored with a 2017 HMS Award for Program Excellence in Mentorship.

3. Expansion of the CDI Faculty Development Award Program.

We received commitment from the MGPO and Executive Committee on Research to double the number of Physician/Scientist and Clinician-Teacher Development Awards. We now fund four awards; two in each category.

4. Leadership involvement in hospital-wide strategic planning for diversity and inclusion, and community health.

CDI staff members were an integral part of developing the hospital-wide strategic plan for diversity and inclusion, which included a new hospital-wide diversity statement, a rapid response team, and the development of a culture survey and diversity metrics. In addition, CDI staff helped lead efforts in community health, developing the first social determinants of health education symposium for the hospital.

5. Champions in race discussions.

Both in our community and across the hospital, CDI and the RFC led important and difficult discussions about race. The CDI was a signature sponsor for the annual Stand Against Racism event at the MGH in 2018, featuring two members of the Boston Globe Spotlight team which published articles about race and racism in Boston. Our ultimate goal is to help build a diverse and inclusive community at Mass General.

Overall

In 2017-18, CDI met individually with Chairs and MGH affiliated residency program directors to help implement diversity and inclusion efforts in all MGH departments. During this past year, CDI served over 450 URM students, trainees and faculty, and provided cross-cultural education and unconscious bias training to approximately 2,500 physicians, scientists and interdisciplinary teams.

Center for Diversity and Inclusion (CDI)

Programmatic Report

Hospital-wide Diversity and Inclusion Committee and Executive Committee on Community Health

CDI has been a key contributor to the hospital-wide MGH/MGPO Diversity and Inclusion Committee and the Executive Committee on Community Health (ECOCH), both of whom report into the General Executive Committee. In addition, CDI has been a leader in developing the hospital-wide strategic plan and implementation for diversity and inclusion, which identifies priorities for diversifying the clinical and research workforce and increasing representation of the community research and clinical trials, among many other priorities. CDI also led part of ECOCH's strategic planning process. Charged with improving the health across populations and throughout the lifecourse, ECOCH focuses on social and economic determinants of health, access to high quality care for low-income patients and collaborates with the MGH Diversity and Inclusion Committee around issues of race and racism.

Professional Workforce Diversity

SRTP was recognized as a program leader for mentorship of the student pipeline: The Summer Research Trainee Program (SRTP) was founded in 1992 to inspire students who are underrepresented in medicine (URM) to consider careers in academic medicine and biomedical research. 2018 marked the third year 20 (up from 15 in prior years) college and medical school students were selected through vigorous national competition to conduct novel research with MGH faculty preceptors in basic science labs, clinical research sites, health policy and health services settings. Students were assigned to investigators in 13 different departments for a nine-week period, and were exposed to group mentorship, career workshops, research seminars, as well as networking and social events with the CDI community. This experience culminated with student research project presentations to the MGH research community, and students received feedback from an evaluation panel of research faculty. 350 students have participated in SRTP since its founding. Several participating students stayed on in labs and have published their work; 4 presented posters in MGH's Clinical Research Day (one received the Departmental award); and two returned as medical students to work with their assigned PIs. Previous SRTP participants state that the program added tangible value to their subsequent training and career decision making, and had a marked impact on their decision to pursue careers in an academic setting. SRTP was recognized this past year for its commitment to mentorship, as the recipient of the 2017 HMS Award for Program Excellence in Mentoring.

CDI helped recruit record numbers of URMs in residency spots: In 2018, 13% (n=31) of the residents who matched in 20 MGH/integrated residency programs were URM, with several programs exceeding 25%. This is above the percentage of URM national medical graduates. CDI worked closely with all MGH affiliated residency programs in their recruiting efforts. CDI hosted 10 applicant receptions during the interview season to provide an opportunity for applicants to meet the CDI community of URM residents, fellows and faculty in a more relaxed setting and receive a perspective on training at MGH and living in the Boston area. CDI also participated in, and sponsored trainees to attend, national recruitment fairs to meet students and potential applicants throughout the year (e.g., SNMA, LMSA, HMS residency showcase).

CDI continued to promote clinical and research faculty through the CDI Faculty Development Award Program (FDA): With funding from ECOR and the MGPO, CDI sponsored four faculty development awards in 2017. Since 2004, CDI has awarded 50 faculty development awards totaling $6 million in funding. The purpose of this program is to increase opportunities for URM faculty, and who are committed to diversity, inclusion and equity, to advance to senior positions in academic medicine and leadership at MGH. The two award categories include: The Clinician/Teacher Development Award (CTDA) and the Physician/Scientist Development Award (PSDA). Each award provides $120,000 over four years and is designed for MGH-appointed faculty pursuing different career goals. In a recent study, CDI found recipients bring in eight times the Award investment to Mass General in the form of external grants. Recipients are also more likely to stay at MGH (88%) than those individuals who do not receive funding (60%).

Critical Race and Equity Initiatives

Throughout the 2017-18 year, CDI hosted a series of cross-cultural education sessions focused on developing strategies for teaching effective cross-cultural dialogue at MGH. Session participants explored challenges in facilitating cross-cultural dialogues and learned how to apply the training to a team-based learning environment. CDI also co-sponsored several focus group and hospital-wide discussions on race, equity and racism, including a Stand Against Racism, featuring two members of the Boston Globe Spotlight team which published articles about race and racism in Boston.

CDI also worked closely with the Mongan Institute for Health Policy and the MGH Diversity Committee to develop metrics of diversity and inclusion for the institution, including a hospital-wide diversity culture survey. Survey results were shared with leadership and the hospital community in town hall formats.

Anne Klibanski, MD, Director
Donna M. Lawton, MS, Executive Director

Mission
The Center for Faculty Development (CFD) facilitates the career advancement and job satisfaction of faculty, research fellows and graduate students at the MGH. Our strategies are to:

- Develop and implement programs for faculty/trainees at all stages in their careers - from early careers to senior leadership - that promote academic and career development.
- Provide information, education and resources to increase faculty effectiveness.
- Provide support and education regarding academic advancement and promotion processes.
- Provide counseling, advice and support.

Focus
The Center for Faculty Development (CFD) is an umbrella organization geared broadly for all faculty and includes three distinct branches, the Office for Clinical Careers (OCC), the Office for Research Career Development (ORCD) and the Office for Women's Careers (OWC), which address specific concerns for each respective constituency. In addition, a Graduate Student Division and Post Doctoral Division are housed within the ORCD branch to address the needs of the graduate student and post-doctoral communities.

Achievements
In 2018 the CFD and its offices saw continued success in the integrated approach to providing services and resources to our faculty and trainees once again. Many of our programs were collaborations between different CFD offices, and where appropriate we opened programs to fellows and residents. This year, the CFD and its associated offices sponsored 82 professional development programs with 2,928 faculty, fellows, students and other professional staff in attendance at these programs. The program themes spanned career development, academic advancement, management, communications, negotiation, Responsible Conduct of Research, leadership, networking and work-life balance. This year, the CFD also expanded the OWC gender parity initiatives supported by the Mass General Physicians' Organization, which include Scholarly Writing Awards (SWA), Advancing Careers through Editing (ACTE) awards and facilitated negotiation skill building training; completed a needs assessment and requirements document and co-created a Statement of Work with developers for Annual Career Conference Automation, as well as an internal HMS Promotion tracking system.

The CFD continued to collaborate with the MGH Center for Diversity and Inclusion by meeting with a subset of URM Assistant Professors to help them advance their careers. The CFD also facilitated five sessions of the new Mass General Research Institute Orientation which started this past year. The CFD again facilitated its Mentoring Program for Research Administrators and chaired the annual HMS wide CHADD Mentoring Course: "M(f)aking it as a Mentor: A toolkit for junior faculty". In addition, a manuscript on the outcomes of the CFD Faculty Pilot Mentoring Program titled "Long Term Impact of a Faculty Mentoring Program in Academic Medicine" was published this year.

In addition, 312 individuals visited the CFD and/or one of its offices this past year for a total of 365 office consultations. 233 of these visits were with a CFD staff member (58% faculty, 42% fellows, graduate students, residents and other staff) and 132 met with an external advisor (43% faculty, 57% fellows, graduate students, residents, and other staff). The clear majority of the visits were for career advice, grant funding and promotion.

Strategic Priorities
- Collaborate with department specific faculty development liaisons to leverage best practices and resources
- Design and develop a new CFD website to enhance ease of use and communication of resources
- Continue to automate CFD processes where indicated and practical to enhance efficiencies.
- Continue to collaborate with the Mass General Physician's Organization on gender parity issues
- Continue to meet with all new Chiefs to review departmental faculty data and CFD resources.
- Provide professional development programs and workshops that meet the needs of our faculty and trainees, as well as networking opportunities for the faculty and trainees.

- Facilitate the annual New Faculty Orientation to familiarize new faculty with MGH/MGPO senior leadership and available resources to enhance their MGH experience.
- Recognize and celebrate outstanding mentorship by continuing to sponsor the annual John T. Potts, Jr., MD, Faculty Mentoring Award.
- Sponsor and administer the Caring for Dependent(s) (CFD) Travel Awards to help defray additional dependent care costs that go above and beyond care needs while a faculty member is traveling to an academic/society meeting.
- Offer individual consultations to help faculty and research fellows with advice and guidance.
- Facilitate consultation services to understand the usage of the Community of Science (COS) PIVOT database.
- Monitor and report on the Annual Career Conference (ACC) statistics.
- Facilitate the implementation of an online system for the ACC process in departments.
- Facilitate the implementation of an online system to track the internal status of HMS faculty promotions.
- Collaborate with the MGH Diversity Committee, MGH Center for Diversity and Inclusion, Harvard Medical School and its affiliates.
- Co-chair the annual Mentoring Course at Harvard Medical School along with the Consortium of Harvard Affiliated faculty Development and Diversity Offices (CHADD).
- Continue to collaborate with CHADD on faculty development best practices.

Office for Research Career Development (ORCD) - Dennis Brown, PhD, Director

Mission

The ORCD, Office for Research Career Development, addresses the specific needs of the MGH research faculty and trainees. Areas of emphasis for this office are to:

- Develop programs to advance the career pathways of research faculty in an academic medical center environment.
- Strengthen the career guidance and mentoring offered to trainees at the pre- and post-doctoral level.
- Enhance communication and collaborations within the research community.
- Provide individual counseling, advice and support.

Focus

The ORCD serves the hospital's large community of faculty investigators as well as its graduate students and postdoctoral research fellows, including administering the MGH Guidelines for Research Fellows and advising the Mass General Postdoctoral Association (MGPA). In 2018, the ORCD continued to offer individual career counseling, to organize professional development seminars (including a Responsible Conduct of Research series required by NIH), to provide networking opportunities, and to advocate on behalf of the research community.

Achievements

- Counseled 51 faculty, fellows and research staff in individual meetings aimed at career advice, promotion, and other matters.
- Continued to guide and collaborate with the Graduate Student Division (GSD) and Post-Doctoral Division (PDD) to enhance existing programming and career support for MGH research trainees.
- Developed a guidance document to clarify the expectations and readiness factors of candidates for role of the (entry-level faculty) instructor appointment. Successfully ushered the instructor guidance document through the review process with MGH senior leadership.
- Collaborated with the MGH Development Office to offer 63 individual consultations on identifying research funding opportunities. Surveyed past consultants of this service and found a high degree of satisfaction.
- Convened the fifth cohort (33 faculty) of the New Investigator Advancement Initiative (NIAI) for MGH faculty who hold their 1st NIH R-level grant or equivalent (including institutional startup packages.) Over six sessions, the NIAI will provide information and networking opportunities to support the continued success of participants.
- Offered a six session Responsible Conduct of Research (RCR) series designed for NIH trainees and open to all MGH researchers. Each session provided credit towards NIH RCR education requirements.
- Provided English as a Second Language (ESL) classes specifically designed for researchers. Two 12-week semesters of ESL each served 80-90 students, who were divided into three class levels based on English skill. In 2018 a fourth-class level was added, offering advanced conversation training for the highest level English language learners.
- Offered seminars and workshops to enhance the professional development of research faculty, including sessions on Laboratory

Leadership: Hiring and Setting Expectations and Grant Writing: Are You Ready to Write an R01?
- Collaborated with the PDD to advise the MGPA, which continues to offer research fellows leadership opportunities, and the chance to develop their own career and networking events.
- Collaborated with the Office for Women's Careers on programs and initiatives for women researchers, including an Academic Careers Mentored Lunch and the Claflin Awards Information Panel.

Strategic Priorities
- The ORCD will work with hospital leadership and departments to clarify the process and resources for resolving authorship disputes. The goal of this initiative is the development of written guidance that can be used by authors to avoid disputes when possible and understand the resolution process when disputes arise.
- The ORCD will continue focus on the needs of research faculty in developing lab management skills. The Lab Management Series will offer seminars on topics that include: Hiring and managing lab staff; communication skills; micro-negotiations; social media for scientists.
- As more labs move towards using digital lab notebooks, the ORCD may create programming to assist research faculty in developing new lab management practices that align with the use of digital data.
- Continue to provide programming and advocacy for MGH research faculty geared toward career development, guidance and career satisfaction, especially considering the complex and difficult funding climate.
- Contribute to efforts to assist researchers in transition due to funding issues or the shrinking faculty job market, including:
    - Raising awareness of the non-faculty track Research Scientist position to retain highly trained individuals.
    - Increasing awareness of/programs for alternative career opportunities (e.g., industry, scientific publishing, college teaching, lab management or administration), and encouraging faculty to support postdocs in career exploration.
    - Educating faculty on the availability of and application process for MGH interim funding.
- Continue to facilitate collaborations between the ORCD, Graduate Student Division and the Post-Doctoral Division to create programs that serve some of the overlapping needs of members of the research community.

Graduate Student Division (GSD) - Thilo Deckersbach, PhD, Director

Mission
The Graduate Student Division (GSD) is designed and intended to serve the practical needs of graduate students from all academic institutions that are associated with clinical and research faculty at MGH and foster a graduate student community at MGH. The GSD areas of emphasis are:
- Serve basic and academic needs of graduate students.
- Provide programs, services, and resources.
- Create a sense of community and enhance the overall experience of students affiliated with MGH.
- Establish relationships with area graduate schools.

Focus
The GSD supports the hospital's graduate student community - more than 550 non-employee PhD students performing their research at MGH. In addition, it provides support and resources to the faculty working with graduate students. The focus of the GSD this past year was to offer targeted educational seminars designed to help graduate students build professional, communication, and networking skills; highlight student publications; provide student travel awards; assist with students' transportation to help to defray the cost of the T-pass and Taxi cab and enhance GSD visibility by increasing communications and support for PIs of PhD graduate students.

Achievements
- Provided 14 educational programs to help graduate students in the following areas: negotiation and conflict management, job search strategy, resume building, interview skills, fellowship applications, funding opportunities, and mentoring.
- Engaged graduate students by offering a new Panel Discussion "How to Survive your Graduate School. We did it...so, can you!" and sponsoring graduate student lunch seminars where they present to their fellow graduate students.
- Counseled 18 graduate students in individual meetings aimed at career advancement and new graduate student orientations.
- Counseled faculty on how to get graduate students and a student on applying to graduate school.

- Connected 11 graduate students with an external career consultant to discuss CV/resume preparation and career development.
- Presented the "GSD Select Paper of the Year" Award to Camilla Engblom, PhD, a former graduate student in Dr. Mikael Pittet's lab, her paper, "Osteoblasts remotely supply lung tumors with cancer-promoting SiglecFhigh neutrophils" was published in Science journal.
- Sponsored the 2018 GSD Mentoring Award to recognize a PI who has demonstrated outstanding contribution in helping graduate students to advance their skills and provide academic support. Raul Mostoslavsky, MD, PhD, the Laurel Schwartz Associate Professor of Oncology MGH Cancer Center, Harvard Medical School Kristine and Bob Higgins MGH Research Scholar is the winner of 2018 GSD PI Mentoring Award.
- Facilitated the GSD International "Buddy" System program to help connect new international students with graduate student s who have been at MGH for a longer period.
- Offered the GSD T-Pass Savings to help eligible graduate students to defray their T-Pass transportation costs.
- Continued to sponsor and administer the GSD Graduate Student Travel Awards to help graduate students when travelling to an academic/society meeting related to their advancement.
- Sponsored 5th annual GSD/ PDD/MGPA Barbeque for MGH grad students and postdoctoral fellows to network and socialize.
- Continued to maintain close relationships with area graduate schools' administration.

Strategic Priorities

- Communication: enhance communication with graduate students and PIs through digital tools including email and web resources.
- Community building: connect interested PIs to students and connect international students to MGH opportunities by building bridges with international schools.
- Networking and Education: collaborate with other offices within the CFD to build strong support for the research community at MGH; Support scholarly activities of PhD graduate students who are currently doing research at MGH.
- Knowledge: continue to provide educational seminars, social events, in-person orientations and career consultations for MGH graduate students.
- Programming: collaborate with Post-Doctoral Division to connect graduate students with MGH post docs and develop graduate student and post docs mentoring program.

Post-Doctoral Division (PDD) – Marcia Goldberg, MD, Director

Mission

The Post-Doctoral Division (PDD), addresses the specific needs and career advancement of the research fellows at MGH. Areas of emphasis for this office are to:

- Provide programming for career advancement, professional development, networking and work life balance.
- Enhance awareness of, and compliance with, the MGH Guidelines for Research Fellows, including its 5-year term limit and extension requests.
- Act as central point of contact for post-doc fellows regarding career development information, resources, and issues.
- Encourage the Annual Career Planning discussion between postdocs and their mentors and the completion of the related form (part of the Guidelines for Research Fellows.
- Facilitate on-boarding and orientation sessions for newly-arrived post-docs to familiarize them with research and career resources the MGH.
- Provide individual counseling, advice and support.

Focus

The Post-Doctoral Division serves over 1600 post-doctoral research fellows at MGH, including administering the MGH Guidelines for Research Fellows and advising the Mass General Postdoctoral Association (MGPA). In 2018, the Division continued to grow programs and professional development seminars for research fellows and offered one-on-one consultations on a wide range of issues including career advice and funding.

Achievements

- Counseled 39 faculty, fellows and research staff in individual meetings aimed at career advice, promotion, and other matters
- Based on feedback from a 2017 survey and focus groups, the PDD provided 28 programs on career exploration, job search strategy,

networking, and writing
- Sponsored the 12th annual Research Fellows Poster Celebration to recognize the excellent research conducted by MGH postdoctoral fellows. Research fellows presented their work, and prizes were awarded to the top research. Short lectures at the awards ceremony offered advice on career development.
- Continued programming to support post-doctoral career and professional development, including, An Overview of the Life Science Eco System, Tips and Tools for Career Development, Networking 101: Strategies for Building Relationships That Move Your Career Forward, a Scientific Writing Workshop, and monthly orientation lunches for new research fellows.
- Continued the enhancement of communications, outreach and engagement by refining mobile-friendly email marketing and event registration platforms. Some of these platforms have been adopted by other CFD offices.
- Gathered information and advice from the PDD Committee, comprised of postdocs from various MGH departments
- Continued to advise the MGPA and collaborated with MGPA leadership to develop programming for each of the sub-committees, including Careers in Academia, Mentoring, Industry Careers, International Medical Graduates, Science Communication, and Social Media and Networking
- Collaborated with MGPA in efforts to organize training and networking for internationally-trained MDs preparing for residency in the United States, including the development of study groups focused on different phases of the USMLE exams.
- Converted the Post Doc Extension Policy process to an online platform to enhance efficiencies.
- Shepherded a change in MGH policy regarding the credentialing of postdoctoral trainees, such that hiring can occur prior to receipt of the applicant's official PhD diploma, as long as there is an official letter stating that all requirements for the PhD degree have been met. To maintain postdoctoral status, the official diploma must be submitted within 6 months of the start date.

Strategic Priorities
- Continue to offer programs in a variety of locations and formats to encourage more participation, including offering programs multiple times and at different locations and creating resources available online and/or on-demand. Utilize new video conferencing resources to record and livestream programs when possible.
- Increase programming in career exploration, to assist postdocs in understanding various career paths
- Investigate efforts to grow the MGH post doc alumni database and build relationships with alumni to help foster community with our current post-doctoral research fellows
- Increase participation in the alumni database and use it to track the outcomes and career pathways of former MGH postdocs
- Continue to enhance and streamline communication through digital tools including email and web resources
- Collaborate with internationally-trained MDs to continue to develop resources and support for their professional development needs
- Explore ways of supporting postdoctoral fellowship grant applications, including the possible development of a peer editing initiative and peer writing accountability groups
- Analyze data on fellowship success rates and faculty job attainment
- Continue to revise the orientation and on-boarding processes
- Create a mentoring award for PIs who show excellence in fostering the careers of postdoctoral fellows

Office for Women's Careers (OWC) – Nancy Rigotti, MD, Director
Mission
The Office for Women's Careers (OWC) facilitates the career advancement of women faculty at MGH. Areas of emphasis for this office are to:
- Increase the number of women faculty in leadership positions.
- Increase the number of women faculty promoted by academic criteria.
- Increase retention and job satisfaction of women faculty.
- Develop and implement programs to promote career development and work life balance.
- Provide individual counseling, advice and support.

Focus
The OWC at MGH is a branch of the Center for Faculty Development (CFD) and was created to foster a gender equitable environment to assure

that women and men faculty will be given the same opportunity to succeed in research and clinical careers at MGH. Through many programs and collaborations, the OWC provides career development resources for women and endeavors to build a sense of community among women faculty across the institution. The office focuses on reducing barriers to career advancement and by request advises women faculty on various career matters. It also develops programs on topics such as leadership skills, negotiation, promotion, mentoring, presentation skills, finance, and academic writing. The OWC also offers opportunities for women faculty to network with peers and female role models in academic leadership positions.

Achievements

The OWC continued efforts to support and advance the careers of women faculty in 2018. Highlights of OWC activity:

- Collaborated with MGH human resources and other offices to expand awareness of the sexual harassment policy and resources.
- Continued and grew a series of initiatives that began in 2017, supported by the Mass General Physicians Organization (MGPO) designed to enhance gender parity in MGH faculty with clinical duties. Initiatives include:
- An expansion of the Caring for Dependents Travel Awards, which offers up to $500 reimbursement to help faculty parents cover child travel/extra childcare during a scientific/medical conference; and expansion of the CV formatting assistance program.
- The Advancing Careers Through Editing (ACTE) initiative, which offers editing services on journal manuscripts and the Scholarly Writing Awards, offering extra child/dependent care reimbursement to allow faculty 'protected' time to finish a manuscript.
- A Negotiation Bootcamp workshop, which ran twice with full capacity, to help women faculty negotiate for career advancement.
- In the fall of 2018, these initiatives were expanded, with pilot funding from ECOR, to include research faculty with no clinical duties.
- Continued to partner with individual departments, with a continuing and expanded focus in 2018 on collaborations to support the career development of female trainees. Advised the formation of a trainee committee that fosters collaborations and information sharing between department-based groups, focusing on advocacy for the trainee parental leave policy, and expansion of networking opportunities.
- Organized the highly successful 21st annual Women in Medicine celebration, which recognizes achievements by female faculty and includes a lecture from a distinguished female leader. This year's speaker was Dr. Kathy Rexrode, MD of Brigham and Women's Hospital.
- Fostered networking between early career faculty and female leader role models with the "Meet and Greet Networking Series," which hosted a discussion with Shelly Greenfield, MD, chief academic officer of McLean Hospital
- Supported the growing community of Claflin Distinguished Scholars with a panel discussion for prospective applicants and the Claflin Consultation Initiative (CCI) to provide individual coaching to applicants by alumnae, and the annual Claflin Luncheon to welcome the newest Scholars. In 2018 the CCI assisted a record number of applicants (28) for the upcoming award cycle.
- Transitioned the annual leadership program into a two-part series, which began in 2018 with a session on "Developing Presence."
- Offered community-building programs such as the Faculty Parents Group and the Managing Parenthood and Your Career series, aimed at providing information and support to faculty and trainees with childrearing responsibilities.
- Negotiated with the MGPO to include critical questions regarding gender bias and parenting on the upcoming MGPO survey.
- Counseled 36 women faculty and trainees aimed at career advice and supporting gender equity and 41 faculty sought guidance from an external career consultant. These individuals visited the office for a total of 76 consultations.

Strategic Priorities

- Continue collaborations with the MGPO and ECOR to refine initiatives and provide/expand resources to ensure gender equity; these may include an expansion of leadership skill building for women and supporting rising leaders to take advantage of outside resources.
- Expand professional development programs and workshops that meet the needs of women faculty, addressing the challenges of career and parenting, leadership issues and negotiating strategies for women. Continue to collaborate with others in these areas as identified.
- Collaborate with MGH Development to advocate for increased funding for initiatives that support the advancement of women
- Continue advocacy efforts in areas such as lactation rooms, sexual harassment awareness, work life balance and gender parity.
- Offer the Claflin Consultation Initiative & panel discussion supporting Claflin Distinguished Scholar Award applicants.
- Collaborate with MGH Diversity Committee, MGH Center for Diversity and Inclusion, DOM Women in Medicine Committee and the HMS Joint Committee on the Status of Women.
- Offer the successful Leadership Series for women faculty covering topics relevant to women faculty interested in leadership growth.

- Provide networking opportunities for all women faculty, especially junior and mid-career faculty who are seeking mentoring and networking opportunities to develop into leaders. Expand these networking opportunities to include more trainees in research and patient care. Develop new ways for women faculty to network via social media.

Office for Clinical Careers (OCC) - Theodore A. Stern, MD, Director

Mission

The Office for Clinical Careers (OCC), facilitates the career advancement and promotion of clinical faculty at the MGH. Areas of emphasis for this office are to:

- Develop and implement programs to promote career development.
- Provide support and education regarding the promotion process.
- Enhance clinical practice/practice management.
- Encourage work-life balance.
- Provide individual counseling, advice, and support.

Focus

The Office for Clinical Careers (OCC) at MGH, a branch of the Center for Faculty Development (CFD), was created to facilitate career advancement/promotion for staff with clinical appointments, to provide career advice to clinical investigators, to enhance clinical practice/practice management, and to encourage/enhance work-life balance.

Achievements

Highlights of OCC activity:

- Advised 90 faculty and fellows from most departments, in 101 consultation sessions, regarding: career advice, CV/cover letter critique, mentorship, and promotion.
- Created new programming content, in conjunction with the OCC Advisory Committee: "Making Connections to Get Ahead."
- Sponsored 7 educational programs: Can I Really Write a Book?, Can I/Should I Be Promoted?, Drafting Your Chief's Letter, Making Connections to Get Ahead, and Speaking Up and Giving Feedback: Mastering Conversations Up and Down the Ladder and collaborated with the CFD to hold Crafting Your CV Narrative and Promoting Academic Advancement to help "demystify" the HMS promotions' process.
- Participated in departmental outreach by speaking at departmental meetings to present on the Center for Faculty Development and to facilitate career advancement via seminars.

Strategic Priorities

- Help clinical faculty to navigate the promotion process.
- Help faculty to balance research and patient care responsibilities
- Enhance collaboration with the MGPO to work on academic advancement and on work-life balance for clinicians.
- Expand professional development programs and workshops to meet the needs of clinical faculty, stressing academic and career advancement.
- Advocate for clinical faculty and their careers and work-life balance.
- Promote awareness of/celebrate promotions of clinical faculty and their academic achievements.
- Advise individual clinical faculty members on career plans and academic advancement.
- Collaborate with departmental initiatives and conduct outreach to departments.
- Implement new strategies to market programs to clinical faculty.
- Conduct "exit interviews" with departing clinical staff, to understand their reasons for leaving the MGH.
- Collaborate with the newly-established Chief Learning Officer, to enhance the career development of clinical educators.
- Continue to contribute to ECOTE and its working committees, to enhance the community of clinician educators.
- Continue to collaborate with the Post-Doctoral Division within the Center for Faculty Development to address the needs of clinical fellows.

Center for Computational and Integrative Biology

Thematic Center Report

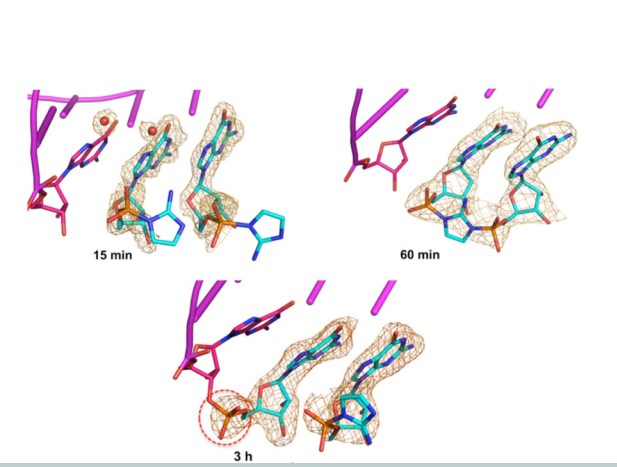
Ramnik J. Xavier, MD, PhD, Director

Center for Computational and Integrative Biology (CCIB) faculty study biological processes using diverse approaches that emphasize interdisciplinary applications of new technology to provide insight into medically important diseases or answers to long-standing questions. Often faculty create new tools to accomplish their goals. In recent years CCIB faculty have increasingly turned to chemistry and chemical biology to provide probes of signaling pathways, to identify important mediators of host-microbe interactions, to understand and simulate the conditions associated with the emergence of life, and to directly address human diseases through therapeutic intervention. Center investigators also conduct translational research to explore the potential utility of early stage drug candidates in phase 1 studies carried out in small populations of individuals with the target disease indication. The drug candidates are developed either in the local academic community or presented to the Translational Medicine Group from the biopharmaceutical industry.

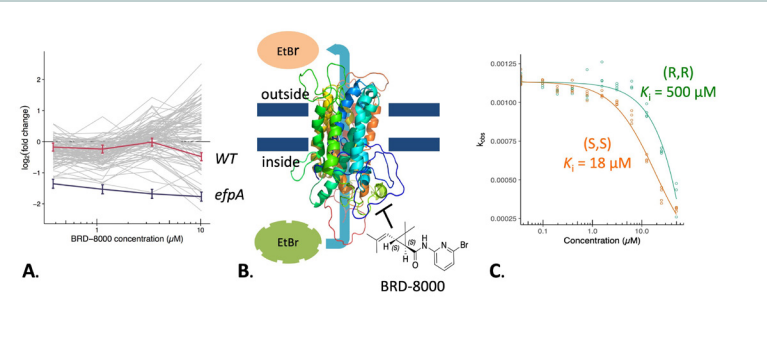
In this year's images we highlight four stories from CCIB groups who are working toward a better understanding of the origin of life, antibiotic resistance as well as the role of disease-associated variants and the microbiome in disease, and who are generating better tools for prevention of CRISPR off-targets.

Achievements

Based on the RNA World hypothesis, a key step in the emergence of life is the chemical replication of RNA prior to the emergence of ribozyme and the question is how was RNA able to replicate without enzymes? The approach used by the Szostak lab to answer this question involved obtaining crystal structures at various times after the initiation of the nonenzymatic RNA polymerization reaction in a sequence of molecular 'snapshots' (PMID:29851379). RNA template copying is mediated by highly activated substrates, which can form covalent dinucleotide intermediates. The study addressed the structure and mechanistic role of the intermediates by direct observation of individual steps in the process. They first crystallized RNA with a non-reactive monomer, then diffused the activated monomer into pre-formed crystals to replace the unactivated monomers. By freezing the crystals at different time points and determining the structures, they observed the formation of the proposed intermediate and a series of subsequent structures representing the entire process. These findings greatly benefit RNA chemists and biologists who study RNA evolution by helping them understand the very simple catalytic processes that contribute to RNA self-replication.

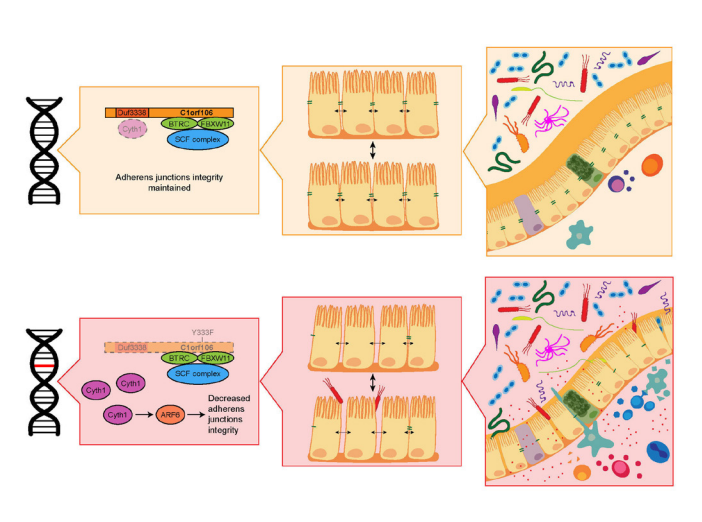


2-aminoimidazolium intermediate forms and reacts with primer in the crystal. Top left: 15 minutes after initiation of crystal soaking with activated monomers. The original 2'-deoxy-G monomers have been replaced with aminoimidazole-activated ribo-G monomers. Top right: After 60 minutes, the two adjacent activated monomers have reacted with each other to form the imidazolium-bridged dinucleotide intermediate, which is seen base-paired to the template, and lying next to the 3'-end of the primer. Bottom middle: After 3 hours, the intermediate has reacted with the primer and a new phosphodiester bond has formed between the primer and the adjacent monomer. The downstream monomer remains bound to the template but has become partially disordered.



Identification of BRD-8000, an inhibitor of a previously uncharacterized target by its unique interaction with a specific hypomorph. A: Chemical genetic interaction profile of BRD-8000, a new putative inhibitor of EfpA, an essential efflux pump in Mycobacterium tuberculosis. B: Schematic depicting the principle of the EtBr efflux assay. C: An EtBr efflux assay showed a large difference in efflux inhibition between the active and the inactive enantiomers of BRD-8000.2.

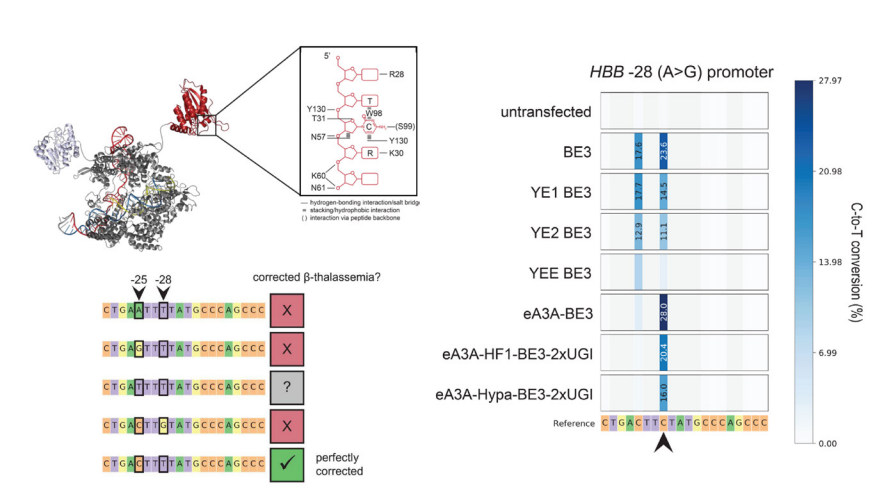
The World Health Organization has declared that antibiotic resistance is one of the greatest threats to human health, and tuberculosis is one of the diseases having the biggest gap between pharmacological need and drug pipeline supply. One of the greatest challenges in antibiotic discovery is finding new classes of compounds with whole-cell activity against diverse cellular targets. The Hung lab has established the PROSPECT (PRimary screening Of Strains to Prioritize Expanded Chemistry and Targets) paradigm for antibiotic discovery against Mycobacterium tuberculosis (Mtb) that allows prioritization of whole cell active compounds by putative target, instead of simply potency, based on mechanism of action (MOA) predictions from the primary screening data (https://doi.org/10.1101/396440). By using large-scale chemical genetic interaction profiling as the primary screening modality against a pooled collection of



The gut epithelial barrier helps maintain mucosal homeostasis by serving as a physical separation between luminal contents and the intestinal epithelium. The integrity of the epithelial barrier is determined by genetic and environmental factors. A loss of integrity allows translocation of commensal and pathogenic microorganisms to the underlying epithelium, eliciting an immune response that may result in chronic inflammation.

engineered Mtb depleted for essential targets, they detected activity in 10 times as many compounds as would be detected by screening wild type Mtb alone, identified and experimentally validated >40 novel compounds against known MOAs, and identified inhibitors of novel targets even in the absence of well-characterized target function, as exemplified by their discovery of a compound, BRD-8000, that inhibits a completely novel target EfpA, which is an essential efflux pump in Mtb. They have chemically optimized BRD-8000 to have very potent activity against wild-type Mtb. Their strategy, which is generalizable to all bacterial species, allows exploration of broader target space and discovery of new chemical scaffolds that could not be identified by conventional screening against wild-type bacteria.

This year, the Xavier team published two studies highlighting the role of genetics and microbiome in inflammation and autoimmunity. Genomewide association studies (GWAS) can uncover hundreds of genetic variants associated with disease. The ensuing challenge is to discover the role variants play in disease. In a study to investigate the association between C1orf106 and increased risk of inflammatory bowel disease (IBD), the Xavier team discovered the Y333F coding variant contributes to barrier defects (PMID:29420262), a common problem in patients with IBD. The C1orf106 protein regulates the degradation of cytohesin-1, a guanine nucleotide exchange factor that activates ARF6, which in turn controls levels of E-cadherin at the surface of epithelial cells. E-cadherin helps epithelial cells adhere to one another, maintaining a tight barrier between the gut and the rest of the body. C1orf106 proteins carrying the Y333F mutation are recycled more rapidly than usual. With less C1orf106 to keep them under control, cytohesin-1 and ARF6 remove too much E-cadherin from epithelial cell surfaces, reducing the gut's barrier integrity. In search of microbial triggers for type 1 diabetes (T1D), a separate study from the Xavier lab analyzed nearly 11,000 metagenomes in stool samples from children at risk for T1D, collected monthly starting at three months of age (PMID:30356183). This work produced the most shotgun metagenomic microbiome profiles published for a single target population to date. Findings indicate that the microbiome gains adult-like functions as early as one year of age and suggest that short-chain fatty acids may protect against early-onset T1D.



On- and off-target activities of eA3A-BE3 variants at a β-thalassemia-causing mutation in human cells demonstrate that engineering the cytidine deaminase in base editors can increase on-target precision and decrease off-target effects.

The benefits of therapeutic applications of CRISPR may be offset by potential off-target edits, which can have harmful effects on patients should they result in, for instance, the activation of an oncogene. With over a decade of work developing robust, open-source reagents and methods that enable targeted genome engineering, the Joung lab published a study this year describing the fine tuning of base editor technology to greatly reduce bystander mutations (PMID:30059493). Base editor technology uses CRISPR-Cas9 to direct cytosine deaminase enzymatic activity to specific genomic loci resulting in precise cytidine to thymidine DNA alterations. One caveat is that base editors have the ability to edit all Cs present in their five-base-pair editing window. The Joung lab's strategy involved the use of an engineered human APOBEC3A domain, which preferentially deaminates cytidines in specific motifs. The engineered enzyme not only performed greatly reduced editing of cytidines unless they were in its preferred sequence context, but also corrected a B-thalassemia mutation with higher precision than the most widely used base editor. This study opens up the possibility of engineering and evolving APOBEC enzymes to create a large series of base editors that can recognize cytidines in any sequence context.

Center for Genomic Medicine

Thematic Center Report

Sekar Kathiresan, MD, Director

The Center for Genomic Medicine (CGM) is leading an effort to complete the genomic medicine cycle – from genetic discoveries to mechanism to the clinic – by assessing where genomic medicine will have the greatest impact on human health, and by driving efforts to implement genomic medicine in those areas, at MGH and beyond. The Genomic Medicine Cycle is a paradigm for disease research that begins by comparing human phenotypes and genetic variation to identify genes of importance in human disease, then moves on to characterizing the mechanisms by which the underlying DNA differences lead to disease, and is completed when the knowledge gained delivers benefit back to patients in the forms of improved diagnosis, disease management and treatments.

Key CGM achievements fell into four domains:

A. Science

1. 307 publications from CGM faculty
2. 37 MGH researchers were named to Clarivate Analytics's annual Highly Cited Researchers 2018 Report; of these 37, seven are faculty in CGM
3. Recruited Heidi Rehm, PhD, FACMG, a world-renowned laboratory geneticist, as a new CGM faculty member
4. Initiated a genomic medicine demonstration project focused on assessing the incremental value of whole genome sequencing as a diagnostic in MGH patients with a suspected genetic disorder. In this randomized controlled trial, >100 patients have already been recruited.
5. Submitted a T32 application to the NHGRI, "Partners Training Program in Precision and Genomic Medicine"
6. CGM faculty made a number of important scientific observations this past year including:
    - Dissecting the Causal Mechanism of X-Linked Dystonia-Parkinsonism by Integrating Genome and Transcriptome Assembly. Cell. 2018 Feb 22;172(5):897-909. Michael Talkowski, PhD and colleagues integrated multiple genome and transcriptome assembly technologies to solve X-linked Dystonia-Parkinsonism (XDP), a Mendelian neurodegenerative disease that is endemic to the Philippines.
    - Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019 Jan;51(1):63-75. Benjamin Neale, PhD and colleagues identified variants surpassing genome-wide significance in 12 independent loci, finding important new information about the underlying biology of ADHD.
    - Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. PLoS Med. 2018 Sep 21;15(9):e1002654. Jose Florez, MD, PhD and colleagues used genetics to deconstruct T2D heterogeneity and identified five robust clusters of T2D loci and traits.
    - Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018 Sep;50(9):1219-1224. Sekar Kathiresan, MD and colleagues developed and validated polygenic risk predictors for five common diseases to find that such predictors can identify individuals at risk similar to monogenic mutations.

B. Community

1. Launched a new seminar series, "Frontiers in Genome Biology and Medicine", a joint effort with the Department of Molecular Biology
2. Launched the CGM Intranet
3. Awarded 6-$1500 travel awards to CGM members as a part of the CGM Travel award competition
4. Held 6 Happy Hour events (some jointly with Molbio and CSB)
5. Held 6 volunteering events with various Boston charities
6. Held 3 charity drives for various Boston Charities
7. Organized and executed the 2017 CGM retreat
8. Held a Summer Get Healthy Challenge culminating with an ice cream social for employees
9. Distributed 8 CGM newsletters
10. Organized CGM Yoga and Pilates; free classes for employees
11. Developed CGM networking lunch program for employees
12. Developed CGM Post-doc networking lunch program for post-docs
13. Held a Post-doc lunch event in July 2018

C. Administration

1. Created a CGM equipment list
2. Developed a CGM equipment fund that allows for $20k in repairs yearly
3. Developed a plan to provide bioinformatics support through the Genomics and Tech Core
4. Streamlined billing and revamped policies for CGM cores
5. Developed list of lab contacts and held meeting to review concerns, labsafety, and policies
6. Created Dropbox accounts for Faculty; in which we will develop newprocesses for sharing information
7. Renovated the Weinberg conference room into aroom with 9 desks for genetic counselors and project coordinators.

D. Honors

1. Mark Daly, PhD, Member, National Academy of Medicine
2. Erin Dunn, ScD, NIMH Biobehavorial Research Award for Innovative New Scientists
3. Florian Eichler, MD, 2018 MGH ECOR Martin Prize for Clinical Research; Clinical Research Excellence Award, The Clinical Research Forum
4. Jose Florez, MD, PhD, 2018 Father of the Year, American Diabetes Association
5. Rakesh Karmacharya, MD, PhD,NIMH Biobehavorial Research Award for Innovative New Scientists; Robert Wood Johnson Foundation Clinical Scholar
6. Sekar Kathiresan, MD, 2018 American Society of Human Genetics Curt Stern Award; 2018 AHA Joseph Vita Award
7. Daniel MacArthur, PhD, Early-Career Award, American Society of Human Genetics
8. Susan Slaugenhaupt, PhD, Elected to the Board of Directors, American Society of Human Genetics
9. Alex Soukas, MD, PhD, 2018 MGH ECOR Research Scholar, Glenn Award for Research in Biological Mechanisms of Aging
10. David Sweetser, MD, PhD, Inaugural Incumbent, Leslie Meyer and Lewis Ball Holmes Chair in Genetics and Teratology
11. HMS Faculty Promotions:
    - To Assistant Professor: Ben Kleinstiver, PhD to Assistant Professor
    - To Associate Professor: Rakesh Karmacharya, MD, PhD, Taylor Kimberly, MD, PhD, Daniel MacArthur, PhD to Associate Professor
    - To Professor: Vijaya Ramesh, PhD, Jose Florez, MD, PhD, Heidi Rehm, PhD, FACMG, and Sekar Kathiresan, MD

Center for Regenerative Medicine

Thematic Center Report

David Scadden, MD, Director

The Center for Regenerative Medicine (CRM) is dedicated to outstanding stem cell and developmental biology informing novel therapies in regeneration and cancer. A collaborative team of scientists and clinicians with diverse areas of expertise and a shared mission comprise this Center.

Key scientific achievements in 2018

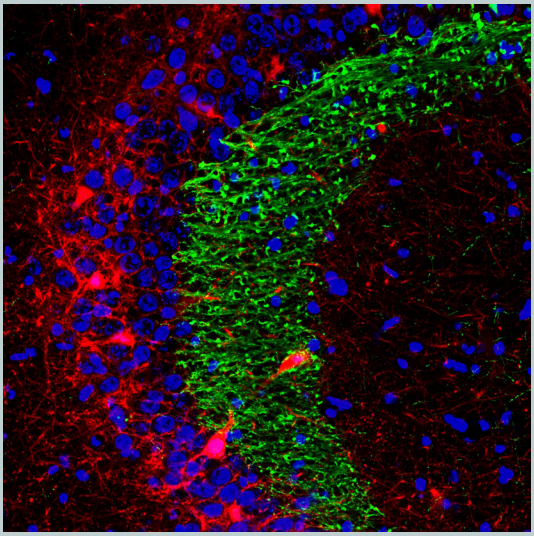
- Defined a new cell type in the lung, the ionocyte, implicated in cystic fibrosis (Rajagopal Lab; Nature).
- Defined a molecular governor of memory implicated in memory imprecision with aging and fear generalization in PTSD (Sahay Lab; Nature Medicine).
- Defined an RNA adenylation molecule selectively enhancing the translation of chromatin modifiers (Hochedlinger Lab; Cell).
- Discovered a new way to rapidly mobilize 'overachieving' hematopoietic stem cells for transplantation (Scadden Lab; Cell).

Focus and contributions of member laboratories

SAHAY LAB

Using in vivo calcium imaging in awake behaving mice, synaptic physiology, optogenetics, viral genetics and behavior, we identified a circuit mechanism by which hippocampal computations are relayed to subcortical circuits to calibrate behavioral responses in response to certain and ambiguous threats.

Besnard A, Gao Y, Kim M, Twarkowski H, Langberg T, Feng W, Xu X, Saur D, Davison I, and Sahay A. Dorsolateral septum somatostatin interneurons gate mobility to calibrate context specific behavioral fear responses (Nature Neuroscience, In Press,)



This image is of a cross section of the hippocampus showing green finger like projections called filopodia contacting red neurons —a substrate for memory precision in adulthood and aging. (Sahay Lab)

This study identifies a molecular, synaptic and circuit mechanism within the hippocampus that dictates the extent to which memories retain details or remain precise over time. By harnessing this mechanism, we show that we can maintain memory precision in adulthood and aging. Our study exemplifies how targeting a specific gene, ABLIM3, may decrease overgeneralization of fear in PTSD and memory imprecision as seen in aging. This study was highlighted by Dr. Francis Collins in his monthly blog on advances in science and medicine.

- News and Views in Nature Medicine
- "Switch" that could improve memory identified, The Harvard Gazette
- Investigators identify neural circuit genetic "switch" that maintains memory precision, EurekAlert 12 March 2018.
- NIH Director discussed this paper in his monthly blog on advances in sciences and medicine, https://directorsblog.nih.gov/2018/05/24/unlocking-the-brains-memory-retrieval-system/

Guo N, Soden ME, Herber C, Kim MT, Besnard A, Lin P, Ma X, Cepko CL, Zweifel LS, Sahay A. Dentate granule cell recruitment of feedforward inhibition governs engram maintenance and remote memory generalization. Nat Med. 2018 May;24(4):438-449. doi: 10.1038/nm.4491. Epub 2018 Mar 12.

RAJAGOPAL LAB

The Rajagopal and Regev groups have identified an entirely new cell in the lung. This cell is the lung cell that expressed the cystic fibrosis gene. Cystic fibrosis was thought to be a disease of the entire lining of the airway, but these findings pinpoint the problem to a rare cell type. This finding has important implications for the therapy of cystic fibrosis: instead of correcting the entire airway with gene therapy, one might be able to repair stem cells that could go on to make small numbers of ionocytes. This type of therapy could be the lung equivalent of a bone marrow transplantation to cure leukemia. Additionally, we have found many other cell types important for many lung diseases, ranging from asthma to

cancer. Some of these cells make specific inflammatory molecules and other possess taste receptors suggesting that the lungs may actually be sensing the air we breathe. The identification of all these new cell types should reframe the way we think about lung disease.
Montoro DT, Haber AL, Biton M, Vinarsky V, Lin B, Birket SE, Yuan F, Chen S, Leung HM, Villoria J, Rogel N, Burgin G, Tsankov AM, Waghray A, Slyper M, Waldman J, Nguyen L, Dionne D, Rozenblatt-Rosen O, Tata PR, Mou H, Shivaraju M, Bihler H, Mense M, Tearney GJ, Rowe SM, Engelhardt JF, Regev A, Rajagopal J. A revised airway epithelial hierarchy includes CFTR-expressing ionocytes. Nature. 2018 Aug;560(7718):319-324. doi: 10.1038/s41586-018-0393-7. Epub 2018 Aug 1.

MOSTOSLAVSKY LAB

Our laboratory explores the crosstalk between metabolism and epigenetics, particularly in the context of cancer and developmental biology. Specifically, we have been studying a mammalian deacetylase called SIRT6, which we found has critical roles in modulating glucose homeostasis, early development, and DNA repair. Through those functions, we found SIRT6 to work as a robust tumor suppressor in multiple cancers, highlighting unique functions for this chromatin factor.

Ferrer CM, Alders M, Postma AV, Park S, Klein MA, Cetinbas M, Pajkrt E, Glas A, van Koningsbruggen S, Christoffels VM, Mannens MMAM, Knegt L, Etchegaray JP, Sadreyev RI, Denu JM, Mostoslavsky G, van Maarle MC, Mostoslavsky R. An inactivating mutation in the histone deacetylase SIRT6 causes human perinatal lethality. Genes Dev. 2018 Mar 1;32(5-6):373-388. doi: 10.1101/gad.307330.117. Epub 2018 Mar 19.

Lin JB, Kubota S, Mostoslavsky R, Apte RS. Role of Sirtuins in Retinal Function Under Basal Conditions. Adv Exp Med Biol. 2018;1074:561-567. doi: 10.1007/978-3-319-75402-4_68.

Etchegaray JP, Mostoslavsky R. A sirtuin's role in preventing senescence by protecting ribosomal DNA. J Biol Chem. 2018 Jul 13;293(28):11251-11252. doi: 10.1074/jbc.H118.004040.

SYKES LAB

Lab focus:

1. Understanding the link between nucleotide biosynthesis and myeloid differentiation.
2. Determining the mechanism of neutropenia in Barth syndrome patients.
3. Developing a system of transfusable neutrophil progenitors.

Sykes DB. The emergence of dihydroorotate dehydrogenase (DHODH) as a therapeutic target in acute myeloid leukemia. Expert Opin Ther Targets. 2018 Nov;22(11):893-898. doi: 10.1080/14728222.2018.1536748. Epub 2018 Oct 17. PubMed PMID: 30318938.

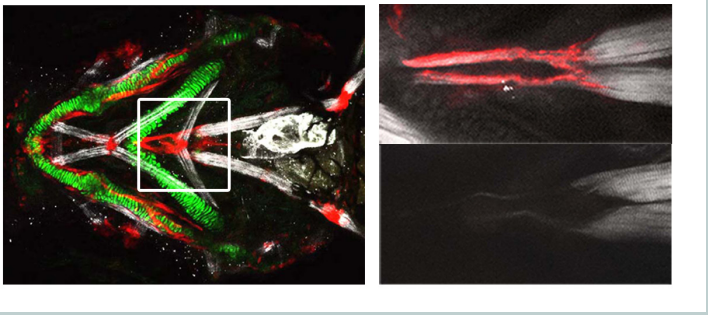
Xu S, Feliu M, Lord AK, Lukason DP, Negoro PE, Khan NS, Dagher Z, Feldman MB, Reedy JL, Steiger SN, Tam JM, Soukas AA, Sykes DB, Mansour MK. Biguanides enhance antifungal activity against Candida glabrata. Virulence. 2018;9(1):1150-1162. doi: 10.1080/21505594.2018.1475798. PubMed PMID: 29962263; PubMed Central PMCID: PMC6086317.

Lin B, Srikanth P, Castle AC, Nigwekar S, Malhotra R, Galloway JL, Sykes DB, Rajagopal J. Modulating Cell Fate as a Therapeutic Strategy. Cell Stem Cell. 2018 Sep 6;23(3):329-341. doi: 10.1016/j.stem.2018.05.009. Epub 2018 Jun 14. Review. PubMed PMID: 29910150; PubMed Central PMCID: PMC6128730.

Sykes DB, Schroyens W. Complete Responses in the TEMPI Syndrome after Treatment with Daratumumab. N Engl J Med. 2018 Jun 7;378(23):2240-2242. doi: 10.1056/NEJMc1804415. PubMed PMID: 29874534.

Dagher Z, Xu S, Negoro PE, Khan NS, Feldman MB, Reedy JL, Tam JM, Sykes DB, Mansour MK. Fluorescent Tracking of Yeast Division Clarifies the Essential Role of Spleen Tyrosine Kinase in the Intracellular Control of Candida glabrata in Macrophages. Front Immunol. 2018 May 16;9:1058. doi: 10.3389/fimmu.2018.01058. eCollection 2018. PubMed PMID: 29868018; PubMed Central PMCID: PMC5964189.

Fites JS, Gui M, Kernien JF, Negoro P, Dagher Z, Sykes DB, Nett JE, MansourMK, Klein BS. An unappreciated role for neutrophil-DC hybrids in immunity to invasive fungal infections. PLoS Pathog. 2018 May 21;14(5):e1007073. doi:10.1371/journal.ppat.1007073. eCollection 2018 May. PubMed PMID: 29782541; PubMed Central PMCID: PMC5983859.



At 3 days of development, the zebrafish muscle (white), cartilage (green), and tendons (red) have formed and begin to function in the craniofacial region. One specific attachment in the central region (white box in left and enlarged upper right image) is important for feeding. Ablation of the tendon cells (bottom right image) results is defects to the tendon matrix and connecting muscle and cartilage tissues. In the next several days and weeks, the zebrafish regenerates its tendon cells in the proper attachment pattern and their matrix organization, which restores the morphological defects to the neighboring musculoskeletal tissues. (Galloway Lab)

GALLOWAY LAB

The Galloway lab is focused on identifying the molecular and cellular regulators of tendon development and regeneration. We use genetics, chemical screening, and live imaging in zebrafish to identify and characterize new pathways important for tendon formation and regeneration. My lab also is using the mouse and mammalian stem cell models to better understand how specific signaling pathways regulate tendon formation and healing. In our mouse studies, we have identified a specific subset of tendon cells that appear to be important for the healing response and are working towards characterizing them and the pathways that regulate their activities. We are establishing tendon and enthesis regeneration models in the zebrafish to understand the function of specific pathways and cell behaviors in the regenerative process. We have recently completed a zebrafish high-throughput chemical screen to identify tendon promoting drugs and we are functionally characterizing the target pathways. In the mouse, we have focused on characterizing how cell proliferation rates change during postnatal growth, adulthood, and aging. From this basic question, we learned a great deal about how tendon cells change their cell cycle activity during these periods, and this has laid the foundation for several projects in the lab.

McGurk PD, Swartz ME, Chen, JW, Galloway, JL, Eberhart JK. In vivo zebrafish morphogenesis shows Cyp26b1 promotes tendon condensation and musculoskeletal patterning in the embryonic jaw. PLoS Genetics. 2017 Dec 11; 13(12):e1007112. PMC5739505

Subramanian A, Kanzaki LF, Galloway JL, Schilling TF. Mechanical force regulates tendon extracellular matrix organization and tenocyte morphogenesis through TGFbeta signaling. Elife. 2018 Nov 26;7. pii: e38069. doi: 10.7554/eLife.38069

SCADDEN LAB

The Scadden lab focuses on hematopoiesis and developing novel therapies for blood diseases and cancer based on hematopoietic stem cell biology. In addition, the IP from the Scadden lab has resulted in the creation of a new publicly traded company, Magenta Therapeutics. David Scadden also published the book, "Cancerland".

Hoggatt J, Singh P, Tate TA, Chou BK, Datari SR, Fukuda S, Liu L, Kharchenko PV, Schajnovitz A, Baryawno N, Mercier FE, Boyer J, Gardner J, Morrow DM, Scadden DT, Pelus LM. (co-corresponding). Rapid Mobilization Reveals a Highly Engraftable Hematopoietic Stem Cell. Cell. 2018 Jan 11;172(1-2):191-204.e10. doi: 10.1016/j.cell.2017.11.003. Epub 2017 Dec 7. PMID:29224778

Dietrich J, Baryawno N, Nayyar N, Valtis YK, Yang B, Ly I, Besnard A, Severe N, Gustafsson KU, Andronesi OC, Batchelor TT, Sahay A, Scadden DT. Bone marrow drives central nervous system regeneration after radiation injury. J Clin Invest. 2018 Jun 1;128(6):2651. doi: 10.1172/JCI121592. Epub 2018 Jun 1. No abstract available. PMID:29856368

Ubellacker JM, Baryawno N, Severe N, DeCristo MJ, Sceneay J, Hutchinson JN, Haider MT, Rhee CS, Qin Y, Gregory WM, Garrido-Castro AC, Holen I, Brown JE, Coleman RE, Scadden DT, McAllister SS. Modulating Bone Marrow Hematopoietic Lineage Potential to Prevent Bone Metastasis in Breast Cancer. Cancer Res. 2018 Sep 15;78(18):5300-5314. doi: 10.1158/0008-5472.CAN-18-0548. Epub 2018 Jul 31.PMID:30065048

Petukhov V, Guo J, Baryawno N, Severe N, Scadden DT, Samsonova MG, Kharchenko PV. dropEst: pipeline for accurate estimation of molecular counts in droplet-based single-cell RNA-seq experiments. Genome Biol. 2018 Jun 19;19(1):78. doi: 10.1186/s13059-018-1449-6. PMID:2992130

Xiao P, Dolinska M, Sandhow L, Kondo M, Johansson AS, Bouderlique T, Zhao Y, Li X, Dimitriou M, Rassidakis GZ, Hellström-Lindberg E, Minato N, Walfridsson J, Scadden DT, Sigvardsson M, Qian H. Sipa1 deficiency-induced bone marrow niche alterations lead to the initiation of myeloproliferative neoplasm. Blood Adv. 2018 Mar 13;2(5):534-548. doi: 10.1182/bloodadvances. 2017013599. PMID:29514790

Ralph Weissleder, MD, PhD, Director

The mission of the Center for Systems Biology (CSB) is to analyze at a systems level how cells, proteins and other biological molecules interact in both healthy and diseased states. Through a multidisciplinary approach that combines clinical insight with powerful analytical technologies, faculty pursue systems-level research that is both fundamental to our understanding of biology as well as directly applicable to the diagnosis and treatment of human disease. While these approaches can be generalizable to a variety of diseases, the Center has particular strengths in complex human conditions such as cancer, cardiovascular and immune diseases. The CSB's mission is enabled by faculty with expertise in advanced bioimaging, immunology, biology, genomics, chemistry, bioengineering and mathematical modeling. The Center is a major node within the Harvard-wide Systems Biology Program, and its faculty maintain joint appointments or affiliations with the HMS Department of Systems Biology, various clinical departments at MGH, other MGH Thematic Centers and the Broad Institute. The CSB is currently structured into 11 PI laboratories (Bernstein, Higgins, Lee, Lin, Im, Miller, Nahrendorf, Naxerova, Pittet, Swirski and Weissleder; the Breton and Brown labs will move to Nephrology in the spring of 2019), Core Platforms (Imaging, Chemical Biology, Biocomputing) and several thematic research programs. The CSB is located within the Simches and CNY Research buildings. There are currently 168 full time employees, including 35 faculty.

Achievements

A metabolic checkpoint that controls energy expenditure in response to diet (Nature. 2019; in press)

The biochemical response to food intake must be precisely regulated. Because ingested sugars and fats can feed into many anabolic and catabolic pathways, how our bodies handle nutrients depends on strategically-positioned metabolic sensors that link a meal's intrinsic nutritional value with intermediary metabolism. The Swirski lab has discovered that a subset of immune cells, specifically integrin β7+ natural gut intraepithelial T lymphocytes (natural IELs), dispersed throughout the small intestine's enterocyte layer, modulate systemic metabolism. β7– mice lacking natural IELs are metabolically hyperactive and, when fed a high fat and sugar diet, resist obesity, hypercholesterolemia, hypertension, diabetes, and atherosclerosis. Protection from cardiovascular disease in the absence of natural IELs, they further show, depends on the enterocyte-derived incretin GLP-1, which IELs normally control via IEL GLP-1 receptor expression. In this metabolic control system, IELs oppose enterocytes by acting as gatekeepers that limit GLP-1 bioavailability. While its function may prove advantageous when food is scarce, overabundance of diets high in fat and sugar render this metabolic checkpoint inimical to health.

He S, Kahles F, Rattik S, Nairz M, McAlpine C, Anzai A, Selgrade D, Fenn AM, Chan CT, Mindur JE, Valet C, Poller WC, Halle L, Rotllan N, Iwamoto Y, Wojtkiewicz GR, Weissleder R, Libby P, Fernandez-Hernando C, Drucker DJ, Nahrendorf M, Swirski FK. Gut intraepithelial T cells calibrate dietary metabolism and accelerate cardiovascular disease. Nature 2019, in press.

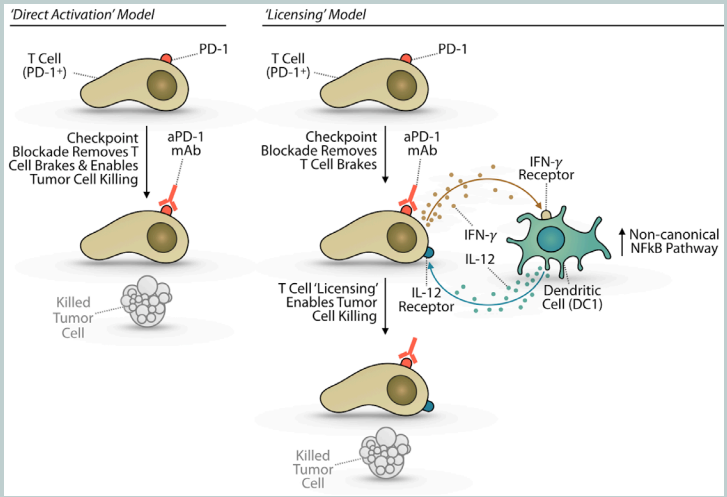


Fig. 1: Profiling the tumor microenvironment
Anti-PD-1 mAbs can induce sustained clinical responses in cancer but how they function in vivo remains incompletely understood. Garris et al. show that effective anti-PD-1 immunotherapy requires intratumoral dendritic cells (DCs) producing IL-12. Anti-PD-1 indirectly activates DCs through IFN-g released from drug-activated T cells. Furthermore, agonizing the non-canonical NF-kB pathway activates DCs and enhances aPD-1 therapy in an IL-12-dependent manner. Courtesy of Mikael Pittet. Immunity 2018;49:1-14

Shortcut to the brain (Nat Neurosci. 2018;21:1209-1217)

White blood cells are our key defenders against infection, they may turn against us if oversupplied. Neutrophils are made in the bone marrow arising from hematopoietic stem cells. The bone marrow is distributed over many bones in our bodies, and the current thinking implies that the supply of leukocytes distributes evenly throughout the body. In work published in Nature Neuroscience, the Nahrendorf lab found that the skull marrow assumes a special role in inflammatory diseases of the CNS. Its proximity to the brain leads to a preferential supply of neutrophils. They detected a previously unknown shortcut that neutrophils use on their way from skull marrow cavities towards the central nervous system. Rather than traveling through the general blood circulation, leukocytes produced in skull bone marrow migrate through channels that directly connect the skull marrow with the meninges the brain is wrapped in. The channels exist in mice and humans.

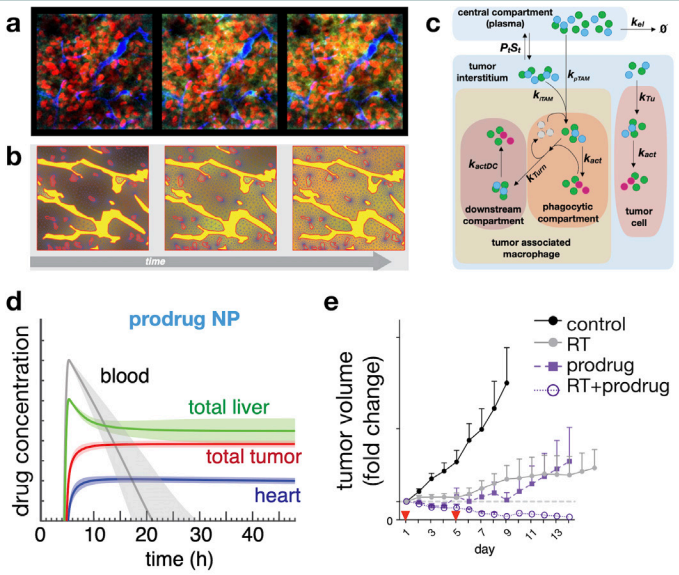


Fig. 2: Optimizing anticancer prodrug therapy using intravital microscopy and systems-level computational modeling
a) Time-lapse IVM monitors the delivery (blue) and local activation (yellow) of a model prodrug nanotherapy and its DNA damage effects on individual tumors cells (red) using a tumor xenograft mouse model. b) Finite element analysis interprets IVM datasets to extract rate constants describing drug delivery and activity, including uptake into immune cells within the tumor (such as macrophages). c-d) Rate constants from high-resolution imaging in the tumor (a-b) are combined with bulk-tissue biodistribution data to understand the transport and clearance of the model prodrug at the organ level, shown as a schematic (c) and as a series of modeling results (d). e) Modeling identified rate-limiting-steps in drug action, which guided combination strategies with radiation therapy (RT) that synergistically eliminate tumor growth. Courtesy of Miles Miller.

Herisson F, Frodermann V, Courties G, Rohde D, Sun Y, Vandoorne K, Wojtkiewicz GR, Santos Masson G, Vinegoni C, Kim J, Kim DE, Weissleder R, Swirski FK, Moskowitz MA, Nahrendorf M. Direct vascular channels connect skull bone marrow and the brain surface enabling myeloid cell migration. Nat Neurosci. 2018;21:1209-1217

Cancer immunotherapy requires T cell-dendritic cell crosstalk (Immunity 2018;49:1-14)

Anti-PD-1 immune checkpoint blockers can induce sustained clinical responses in cancer but how they function in vivo remains incompletely understood. In this study, Pittet et al show that effective anti- tumor responses requires a subset of tumor-infiltrating dendritic cells (DCs), which produce interleukin 12 (IL-12). These DCs do not bind anti-PD-1 but produce IL-12 upon sensing interferon g (IFN-g) that is released from neighboring T cells. In turn, DC-derived IL-12 stimulates antitumor T cell immunity. These findings suggest that full-fledged activation of antitumor T cells by anti-PD-1 is not direct, but rather involves T cell:DC crosstalk and is licensed by IFN-g and IL-12. Activating the non-canonical NF-kB transcription factor pathway amplifies IL-12-producing DCs and sensitizes tumors to anti-PD-1 treatment, suggesting a therapeutic strategy to improve responses to check-point blockade. See Fig. 1.

Christopher S. Garris, Sean P. Arlauckas, Rainer H. Kohler, Marcel P. Trefny, Seth Garren, Cécile Piot1, Camilla Engblom, Christina Pfirschke, Marie Siwicki, Jeremy Gungabeesoon, Gordon J. Freeman, Sarah E. Warren, SuFey Ong, Erica Browning, Christopher G. Twitty, Robert H. Pierce, Mai H. Le, Alain P. Algazi, Adil I. Daud, Sara I. Pai, Alfred Zippelius, Ralph Weissleder, Mikael J. Pittet. Successful anti-PD-1 cancer immunotherapy requires T cell-dendritic cell crosstalk involving IFN-?? and IL-12. Immunity, 2018;49:1-14

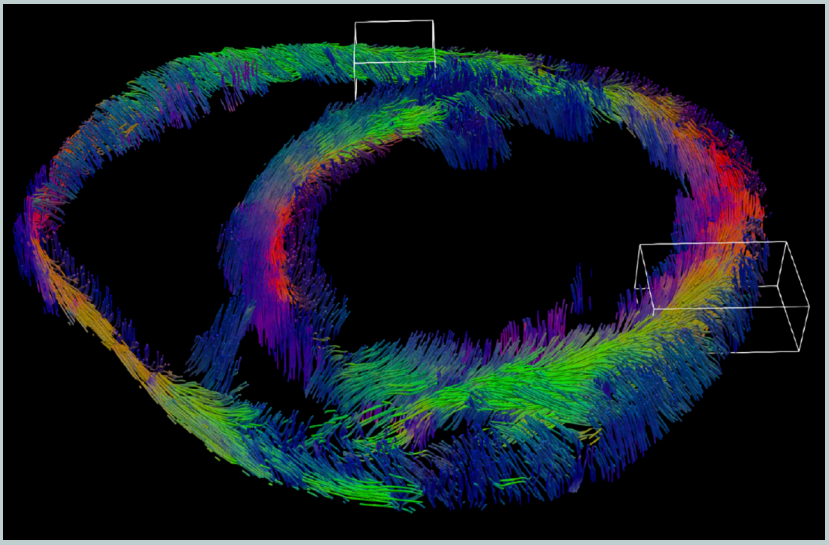


Fig. 3: Visualizing new biology at the organ level
Single cell imaging of whole organs requires new analytical and visualization techniques to display complex biological information. In this example, all cardiac macrophages were imaged in a Cx3cr1-GFP mouse heart. Using AI algorithm, all cells were identified, digitized and their spatial orientation vectorized. Shown is a tractographic tensor field representation of cardiac macrophage orientation where the 3 different colors indicate the spatial coordinates (x/y/z axes). Interestingly, macrophage orientation is highly structured and follows that of myocardial microvasculature. Courtesy of Claudio Vinegoni.

Artificial Intelli-sense (Nature Biomedical Engineering 2018;2:666-674)

Automating cellular diagnostics could have far reaching impact in healthcare. Cells - often obtained by aspirations, biopsies, swabs or through body fluids - typically require sophisticated instrumentation and time consuming experts analysis to provide diagnoses. The CSB engineering team has now developed a highly sensitive platform powered by digital imaging and artificial intelligence to automate such painstaking

analyses. Moreover this platform is affordable and portable, thus uniquely suited for point-of-care diagnostics in low and middle income countries (LMIC). A recent study published in Nature Biomedical Engineering highlights the first clinical trial for lymphoma diagnostics.
Im H, Pathania D, McFarland PJ, Sohani AR, Degani I, Allen M, Coble M, Kilcoyne A, Hong S, Rohrer L, Abramson JS, Dryden-Peterson S, Fexon L, Pivovarov M, Chabner B, Lee H, Castro CM, Weissleder R. Design and clinical validation of a point-of-care device for the diagnosis of lymphoma via contrast-enhanced microholography and machine learning. Nature Biomedical Engineering. 2018;2:666-674

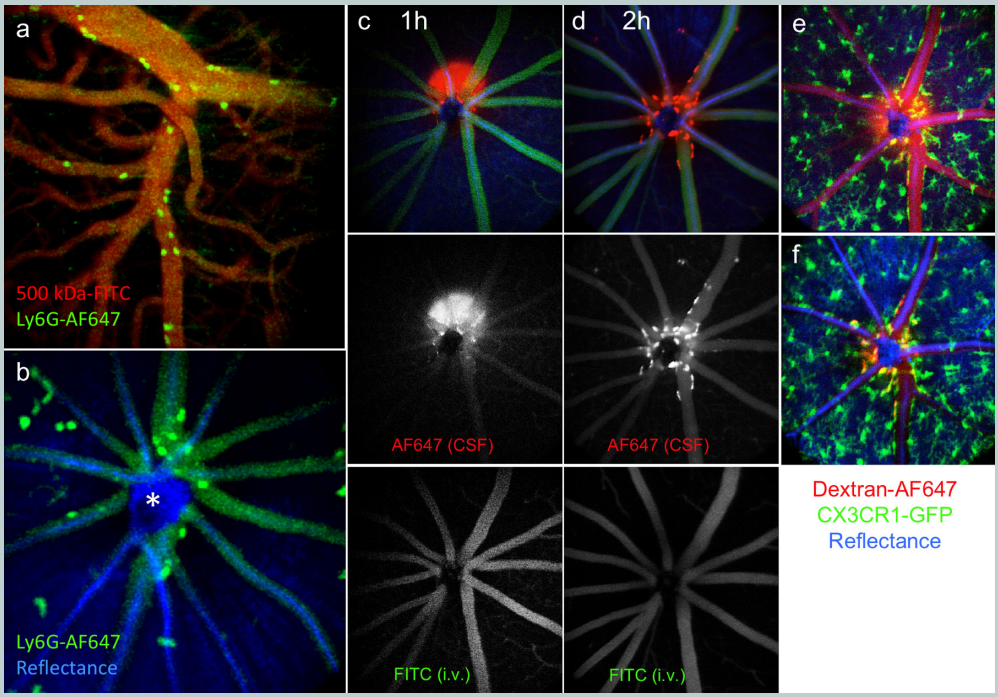


Fig. 4: CSF transport extends into the retina and provides a means to detect CNS inflammation
The Lin lab recently introduced a novel method for detecting CNS inflammation, by non-invasive imaging of leukocyte-endothelial interaction (LEI) in the vasculature of the retina. LEI, rolling and adhesion of leukocytes on vascular endothelium, is an early hallmark of inflammation that is absent in the healthy CNS, yet it cannot be detected non-invasively in the brain, meninges or spinal cord. The retina is a part of the CNS that is readily accessible to optical imaging through the pupil of the eye. a) After induction of meningitis by injection of 50 ng LPS into the CSF at the cisterna magna, rolling cells (green, anti-Ly6G) are observed in meningeal vasculature (red, 500 kDa dextran) by intravital microscopy through a cranial window. b) Retinal LEI near the optic nerve head (ONH, asterisk) accompanies the meningeal inflammation, imaged by confocal scanning laser ophthalmoscope (SLO). Vasculature is shown by backscattering contrast (blue). This method is enabled by newly discovered transport of CSF into the retina. (c,d) Fluorescent dextran injected into the CSF (red) reaches the retina and is taken up by perivascular cells, while concomitantly IV- injected dextran (green) remains confined to the vasculature. (c) Intrathecally injected dye arrives as a pool in the ONH after 1 hour and (d) is subsequently taken up by perivascular cells. Detail images show the corresponding red (CSF-injected 10 kDa Dextran-AF647) (middle row) and green channels (IV-injected 10 kDa Dextran-FITC) (bottom row). (e,f) Intracisternally injected 10 kDa Dextran-AF647 is taken up by retinal microglia. (f) The dye was detected first as a pool in the ONH at 90 minutes, (g) then taken up by microglia, as indicated by co-localization of AF647 signal with CX3CR1-driven GFP expression. (c-f) No cell migration was observed that would indicate cellular transport of the dye. Field of view approximately 575 μm. Courtesy of Clemens Alt. Nat Neurosci 2019, under revision.

Antibody-DNA conjugates bring patient biopsies to light (Nat Commun. 2018;9:4550)
Modern oncology relies on molecular assessments of tumor tissue to develop new therapeutic combinations and select optimal treatments for individual patients. Conventional approaches to cellular fluorescence imaging allow for visualization of just 3-5 proteins at a time, limiting the amount of information one can gain from precious patient biopsy samples. In a new study published in Nature Communications, investigators from the Weissleder lab developed an approach that uses antibody-DNA conjugates to efficiently "cycle" through the detection and quantification of multiple proteins of interest, dramatically increasing the number of pathways/targets that can be imaged from a single biopsy. This technique allows scientists/physicians to directly visualize complex protein signatures in the biopsied cells and has important implications for understanding how drug therapies affect patients' individual tumors.
Giedt RJ, Pathania D, Carlson JCT, McFarland PJ, Del Castillo AF, Juric D, Weissleder R. Single-cell barcode analysis provides a rapid readout of cellular signaling pathways in clinical specimens. Nat Commun. 2018;9:4550

White blood cell population dynamics for risk stratification of acute coronary syndrome
The human innate and adaptive immune systems are composed of white blood cells that can detect and begin to respond to disease long before most current clinical diagnostic tests would detect a problem. This study from the Higgins lab developed a coarse model of white blood cell population behaviors. The model uses existing routine patient clinical blood count data to provide a quantitative glimpse of the state of a patient's immune system. In retrospective analysis, the model was able to distinguish healthy and acutely ill patients whose overall blood counts are indistinguishable and also identify patients being evaluated for heart attacks (acute chest syndrome) in the emergency room whose initial screening tests were negative but who were at greatest risk of becoming positive in the next 48 hours and requiring emergency

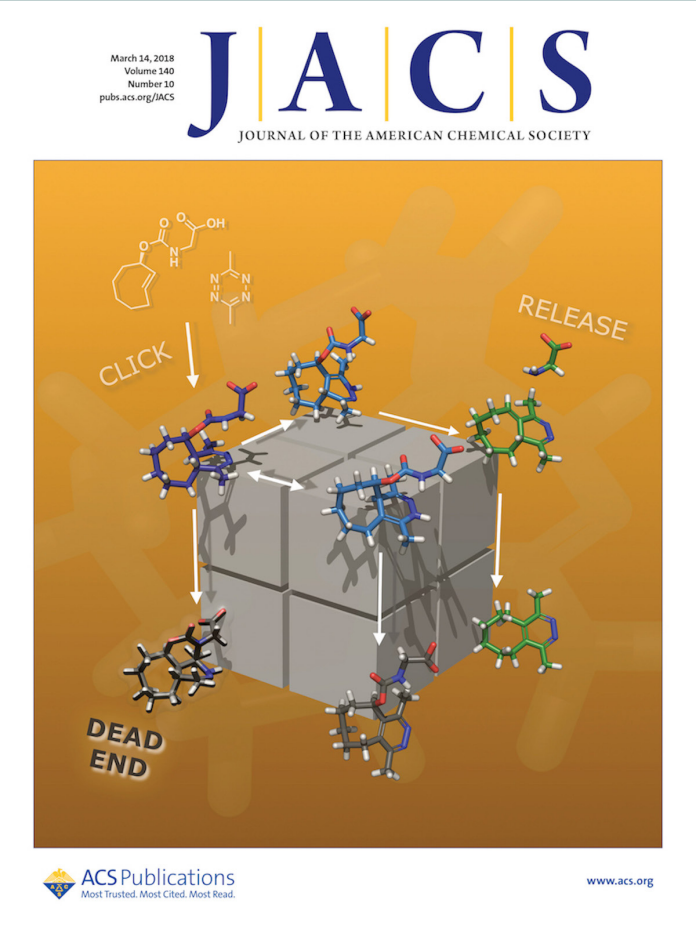


Fig. 5: A ghost in the mechanism
Tetrazine/trans-cyclooctene click-to-release chemistry has driven recent developments in bioorthogonal bond cleavage, but has proven difficult to optimize. Unraveling the post-click reaction network, the "release cube", revealed a previously unrecognized tricyclic dead-end isomer and enabled strategies to block its formation to achieve complete and ultrafast release. This has direct implications for the generation of new, activatable "smart drugs". Courtesy: Jonathan Carlson. J Am Chem Soc. 2018;140(10):3603-3612

treatment. This overall approach of characterizing the hematologic and immunologic state of patients may be useful in the early detection and more precise diagnosis of many other diseases involving inflammation, like infection, cancer, and autoimmune disease.
Anwesha Chaudhury, Lorette Noiret, and John M. Higgins. PNAS November 14, 2017 114 (46) 12344-12349; published ahead of print October 27, 2017 https://doi.org/10.1073/pnas.1709228114

For a complete list of 2018 publications, please see here: https://csb.mgh.harvard.edu/publications?year=2018

R. Rox Anderson, MD, Director

Wellman is a prolific translational research center. The field of Photomedicine encompasses all of light's beneficial, harmful, diagnostic, therapeutic, surgical, medical and technological aspects in biology and medicine. Our mission is to improve people's lives through research, innovation, technology development, and education. If fulfilling our mission leads us beyond photomedicine... OK. Current topics include: advanced live microscopy, point-of-care optical diagnostics, light-activated cancer treatments, wound repair and healing, trauma interventions, photobiomodulation (light-stimulated metabolism and signaling), melanoma genetics and treatment strategies, bio-inspired optical technologies and dozens of problem-driven projects.

Strategic priorities

- Leadership. We are the world's largest research center in a rapidly expanding field, with over 280 personnel, and an annual budget near $30M. Our core strength is the intellectual diversity of excellent faculty who aim for real impact. We are now recruiting two new faculty through a competitive search.
- Innovation. WCP is the birthplace of many inventions and discoveries now in widespread use. We are the leading source of royalty income at MGH, which helps support the capabilities and operations at WCP. In 2018, 59 new patents were issued on WCP inventions. Dozens of biomedical companies have been created and sustained through our work.
- World Health. We are pursuing collaborative research on every continent, with emphasis on trauma, malnutrition, child health, infections and cancer in developing countries.
- Education. We offer courses, regular seminar and lecture series, CME courses, student and postdoctoral fellow education, a summer school for undergraduates, and three endowed research fellowships in biomedical optics (Bullock, Deutsch, Hillenkamp).
- Return value to MGH. Wellman is non-departmental, and highly collaborative (>50 projects) for both basic and clinical research at MGH. Our faculty serve on many MGH committees. We welcome, solicit and support collaborative research at all stages.

A Sample of 2018 Research Highlights

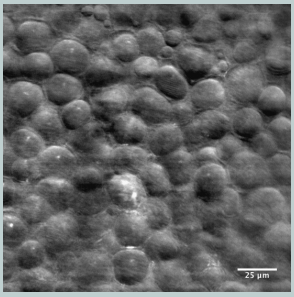
Wellman Center published 168 research papers in 2018. Here are just a few highlights:

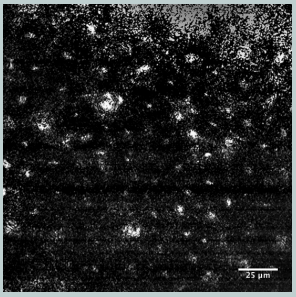
Wellman Center creates new microscopy, imaging and diagnostic systems – including novel "front end" technologies for research, delivery devices, image analysis including artificial intelligence, validation through a host of clinical studies, and commercialization.

IMAGING

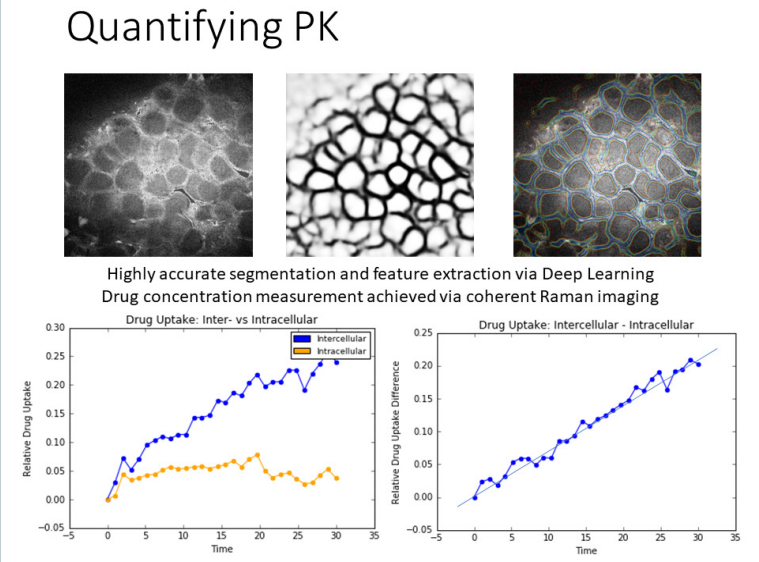
Gary Tearney (who in 2018 became the Remondi Family Endowed MGH Research Institute Chair) leads a large effort that creates, develops, verifies and launches innovative point-of-care medical imaging systems. The example shown to the left is a novel imaging tethered capsule microscope, which his team recently used in unsedated teens to diagnose eosinophilic esophagitis, an allergic condition that causes esophageal inflammation in kids and adults. The capsule microscope is shown next to a Flintstones (TM) vitamin tablet; both can easily be swallowed.

Laser scanning reflectance confocal microscopy was invented at WCP 20 years ago, and is used worldwide for live tissue imaging. This year, Charles Lin's laboratory invented a new laser scanning, differential interference contrast microscope capable of high-resolution imaging in live, thick tissues. The absence of speckle noise allows this new microscope (left image below) to resolve fine detail in intact, unstained, live tissue much better than conventional reflectance confocal microscopy (right image below). Both images are of live adipose tissue. [Paudel HP, Alt C, Runnels J, Lin CP. Pupil plane differential detection microscopy. Optics Lett. 2018; 43:4410-4412]

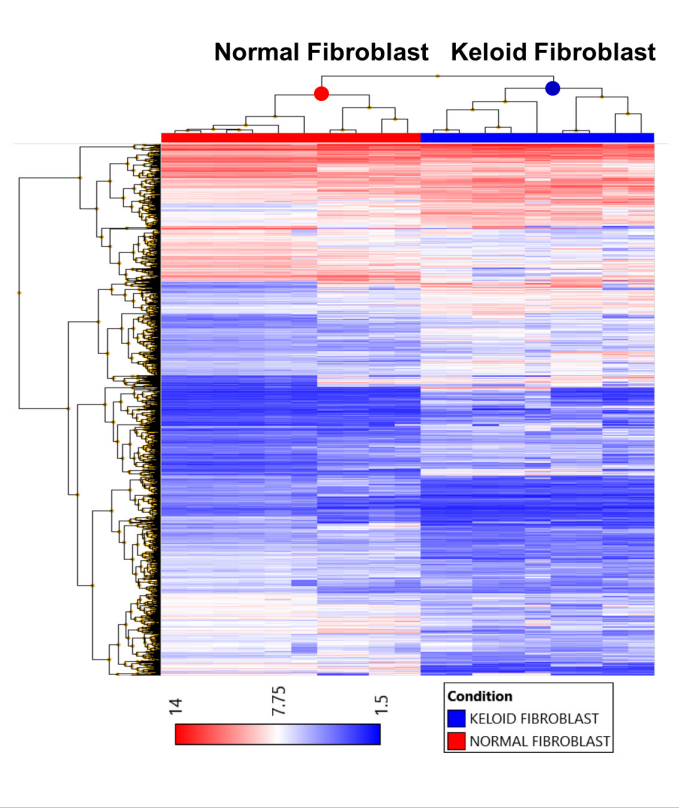




Conor Evans' lab is pioneering ways to image drugs and other molecules in live tissue, without labels or stains, using coherent anti-Stokes Raman scattering. Drug uptake pathways, pharmacokinetics, pharmacodynamics and drug metabolism can be seen and directly quantified. Here is an example of a retinoid uptake into human skin.

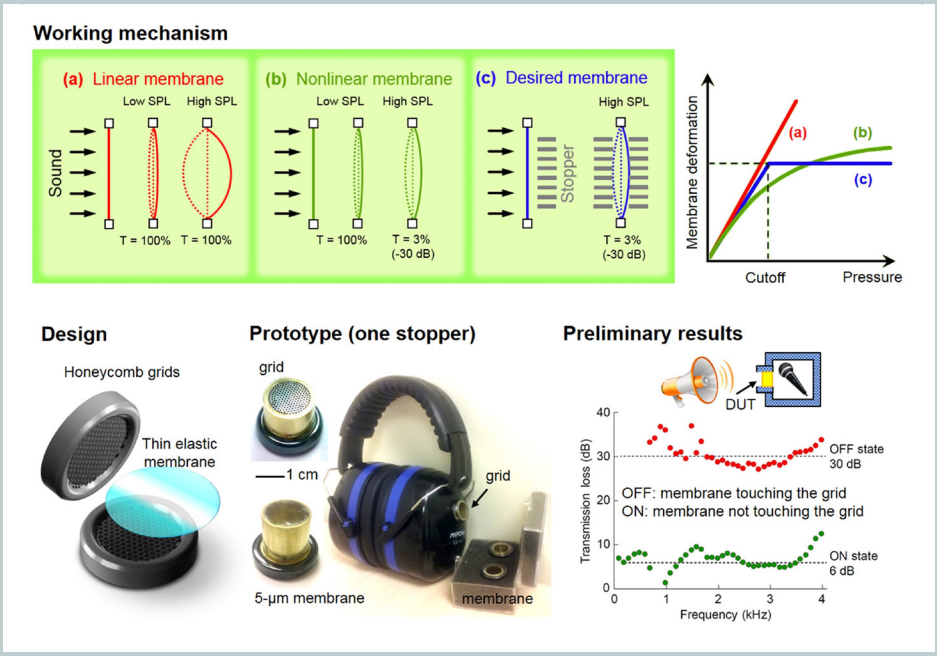


Conventional endoscopes, microscopes and surface imaging devices miss many sub-surface tissue features, and are difficult to navigate when the anatomy is complex and/or moving. To solve these problems, Ben Vakoc's laboratory invented and is developing a high-speed, high-resolution, wide-field and long ranging form of optical coherence tomography that is promising for this broad set of diagnostic and endoscopic surgical uses. [Siddiqui M, et al. High-speed optical coherence tomography by circular interferometric ranging, Nat Photonics 2018 12:111-116]



KELOIDS

What drives keloids to be painful, thick tumors that keep growing long after a wound is healed? Hensin Tsao's laboratory discovered that keloids are in a constant state of "hypoxic alarm", expressing high levels of HIF-1 and a related symphony of genes (shown here in a heat map) that suggest new targeted treatment strategies.

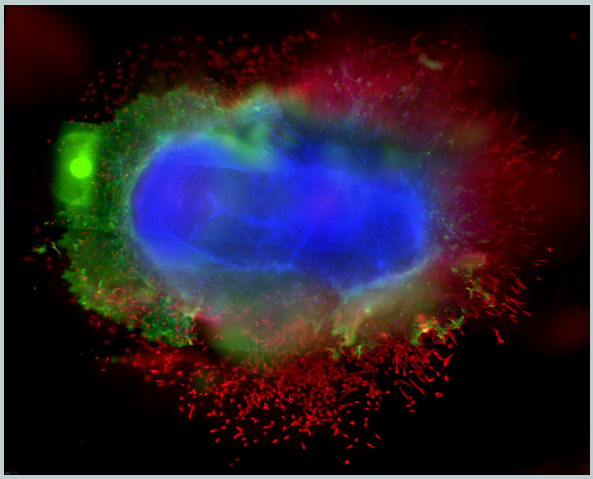


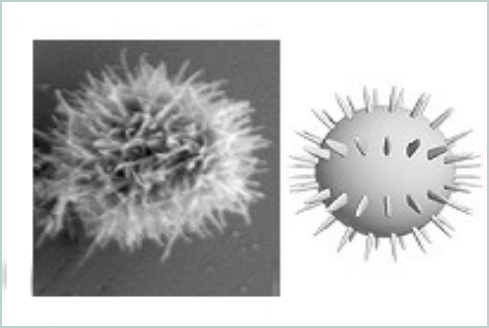
PREVENTION OF HEARING LOSS

Andy Yun's laboratory is well known for surprising bio-optics inventions such as the world's first living laser, creation of nano-scale intracellular lasers, and first imaging of the intrinsic mechanical properties of cells. However it's not all about optics. Hearing loss from barotrauma and loud noise is a major, potentially preventable problem. With support from DOD, a passive bistable "earplug" was devised, capable of 1000x attenuation when needed, yet allowing otherwise normal hearing.

HARMLESS SKIN GRAFTS

By removing skin tissue in small columns rather than conventional split- or full-thickness grafts, Rox Anderson's lab group created the first form of full-thickness skin grafting that does not leave a donor site scar. A device that rapidly extracts and transfers skin columns was cleared this year by FDA. The columns contain all normal skin structures, secrete many growth factors, and provide migrating autologous cells (fibroblasts shown in red; keratinocytes green; nuclear staining blue) that promote rapid healing.





ENHANCING IMMUNE RESPONSES

Mei Wu's laboratory has discovered several ways to enhance response to vaccination other than traditional adjuvants. Previously, she found that laser microbeam injury can rapidly activate dermal antigen presenting cells, leading to greater humoral response. How can innate immune responses also be enhanced? Her recent work shows that spiky, not merely rough, nanoparticles cause physical activation of innate immunity. [Wang J, et al. Physical activation of innate immunity by spiky particles. 2018 Nature Nanotechnology (11):1078-1086]

COLLABORATIONS

Wellman Center welcomes collaboration and inquiry – about anything. Visit us at https://www.massgeneral.org/wellman

Anesthesia, Critical Care and Pain Medicine

Department Report

Jeanine Wiener-Kronish, MD, Chief

Research activities at the Department of Anesthesia, Critical Care and Pain Medicine (DACCPM) are an integral aspect of the departmental overall mission focusing on patient care, education, research innovation, and community service. (1) DACCPM research activities have an international reputation and encompass a broad range of disciplines with active research units focused in the areas of cardiac and pulmonary pathophysiology, molecular and system neuroscience, pharmacology, pain neurobiology, neuroimaging, stem cell research, genetics, comparative outcome research, biomedical engineering, and new drug and medical device development. (2) DACCPM has over 200 research staff including M.D. and/or Ph.D. investigators, post-doctoral fellows, and graduate students. (3) The laboratories and clinical research units are located on the main MGH campus and at the MGH-East research facility at the Charlestown Navy Yard. (4) Research activities at DACCPM are supported by about 80 grants per year, including 44 NIH grants in 2018. (5) The DACCPM faculty publishes annually over 200 journal articles and numerous books/book chapters.

There are three strategic research priorities at DACCPM. (1) Retaining and expanding a premier research team: We have a long-term plan to foster the growth of three tiers of investigators, including a) T32 and K08 trainees, b) junior and mid-level investigators, and c) well-established senior investigators. Over the years, we have provided a significant investment in expanding and retaining our research staff, including salary support to T32/K08 trainees, gap funding for M.D. and/or Ph.D. investigators, and supplemental salary support for basic science and clinical researchers. (2) Establishing a research platform that promotes integration between basic science and clinical research: We have implemented several initiatives to support clinical and comparative outcome research including competitive intra-departmental clinical research funds and a clinical research core with a first-tier statistical faculty and study coordinators to support clinical investigations. We also have internal clinical research funding mechanisms that provide financial support for conducting clinical research. (3) Using innovation to advance translational research and expand the overall scope of basic science and clinical research: We have an internal funding mechanism that supports invention and innovation through fruitful translational research. A significant number of pending or awarded patents from our department offer a promising pipeline of innovative products that will ultimately advance patient care and provide sustainable support for research activities in the department. This effort is further strengthened over the last several years.

Achievements

The excellence of research at the DACCPM is reflected by a combination of basic science, clinical and translational research led by the nation's largest physician-scientist group in the anesthesia field as well as top-notch non-clinician Ph.D. investigators in our department. The following are four representative achievements from our research faculty in 2018:

Emery N. Brown, MD, PhD, was named the 2018 recipient of its Dickson Prize in Science by Carnegie Mellon University. Awarded annually since 1970, the Dickson Prize in Science recognizes substantial achievements or sustained progress in the fields of the natural sciences, engineering, computer science or mathematics. Dr. Brown is considered the "world's expert on statistical analysis of neuronal data," according to Carnegie Mellon faculty member Dr. Robert E. Kass, and his research on anesthesia has been "truly transformative" to that field. His outstanding achievements have earned him the distinction of being one of only 21 people elected to all three branches of the National Academies of Science.

Dr. Warren M. Zapol's lab found that TD-3, and possibly other triazole disulfide compounds that bind to Hb β-Cys93, may provide new treatment options for patients with sickle cell disease. Using small molecules to increase the affinity of Hb for oxygen is a potential approach to treating sickle cell disease, because oxygenated Hb interferes with the polymerization of deoxyHbS. They have identified a triazole disulfide compound (4,4'-di(1,2,3-triazolyl)disulfide, designated TD-3), which increases the affinity of Hb for oxygen. The crystal structures of carboxy- and deoxy-forms of human adult Hb (HbA), each complexed with TD-3, revealed that one molecule of the monomeric thiol form of TD-3 (5-mercapto-1H-1,2,3-triazole, designated MT-3) forms a disulfide bond with β-Cys93, which inhibits the salt-bridge formation between β-Asp94 and β-His146. This inhibition of salt bridge formation stabilizes the R-state and destabilizes the T-state of Hb, resulting in reduced magnitude of the Bohr effect and increased affinity of Hb for oxygen. This work is published in Mol Pharm. 2018 May 7;15(5):1954-1963.

The Massachusetts Digital Health Council has selected the Medical Device Plug & Play (MD PnP) Interoperability and Cybersecurity Program, founded by **Julian Goldman, MD**, as the first Digital Sandbox initiative created by the Massachusetts Digital Health Council. MD PnP will use its expertise to test innovators' equipment, network infrastructure and information systems devices will be integrated and tested for ease of use, safety, data collection and review. MD PnP will assess innovators' business plans and technology to identify potential clinical and IT related

roadblocks. Based on experience with medical interoperability and hospital integration projects, MD PnP will determine whether the proposed products are likely to encounter any critical problems when operating in real clinical environments. MD PnP will offer guidance on how to structure product offerings to minimize risks and mitigate risks that cannot be avoided. Identifying and addressing issues early in product development helps to avoid wasting development effort and reduces time to market.

Karen C. Nanji, MD, MPH, was awarded the Doris Duke Clinical Scientist Development Award from the Doris Duke Charitable Foundation for her project entitled "Preventing Perioperative Medication Errors Through the Reduction of Clinical Decision Support Alert Overrides." This is a 3-year award. Dr. Nanji was also elected Chair of the Task Force on Global Perioperative Medication Safety at the World Federation of Societies of Anesthesiologists (WFSA).

Cancer Center

Department Report

Daniel A. Haber, MD, PhD, Director

The mission of the Massachusetts General Hospital Cancer Center (MGH Cancer Center) is to deepen our understanding of cancer and to rapidly translate our discoveries into exceptional, personalized care for all cancer patients. The MGH Cancer Center is a comprehensive center, with a focus on creating a highly collaborative environment between scientists and clinicians that will enhance innovative fundamental research and improve patient treatment and care. Our faculty research interests include genetics, genomics, epigenetics, metabolism, proteomics, chemical biology, developmental and stem cell biology, cell signaling, immunology, RNA and miRNA biology, computational biology, therapeutics, and bioengineering.

Our strategic priorities include building platforms that enable blood-based detection of cancer; establishing paradigms for precision oncology by using genetically-informed small molecule inhibitor therapies; creating a leading immune therapy program, including checkpoint inhibitors and engineered T cell therapies; and expanding our support for fundamental discoveries, which we believe to be the centerpiece of our successful research and translational enterprise.

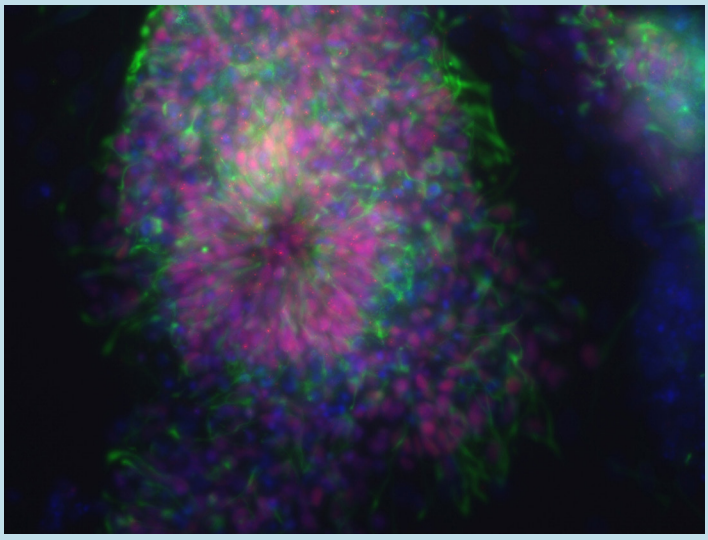
Our research highlights from 2018 include major discoveries and observations from investigators within the multi-departmental Center for Cancer Research (CCR) and the Division of Hematology Oncology (Department of Medicine), both of which are administered through the Cancer Center. Dr. David Ryan is Clinical Director of the Cancer Center and Chief of Hematology/Oncology; Dr. Nick Dyson serves as Scientific Director (CCR); and Dr. Keith Flaherty is Director of Clinical Research.

Total annual research expenditures for CCR and Hematology/Oncology in FY18 were $96 million (including industry clinical trials contracts). In 2018, the MGH Cancer Center enrolled 3,300 patients on over 500 clinical trials (1,263 patients on therapeutic/interventional trials, 40% of which were early Phase 1/II trials of first-in-human drugs).

Highlighted accomplishments for the Cancer Center during 2018 are grouped into four thematic areas:

1. Fundamental Mechanisms of Tumorigenesis

Dr. Lee Zou's lab discovered a novel signaling pathway that is initiated by DNA/RNA "R loops", and that is specific to mitotic regulation using the ATR gene pathway, promoting whole chromosome segregation. This mitotic ATR pathway opens a whole new area in R loop biology, and it raises the possibility that ATR inhibitors may be useful for treating cancers with both DNA repair defects and "chromosome instability" (Kabeche et al, Science. 359:108-114, 2018). **Dr. Raul Mostoslavsky's group** reported a germline mutation in the human SIRT6 gene as a cause for fetal demise, defining this cancer and metabolism-related chromatin factor as critical to human development (Ferrer et al, Genes & Dev.32:373-388, 2018). **Dr. Johnathan Whetstine's laboratory** uncovered a collection of H3K4-modifying chromatin regulators that function with H3K9 and H3K36 regulators to orchestrate transient site-specific chromosome copy number gains. These pathways comprise an epigenetic addressing system for defining focal DNA re-replication and amplifications in cancer cells (Mishra et al,Cell. 174:803-81, 2018). **Dr. Nabeel Bardeesy and his team** uncovered Gnas-driven oncogenic mechanisms, pointing to a role for the Sik genes as potent tumor suppressors in pancreatic cancer and demonstrating pronounced metabolic heterogeneity among Kras-mutant pancreatic neoplasms (Patra et al, Nature Cell Biology. 20:811-822, 2018).

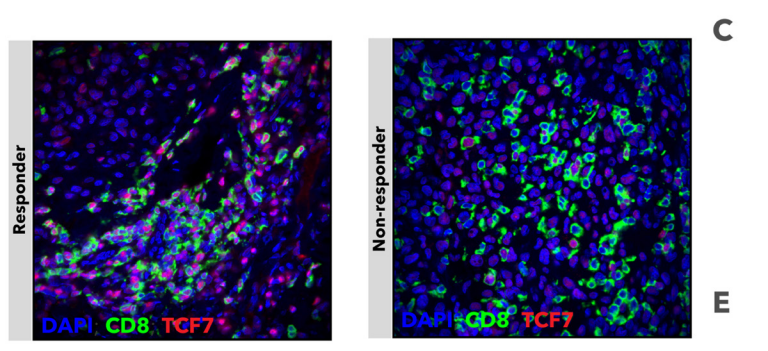


Featured image from Ferrer et al, Genes & Dev.32:373-388, 2018 (Mostoslavsky Lab). The image represents Patient-derived Neural Progenitor Cells (NPC) from SIRT6 D63H homozygous fetuses simultaneously displaying nestin (green) and sustained Sox2 expression (red). Cells were differentiated from induced Pluripotent Stem (iPS) cells prepared from patient-derived amniocytes (normal NPCs at this stage have already silenced Sox2 expression)

In a collaboration between the groups of **Drs. Gaddy Getz, Vamsi Mootha and David McFadden**, investigators defined frequent mitochondrial mutations that drive Hurthle Cell Carcinoma (Gopal, Kubler, et al., Cancer Cell 34: 242-255, 2018).

2. Cancer Immunotherapy

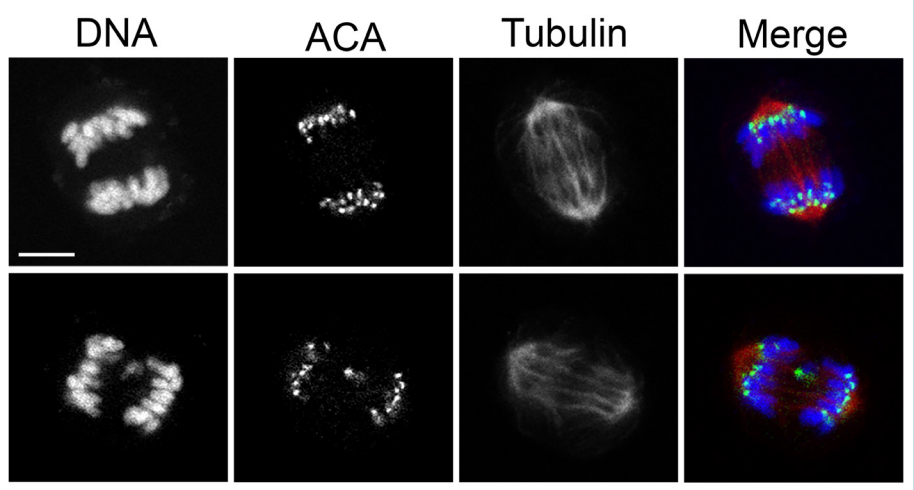
Dr. Nir Hacohen's lab studied single cell transcriptomes of immune cells from primary turmo specimens, demonstrating a strategy for identifying predictors of response to immune checkpoint inhibitors, and potential targets for enhancing checkpoint immunotherapy. Specifically, two distinct states of CD8+ T cells defined by clustering were associated with patient tumor regression versus progression, and expression of a single transcription factor, TCF7, was predictive of clinical outcome (Sade-Feldman et al, Cell. 10.038, 2018). Dr. Marcela Maus developed a novel CAR-T cell construct targeting CD37 in B and T-cell lymphomas, which is poised to enter early clinical trials (Scarfo et al., Blood 132: 1495-1506, 2018). Drs. Jonathan Hoggatt and David Scadden developed a potential new strategy for a rapid stem cell mobilization regimen utilizing a unique CXCR2 agonist, GROβ, and the CXCR4 antagonist AMD3100. This mobilization regimen results in preferential trafficking of stem cells that demonstrate a higher engraftment efficiency than those mobilized by G-CSF (Hoggatt et al, Cell. 172:191-204. 2018)



Featured image from Sade-Feldman et al, Cell. 10.038, 2018 (Hacohen Lab) Staining for the transcription factor/biomarker TCF7 identifies T cells within tumor specimens from cases that are responsive to immune checkpoint inhibitors, while non-responsive tumors have few TCF7 positive T cells.

3. Molecular Therapeutics

Drs. Nick Dyson and Anna Farago established a clinical translational collaboration to establish patient-derived "PDX" mouse models of Small Cell Lung Cancer, either from primary tumor biopsies or from Circulating Tumor Cells (CTCs) found in patient's blood. Molecular and therapeutic modeling showed high concordance with clinical outcome and are poised to enable "co-clinical trials" in this refractory form of lung cancer (Drapkin et al, Cancer Discovery. 8:600-61,2018). Drs. Shyamala Maheswaran, Daniel Haber and Aditya Bardia described a 17-gene digital signature of breast CTC-derived transcripts that enabled noninvasive monitoring of intracellular Estrogen Receptor signaling before and after therapeutic intervention in advanced breast cancers. (Kwan, Bardia et al, Cancer Discovery. 8:1286-1299, 2018); and together with Dr. David Miyamoto, they established a sensitive and high-throughput digital measurement of prostate CTCs predictive of abiraterone response in metastatic cancer and of early dissemination in localized cancer. (Miyamoto DT et al, Cancer Discovery, 8:288-303. 2018). Dr. Ryan Corcoran defined theefficacy of triple targeting of BRAF, EGFR and MAPK in BRAF-V600E-mutant colorectal cancer (Corcoran et al, Cancer Discovery. 8: 428-443, 2018) and the application of liquid biopsies to identify recurrent markers of acquired resistance to drive therapeutic strategies (Hazar-Rethinam et al, Cancer Discovery. 8: 417-427. 2018). Drs. John Iafrate and Leif Ellisen used anchored next-generation sequencing to discover new expressed chromosome fusions transcripts in advanced breast cancer, revealing both the high frequency of such chimeric oncogene drivers, and their clinical significance (Matissek et al, Cancer Discovery. 8:336-353, 2018).

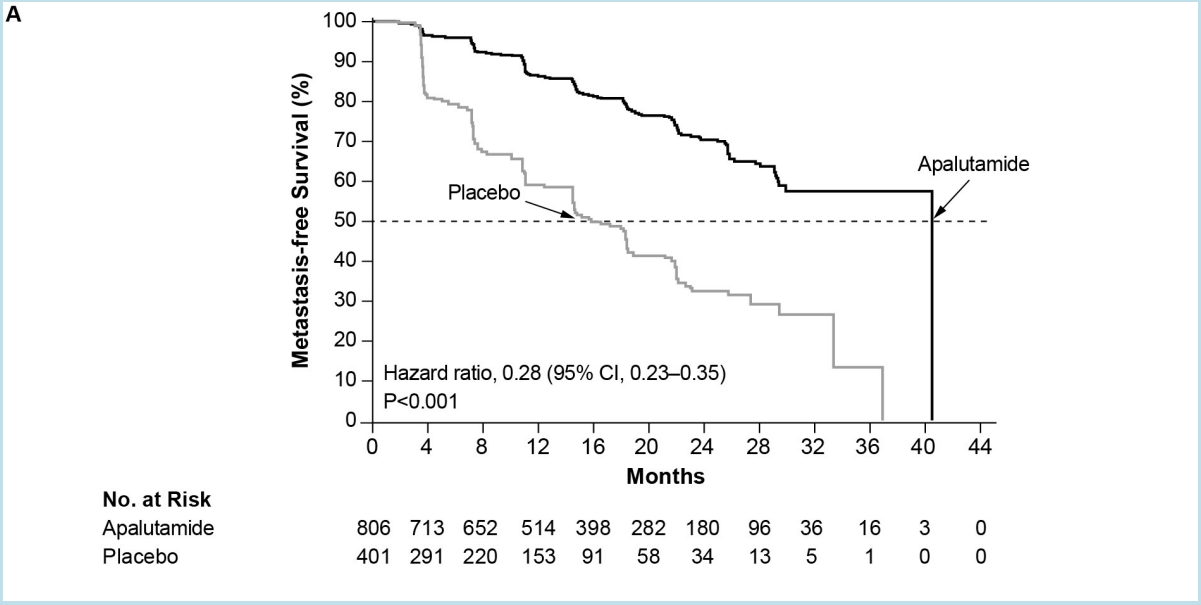


Featured image from Kabeche et al, Science. 359:108-114, 2018 (Zou Lab) ATR inhibition leads to abnormal mitotic checkpoint and increased chromosomal instability.

4. Oncology Clinical Trials

Dr. Dejan Juric led the first-in-human trial of the PI3K inhibitor Alpelisib (BYL719) in patients with PIK3CA-mutant cancer, successful phase 1 studies (Juric et al., J. Clin Oncol 36: 1291-1299, 2018) and (Juric et al., JAMA Oncol. 2018 Dec 13:e184475) that is now enrolling patients into the SOLAR-1 phase 3 registration trial, aiming for FDA approval. Dr. Alice Shaw led the global phase 2 study of the ALK inhibitor Lorlatinib in this

genotype-positive subset of lung cancer (Solomon et al., Lancet Oncol 19: 1654-1667, 2018), and collaborated with Drs. Justin Gainor and Dagogo-Jack in tracking ALK drug resistance mechanisms using monitoring of circulating tumor DNA (Dagogo-Jack et al., JCO Precis. Oncol 2018). Dr. Lecia Sequist led a multi-disciplinary clinical and pathology team, including Drs. Piotrowska, Lennerz, Mino-Kenudson, Iafrate, Heist, Hata and Shaw in defining the landscape of drug resistance in patients with EGFR-mutant lung cancer treated with the third-generation inhibitor Osimertinib (Piotrowska et al., Cancer Discovery 8: 1529-1539, 2018). Leading a multi-institutional, placebo-controlled randomized clinical trial, Dr. Matthew Smith reported that treatment of men with non-metastatic, castration-resistant prostate cancer using the Androgen Receptor inhibitor apalutamide resulted in significantly improved metastasis-free survival (Median metastasis-free survival of 40.5 months versus 16.2 months in controls) (Smith et al, N Engl J Med; 378: 1408-18, 2018). This study is expected to change the standard of care for patients who develop a recurrence of their prostate cancer despite androgen withdrawal therapy (ADT), before detectable metastatic lesions.



Featured image from Smith et al, N Engl J Med; 378: 1408-18, 2018. In a placebo-controlled randomized study of men who have a rising PSA but no radiographic evidence of metastasis following curative-intent therapy of localized prostate cancer and exhibiting resistance to androgen withdrawal therapy (leuprolide), treatment using the new androgen receptor inhibitor Apalutamide results in dramatically improved metastasis-free survival compared with placebo (median metastasis-free survival 40.5 vs 16.2 months, HR 0.28, P<0.001). This study led to an FDA-approved indication for Apalutamide.

Consortia for Improving Medicine Through Innovation and Technology (CIMIT)

Department Report

John A. Parrish, MD, CEO

The Consortia for Improving Medicine with Innovation & Technology (CIMIT; http://cimit.org/) was founded in 1998 by MGH, BWH, MIT, and Draper Laboratory as a "center-without-walls" to foster multidisciplinary collaborations that bridge silos of medicine and technology to improve patient care. CIMIT leverages technological expertise from academia, industry, and the Department of Defense (DoD) to target unmet medical needs of civilians and wounded warriors through close collaborations among innovative clinicians, engineers, scientists, and implementation experts across institutions. Based on its success, CIMIT has now grown to become a portal for international groups to access and collaborate with Boston's world-class MedTech communities.

CIMIT leadership and its funded investigators conducted a Clinical Impact Study to assess the outcomes of supported projects and learn how to improve innovation in healthcare. The first study was conducted in 2012 (CIS; http://cimit.org/web/cimit/clinical-impact) and was updated in 2014. Based on the size of CIMIT's investment, the impact of its projects on clinical care exceeds that of published outcomes from other organizations. Highlights of the CIS were that the $50M of projects studied resulted in: 1) More than $500M in follow-on funding at CIMIT institutions plus another $600M in commercial investment; 2) Over 460 issued US patents and 2,300 publications; 3) Over 70 NewCo's or commercial licenses with more than 20% had received regulatory approval for human use and 4) more than 30% of the PI's surveyed reported that the project support made a major impact on their career development.

CIMIT's support of Translational Research Institute for Space Health

NASA funded the Translational Research Institute for Space Health (TRISH) in 2016 to lead a national effort to translate innovative, emerging terrestrial medical research into applied space flight solutions which mitigate human health risk and improve health outcomes on exploration missions. Its scope includes human performance, biomedical, and cognitive and behavioral science.

CIMIT entered into an agreement with TRISH in 2017 and during 2018 solicited proposals in two areas of interest identified by TRISH in connection with NASA's Medical Conditions List: Point-of-care Diagnostics and Deep Artificial Intelligence Medical Support.

Point-of-Care Translational Research Network

The Point-of-Care Technologies Research Network (POCTRN) was created by NIH to drive the development of appropriate point-of-care diagnostic technologies though collaborative efforts that simultaneously merge scientific and technological capabilities with clinical need. Additionally, the Network provides parallel educational activities that advance evidence-based medical practice in point-of-care testing in primary outreach, and low-resource environments, including global health settings.

In 2018, CIMIT was selected to be a Coordinating Center for the third 5-year cycle of POCTRN and in that role will assist each of the 4 other Centers across the U.S. to create multidisciplinary partnerships necessary to move technologies from an early stage of development into clinical testing.

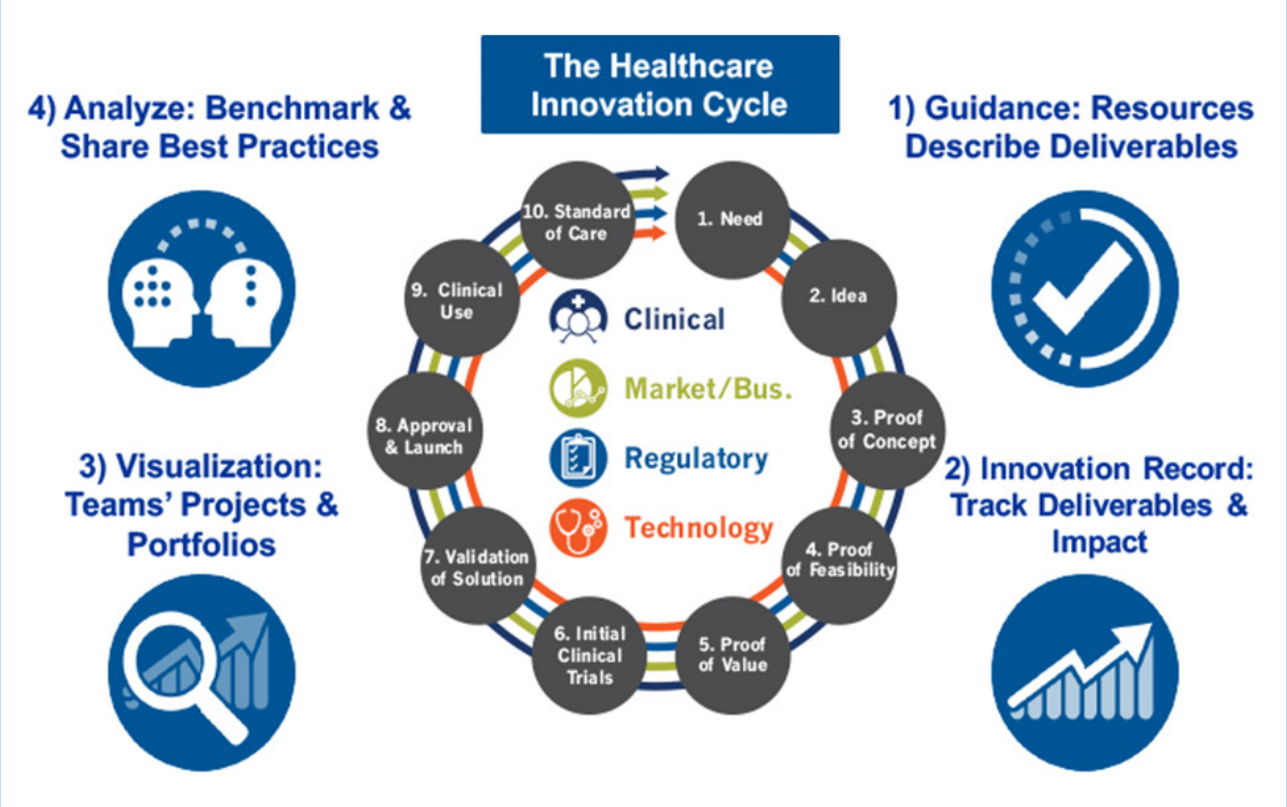
CIMIT's CRAASH Course

In 2018, CIMIT continued to hold healthcare commercialization boot camps, including in Europe. With funding from the National Science Foundation, CIMIT customized the traditional I-Corps program to focus on healthcare. The 10-week program facilitates the acceleration of healthcare innovations from the academic lab through commercialization. It is taught by industry veterans and is based on decades of experience from the Coulter Foundation, MIT, Yale, and CIMIT. The program formalizes development of a tested business model through the process of validating business hypotheses. Emphasis is placed on understanding economic buyers and their problems to be solved. Teams from around the country collect evidence to support the assumptions around the entire business (not just the science) through interviews and market testing. Each week teams present and defend findings to a panel of experts, attend lectures, and complete readings. Teams develop a commercialization roadmap based on data from actual customers and other stakeholders. Teams also receive 1:1 mentoring from successful healthcare entrepreneurs and group coaching from commercialization experts and investors.

CIMIT's GAITS

Based on lessons learned since its first Clinical Impact Study in 2010, CIMIT created the CIMIT Innovation Guidance and Impact Tracking System (GAITS) in 2017 and further developed its functionality in 2018. GAITS parallels the Department of Defense's well-established Technology Readiness Levels (TRLs) and establishes a sequence of 10 healthcare specific milestones. GAITS helps innovators navigate the complex journey

of innovation in healthcare and adds significant guidance to teams by defining core set of deliverables at each milestone in four domains critical to success in healthcare innovation: Clinical, Market/Business, Regulatory/ Approvals, and Technology. In addition, GAITS curated resources (descriptions, videos, templates, examples, etc.) are provided to help teams complete the deliverables. It also enables funders/institutions to provide teams with a secure site to track their progress and measure their impact. CIMIT has organized a consortium of leading healthcare innovation organizations across the globe to use GAITS and to build on CIMIT's experience of facilitating teams by providing an online tool that supports teams and portfolio managers to -increase the likelihood of innovations reaching patient care. The consortium will provide a robust database to study the innovation process in healthcare to establish and share best practices.



David E. Fisher, MD, PhD, Chief

The MGH Department of Dermatology has a distinguished role in the history of dermatology. This has manifested itself in delivering outstanding care, research, community outreach, and education of trainees across multiple stages of their careers. The core mission of the Dermatology Department is to provide patients from our community and from around the globe outstanding medical care that is tightly linked to our commitment to move the field of skin diseases into new frontiers of understanding and innovation. Our department houses an extremely busy dermatology clinic that this past year provided ~87,000 patient visits. In additional to general dermatologic care, our department offers specialized clinics in numerous areas including Pediatric Dermatology, Cosmetic Dermatology, High-Risk Non-melanoma Skin Cancer, Rheumatologic Dermatology, Hair-loss, Urgent-care, Dermatologic Surgery, and Inpatient Consults. Our Multi-disciplinary Pigmented Lesions/ Melanoma Clinic is tightly coordinated with MGH Cancer Center and was the first of its kind in the US, over 50 years ago. A laboratory research arm of our department is the Cutaneous Biology Research Center, which houses laboratories of 13 Principal Investigators who are faculty members of the department and conduct independent research programs. The topics covered by their investigations include stem cells, inflammation, drug discovery, skin signaling, ultraviolet radiation, itch, pain, pigmentation, epigenetics, hair biology, cancer immunotherapy, targeted therapy, metabolomics, cryobiology, lasers, and cell death mechanisms. This unit houses an unusually rich collection of cutting edge investigations ranging from basic biology to applied cutaneous medicine, and harbors numerous academic-industry collaborative initiatives. A portion of the Cutaneous Biology Research Center is dedicated to cancer immunotherapy research in a collaborative initiative together with MGH Cancer Center. Additional research faculty whose academic home is in Dermatology include researchers in the Wellman Center for Photomedicine, an MGH Thematic Center that has made seminal contributions to the current practice of dermatology.

In the year 2018, research and scholarly activities undertaken by faculty in the Department of Dermatology gave rise to 231 publications, as well as 267 speaking engagements. $20.6M research funding was spent from a cross section of funding sources which include NIH, Department of Defense, multiple Foundations, Industry partners, royalties, and philanthropy. The Department holds the leadership role and is home to a National Cancer Institute sponsored multi-million dollar Program Project Grant in Melanoma which is shared collaboratively with researchers across Harvard Medical School. Active research in Cancer Immunotherapy is prominent and includes a preclinical research partnership with MGH Cancer Center as well as multiple clinically oriented programs in skin cancer, including research initiatives. Our Dermatologic Epidemiology Program includes an active partnership with Harvard Medical School's Population Medicine Department as well as Global Health research which is carried out in collaboration with the Infectious Disease Unit at MGH and includes extensive studies on HIV-related dermatology in Kenya. The Clinical Unit for Research Trials in Skin (CURTIS) typically runs 15-20 active dermatology focused studies in our clinic. The MGH Department of Dermatology is very proud of its Community Service and Educational missions, which represent core priorities of the department. Free skin cancer screenings, dermatologic care to the homeless (including Boston Healthcare for the Homeless), and teaching of trainees from diverse constituencies, including high school, undergraduate college, medical school, and postgraduate clinical or research stages, comprise these valuable activities. Trainees travel to MGH Dermatology from overseas, and share the teachings at their home institutions. Finally, MGH Dermatology is proud of the numerous collaborations which exist across departments at MGH, including extensive interactions with the Cancer Center, Pathology, Anesthesia, Plastic Surgery, Radiation Oncology, Psychiatry, Infectious Diseases, Rheumatology, and many others.

Key research achievements

Baoen Chen, Jixiao Niu, Johannes Kreuzer, Baohui Zheng, Gopala K Jarugumilli, Wilhelm Haas, and Xu Wu* "Auto-fatty Acylation of Transcription Factor RFX3 Regulates Ciliogenesis", Proc. Natl. Acad. Sci. U S A, 2018,115(36):E8403-E12.

Regulatory Factor X 3 (RFX3) is a key transcription factor for cilia formation and function. This study revealed that auto-fatty acylation is a critical regulatory mechanism for RFX3 function. Fatty acylation is required for RFX3 dimerization, leading to transcription of cilia-associated genes. Importantly, fatty acylation of RFX3 regulates ciliogenesis and Hedgehog signaling pathways, which are associated with developmental and degenerative disorders known as ciliopathies. These results indicate a major role of auto-fatty acylation in the regulation of RFX3 function and cilio-genesis, providing a potential link between deregulation of fatty acid metabolism to ciliopathies and diabetes.

Al Labban, D., Jo, S.H., Ostano, P., Saglietti, C., Bongiovanni, M., Panizzon, R., and Dotto, G.P. (2018). Notch-effector CSL promotes squamous cell carcinoma by repressing histone demethylase KDM6B. J. Clin. Invest. 128, 2581-2599, doi.org/10.1172/JCI96915.

Whereas Notch genes play tumor-suppressing roles in squamous cell carcinoma (SCC), the transcription factor CSL promotes SCC development.

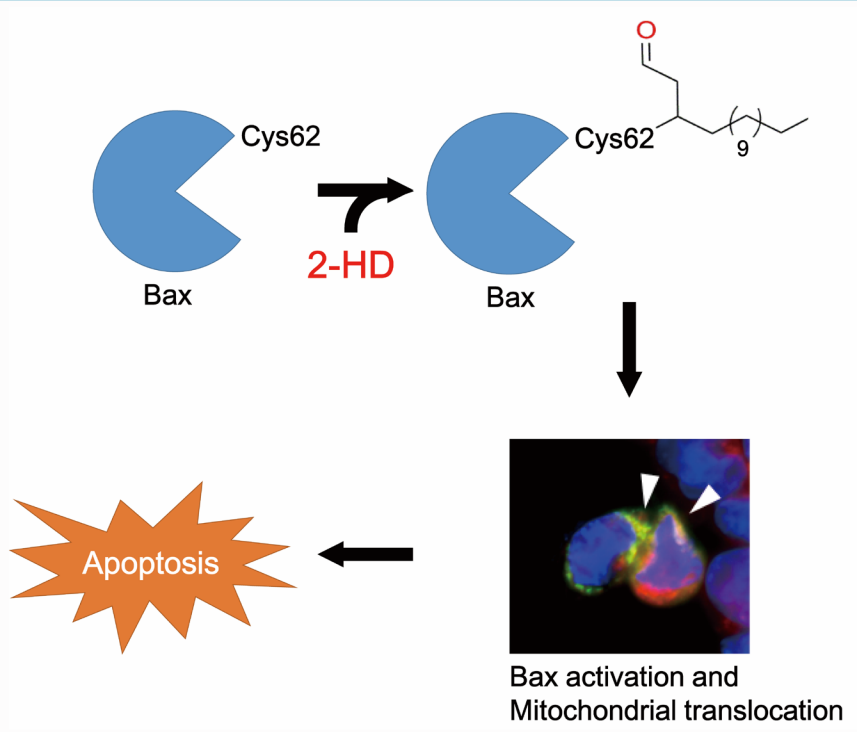
CSL expression decreased differentiated epidermal cells while increasing premalignant and malignant SCC lesions in skin, head/neck, and lung. Transcriptomic analyses revealed modulation of apoptotic, cell-cycle, and proinflammatory genes. The histone demethylase KDM6B is a direct CSL-negative target, with inverse roles of CSL in these malignancies.

Choo, M.-K., Kraft, S., Missero, C. and Park, J.M. The protein kinase p38α destabilizes p63 protein to limit epidermal stem cell frequency and tumorigenic potential. Sci. Signal. 2018; 11: 551

Analyzing skin tissue and cells from normal donors, premalignant keratoses or squamous cell carcinoma (SCC), and mouse models this paper found that p38α phosphorylates and thereby induces degradation of the transcription factor p63, particularly its tumor-associated isoform ΔNp63α. Loss of p38α increases p63 abundance in skin and thereby enhances expression of stem cell–associated genes, promoting stem cell outgrowth in skin. The findings also raise the possibility that p38α inhibitors used to treat other cancers (where p38α is tumor promotive) may cause secondary SCC in patients.

Gopala K. Jarugumilli, PuiYee Chan, Meilan Yang, Yang Sun, Baoen Chen, Jixiao Niu, Michael DeRan, Baohui Zheng, Rapheal A. Zoeller, Cheng Lin and Xu Wu. Chemical probe to identify the cellular targets of the reactive lipid metabolite 2-trans-hexadecenal. ACS Chemical Biology, 2018 May 18;13(5):1130-1136. doi: 10.1021/acschembio.7b01063.

Lipid-derived electrophiles (LDEs) are reactive metabolites which can covalently modify proteins and regulate diverse cellular processes. 2-trans-Hexadecenal (2-HD) is a byproduct of sphingolipid metabolism that accumulates in Sjörgen-Larsson Syndrome due to deficiency of its metabolizing enzyme ALDH3A2. This study generated an alkyne-2-HD derivative as a bioorthogonal probe to explore the functions of 2-HD, identifying >500 potential cellular targets. Among them, the pro-apoptotic protein Bax was covalently modified by 2-HD at a conserved Cys62 site. This work provides new chemical tools to explore cellular function of LDEs and study lipid metabolism in disease.



From Gopala et al: The lipid derived electrophile 2-trans-hexadecenal (2-HD) accumulates in patients lacking its metabolizing enzyme. An alkyne-2HD derivative was generated which identified proteins with which 2HD interacts, including the apoptosis regulator Bax.

David F. M. Brown, MD, Chief

Mission
The departmental research mission is to conduct innovative research that leads to improvement in the diagnosis and treatment of patients with emergency conditions. The scope of our research includes translational basic science, clinical investigation, and population health.

Focus
The role of the emergency physician is to provide rapid diagnostics and therapies for those with acute illness and injury. As such, our research focuses on the development and validation of new diagnostic strategies, treatments, and care delivery systems across a broad range of health conditions. Areas of active investigation include: cardiovascular and thrombotic emergencies, respiratory and allergic emergencies, neurologic emergencies, infectious disease emergencies, global health, emergency systems engineering, ultrasound, simulation in medical education, disaster preparedness, quality improvement and patient safety, physiologic monitoring, pediatric emergencies and health services research.

Over the past year we have continued to broaden our research portfolio to include more studies on pediatrics, geriatrics, vascular emergencies, telehealth, and critical care. We have increased our research support from federal sponsors, and continue to grow our research faculty, fellows and clinical research coordinator team.

Goals for 2019:
1. Continue to develop a strong pipeline of clinical investigations, and clinician and non-clinician researchers, to support a robust research infrastructure that can drive forward the departmental research mission.
2. Further leverage Epic to enable automated data acquisition methods where possible to support both interventional and observational investigations.
3. Hone departmental resources available to support and optimize our research infrastructure, including grants administration and finance, statistical support, and mentoring for young investigators.
4. Identify ways to leverage new technologies such as telehealth to support real-time research operations.

Achievements in 2018:

1. Hasegawa K, Stewart CJ, Celedón JC, Mansbach JM, Tierney C, Camargo CA Jr. Circulating 25-hydroxyvitamin D, nasopharyngeal airway metabolome, and bronchiolitis severity. Allergy. 2018 May;73(5):1135-1140.
Low circulating 25-hydroxyvitamin D (25OHD) levels are a risk factor for acute respiratory infection (e.g., bronchiolitis) in children. However, little is known about the relation of circulating 25OHD with the many downstream functional molecules in target organs (e.g., the airway) and with clinical outcomes. In this prospective multicenter study of infants hospitalized with bronchiolitis (MARC-35), we measured serum 25OHD levels and profiled the metabolome of 144 nasopharyngeal airway samples. Among 254 metabolites identified, we defined a set of 20 metabolites that are related to lower serum 25OHD and higher vitamin D-binding protein levels. Of these metabolites, 9 metabolites were associated with a significantly higher risk of positive pressure ventilation use. These metabolites were glycerophosphocholines esterified with proinflammatory fatty acids and sphingomyelins. The work not only delineates the pathobiology of infant bronchiolitis but also offers new avenues for bronchiolitis treatment.

2. Filbin MR, Lynch J, Gillingham TD, Thorsen JE, Pasakarnis CL, Nepal S, Matsushima M, Rhee C, Heldt T, Reisner AT. Presenting symptoms independently predict mortality in septic shock: Importance of a previously unmeasured confounder. Crit Care Med 2018 Oct; 46(10): 1592-1599.
We enrolled 654 emergency department patients admitted to MGH with septic shock over 1 year. We found that 37% of patients presented with vague symptoms, such as general weakness, malaise, fatigue, shortness of breath, or confusion: symptoms that lack any indication that infection is present. These patients had more delays in receiving antibiotics (likely due to delayed recognition of infection), and much higher rate of hospital death compared to those who presented with obvious symptoms of infection (34% versus 16%, $p < 0.01$). However, our analysis showed that the elevated death rate was not due to antibiotic delay or any other identifiable characteristic of the patients with vague symptoms. In addition to highlighting the difficulty of sepsis diagnosis upon initial presentation, our work uncovered a subgroup of patients with sepsis who have extremely high mortality, who do not respond in expected ways to standard therapies, and whose underlying biology must be explored to understand why sepsis is so deadly, and how to stop it.

3. Yun BJ, Borczuk P, Wang L, Dorner S, White BA, Raja AS. Evaluation of a Low-risk Mild Traumatic Brain Injury and Intracranial Hemorrhage Emergency Department Observation Protocol. Acad Emerg Med. 2018 Jul; 25(7):769-775.

We studied 296 patients admitted to the Emergency Department Observation Unit (EDOU) with traumatic intracranial hemorrhage, a population of patients who traditionally required hospital admission. Our EDOU has developed protocols to safely accommodate these patients and provide focused care, expert consultation and appropriate disposition, without requiring full hospital admission. This study demonstrated that an EDOU protocol safely reduced the need for hospital admission for traumatic intracranial hemorrhage from 26% pre-protocol to 13% post-protocol ($p < 0.01$). This work is important because it further demonstrates that thoughtful implementation of EDOU protocols can reduce the need for costly and unnecessary inpatient hospitalizations.

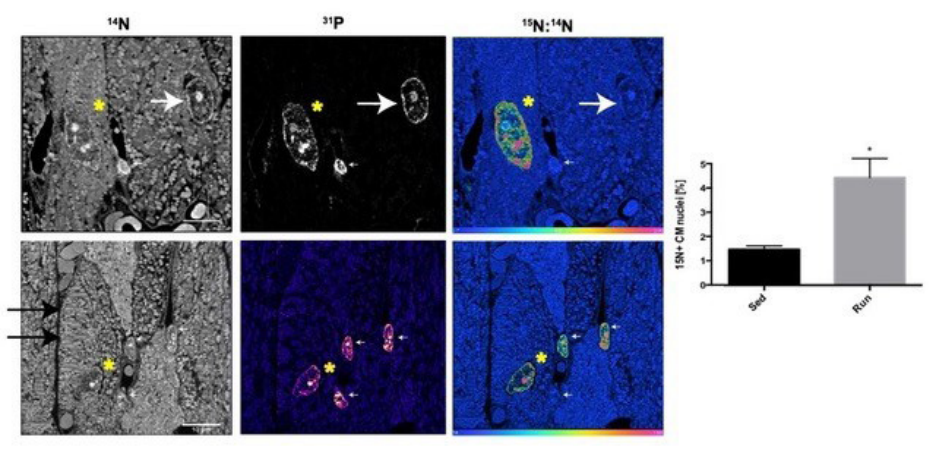
4. Samuels-Kalow M, Peltz A, Rodean J, Hall M, Alpern ER, Aronson PL, Berry JG, Shaw KN, Morse RB, Freedman SB, Cohen E, Simon HK, Shah SS, Katsogridakis Y, Neuman MI. Predicting Low-Resource-Intensity Emergency Department Visits in Children. Acad Pediatr. 2018 Apr;18(3):297-304.

This large, retrospective national administrative database analysis focused on Medicaid-insured pediatric patients who presented to emergency departments over one year that had low-resource-intensity (LRI) utilization visits. LRI visits are defined as ED visits without laboratory testing, imaging, procedures or hospitalization. Of 743,016 children studied, 5% had 3 or more emergency department (ED) visits over the following year, which accounted for over 20% of LRI ED visits. We found that children with chronic conditions, and children with a history of high ED use were at risk for high utilization in the future. Furthermore, we developed and validated a population claims-based predictive model for future high-frequency LRI ED use in Medicaid-insured children. This model can be used by clinical programs aimed at reducing high ED use in children by prospectively identifying high-risk children for interventions that aim to reduce low-value care and improve appropriate use of the ED. This study is an important example of leveraging large, claims-based databases to inform clinical programs in emergency medicine that influence care and enable targeted interventions to improve appropriate utilization.

Katrina A. Armstrong, MD, Physician-in-Chief

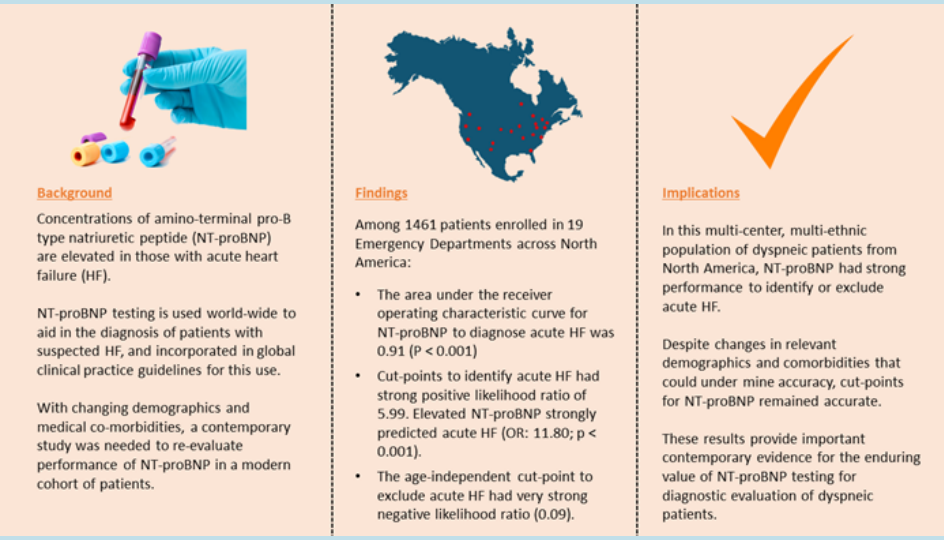
Driven by its core pillars of clinical care, education, and research, the Department of Medicine continues to raise the bar for excellence in health care. By virtue of being the largest department at the Massachusetts General Hospital, the Department plays a critical role in advancing the strategic priorities of the entire hospital and the MGPO. From high quality care to diversity and inclusion initiatives to innovative medical discoveries, the Department's faculty, researchers, and staff hold crucial responsibilities in fulfilling MGH's mission.

The Department cultivates multidisciplinary relationships that breed success, in collaboration with similarly focused hospital-wide initiatives. The Department remains motivated in its efforts to foster inquiry and learning, transform training, invest in diverse human capital, and provide exceptional care to patient populations. In research, the Department continues to build a community that incubates innovation and leads to major developments in medicine. The Department boasts internationally recognized investigators who are dedicated to producing research that advances science and improves care for patients. Through our multiple, standard-setting research units, centers and programs, the Department of Medicine has become a leader in medical research.



Increased cardiomyogenesis in the exercised adult mouse heart. A) 15N-Thymidine was administered for 8 wks to 8-10 wk old adult mice undergoing voluntary wheel running. Mass 14N image (top left, bottom left) shows histological details such as sarcomeres (large black arrows), mass 31P image (middle, top and bottom) shows nucleus and chromatin condensation, while the hue-saturation-intensity-image (mosaic, top right) demonstrates nuclear 15N labeling of a cardiomyocyte (yellow asterisk), non labeled-cardiomyocytes (large white arrow) can also be found in that section. B) Quantification reveals a 4.6-fold exercise-induced increase in cardiomyocytes that have undergone mitosis after 8 weeks of exercise in comparison to sedentary controls.

In the **Cardiology Division,** Anthony Rosenzweig, working with the Lee Laboratory at BWH, were interested in the many forms of heart disease associated with a loss of cardiomyocytes. Unfortunately, the adult heart has a very limited capacity to regenerate or grow the new cardiomyocytes needed for repair after injury. Moreover, little is known about the physiological cues that regulate this process in the adult heart. Collaboratively, these two labs used multiphoton ionization mass spectrometry (MIMS)-based imaging using thymidine labeled with the stable isotope, 15N to demonstrate that exercise increases cardiomyogenesis 4.6-fold in the adult heart over 2 months. These studies establish exercise as the first physiological stimulus capable of driving birth of new cardiomyocytes in adult mammals. The investigators went on to identify a microRNA pathway necessary for this process. These studies were published in Nature Communications (1).



Since seminal studies performed at the MGH more than 15 years ago established value of testing for N-terminal pro-B type natriuretic peptide (NT-proBNP) for diagnosis or exclusion of acute heart failure (HF), this biomarker is used world-wide to support to clinical judgment for this role and diagnostic cut-offs for NT-proBNP first established by MGH investigators are now in clinical practice guidelines from several continents. Accordingly, need existed to re-visit the optimal application of NT-proBNP in a contemporary population of patients with acute dyspnea. James Louis Januzzi and Hanna Gaggin (2) led a multi-center study of 1,461 patients presenting to Emergency Departments in North

America with acute dyspnea were studied (2). NT-proBNP results had high area under the receiver operating characteristic (ROC) curve of 0.91 ($p<0.001$). For diagnosis of HF, previously established age-stratified cut-offs (450 pg/mL, 900 pg/mL, 1800 pg/mL for ages <50, 50–75 and >75 years) remained accurate (positive likelihood ratio of 5.99); elevated NT-proBNP strongly predicted acute HF (OR: 11.80; $p < 0.001$). For excluding HF, the established age-independent rule-out cut-off (300 pg/mL) had superb performance (negative likelihood ratio of 0.09). Thus, the ICON-RELOADED Study provides useful evidence for the enduring value of NT-proBNP testing for the diagnosis or exclusion of acute HF in dyspneic patients.

The **Clinical and Translational Epidemiology Unit**, a research unit within the Mongan Institute, studied factors predisposing to diverticulitis. In a study published in Gastroenterology (3), Wenjie Ma, found that body mass index >35 was associated with 42% increase in risk of diverticulitis among 46,079 women participating in the Nurses' Health Study, and that higher waist circumference, higher waist-to-hip ratio and weight gain of over 20 kg from weight at age 18, were all risk factors for diverticulitis. Furthermore, Manol Jovani in a study accepted for publication in the American Journal of Gastroenterology reported for the first time that both current and past use of menopausal hormones are risk factors for diverticulitis. In a study published in JAMA Oncology (4), Tracey Simon examined the influence of aspirin on the risk for developing hepatocellular carcinoma (HCC), in two prospective, nationwide cohorts of 133,371 men and women, with more than 26 years of follow-up. Compared with non-regular aspirin use, regular aspirin use (i.e. ≥2 standard-dose tablets per week), was associated with a 49% reduction in risk for developing incident HCC. This association appeared dose-dependent, with the greatest magnitude of risk reduction found in those taking >5 tablets per week. Similar associations were not found with use of non-aspirin NSAIDs. This study provided the first prospective evidence from a nationwide population for a dose-dependent inverse association between aspirin use and incident HCC risk. Erica Warner examined the impact of a 2015 Massachusetts law requiring that women receive written notification of their breast density following a mammogram. Published in Academic Radiology (5), a survey of 338 MGH patients found that most women were unaware of the law, unsure what breast density meant and what they were supposed to do after notification. Similar results were observed in a qualitative interview study of 20 patients at BWH, accepted for publication at BMC Women's Health. Women reported the need for additional information, guidance and support from healthcare providers to make sense of breast density notification and its personal implications. Alisa Manning in a study published in the PNAS (6) described rare genetic variants associated with type 2 diabetes risk within the non-coding genome. In a paper published in PLoSOne she studied the contribution of lifestyle factors to cardio-metabolic disease. Subsequently, in the largest study of gene-lifestyle interaction performed to date, published in the American Journal of Human Genetics, she and collaborators describe potential genetic mechanisms through which alcohol consumption and smoking behavior increased risk for hypertension.

In the past year, the **Disparities Research Unit** reported the results of our NIDA-funded International Latino Research Partnership clinical trial in a paper accepted for publication in JAMA Network Open. This project tested a novel intervention to treat migrant Latinos with co-occurring substance use and mental health problems in primary care and community agencies in the US and Spain. They additionally successfully completed recruitment for the NIA/NIMH-funded Positive Minds Strong Bodies clinical trial, which tests an intervention to reduce mental and physical disability among ethnic minority elders. Working together with organizations in Massachusetts, New York, Florida, and Puerto Rico, they enrolled 307 participants in the trial, and offered in the intervention in English, Spanish, Mandarin and Cantonese. Their NIMHD-funded Mechanisms Underlying Racial/Ethnic Disparities in Mental Disorders study joins together data from 5 US epidemiological surveys linked to the Collaborative Psychiatric Epidemiological Surveys (CPES) to address racial/ethnic disparities in onset, persistence, and severity of mental disorders. In the past year three papers were accepted for publication stemming directly from project analyses. These include analysis of race/ethnicity, nativity, and lifetime as well as 12-month risk and prevalence of mental disorders, and racial/ethnic variation in trauma-related psychopathology. Their William T. Grant Foundation-funded youth and community-partnered research project, MGH PhotoStories, completed data collection (including 150 qualitative interviews and over 700 photos) and worked with community members to interpret results through four community forums in Revere, East Boston, Charlestown, and Chelsea.

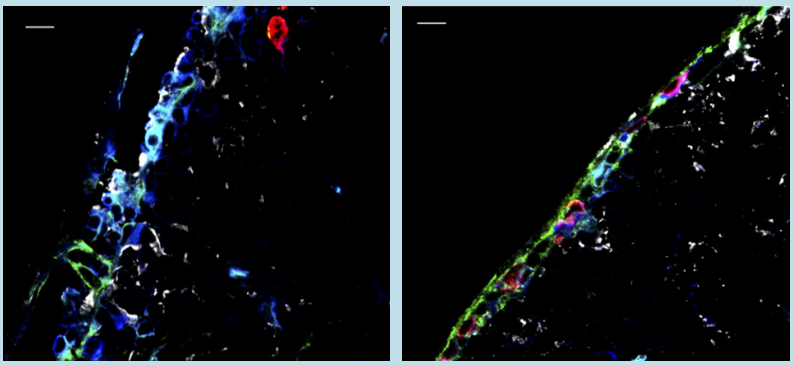
In the **Reproductive Endocrine Unit**, Margaret Lippincott led a study to design new methods to uncover the cause of mendelian disease. The genetic causes of many Mendelian disorders remain undefined. Factors such as lack of large multiplex families, locus heterogeneity, and incomplete penetrance hamper these efforts for many disorders. The increasing availability of large-scale public sequencing databases such as Genome Aggregation Database (gnomAD) can enable burden testing using these databases as controls. However, there exist various challenges with using public databases as controls, including lack of individual-level data, differences in ancestry, and differences in sequencing platforms and data processing. The current study used whole-exome sequencing from 393 individuals with congenital hypogonadotropic hypogonadism to develop new methods for gene discovery. For controls, publicly available large-scale exome sequencing data from gnomAD ($n = 123{,}126$) was

used. A gene-based burden testing strategy and software to perform burden testing against publicly available data was developed and tested sequentially to identify genes with enrichment of rare protein-altering variants in the case cohort. Ultimately, this methodology reliably "re-discovered" genes previously implicated in this disease and bolstered evidence for an existing candidate gene. These methods demonstrate that even in a rare disorder with substantial locus heterogeneity, it is possible to rediscover known genes as well as validate candidate genes. This work was published in the American Journal of Human Genetics (7).

In the **Diabetes Unit**, to identify biological pathways causing type 2 diabetes, Miriam Udler and Jose Florez performed cluster analysis of 94 genetic loci associated with type 2 diabetes using available genome-wide association data for 47 metabolic traits. In a study published in PLoS Med (8) the authors applied the novel clustering approach Bayesian Non-negative Matrix Factorization in 17,365 individuals with type 2 diabetes. In contrast to previous attempts, this method allows for "soft" clustering, whereby a locus can belong to more than one cluster. This approach is better suited for diabetes genetics research, since each genetic locus can affect one or more genes, impacting one or more pathways. They found five predominant clusters, likely representing two different forms of insulin deficiency and three different forms of insulin resistance. Additionally, they showed that genetics can be used to stratify individuals with type 2 diabetes, defining groups of individuals based on their genetics who in aggregate displayed distinct clinical features representative of the five clusters. Approximately 30% of individuals could be placed in the extreme of one cluster, and 75% of these were placed in the top decile of a single cluster. In addition, the genes captured by each cluster seemed to be transcriptionally active in tissues relevant to the physiology represented by each cluster. This analysis yielded biological interpretable groupings of genetic loci, pointing to key biological pathways and a more holistic understanding of diabetes genetics. This genetically anchored but physiologically informed framework is therefore a first step toward precision medicine for type 2 diabetes, and illustrates an approach that could be applied to many other complex diseases.

Camille Powe and Marie-France Hivert leveraged the data accrued in two large pregnancy cohorts (Genetics of Glucose regulation in Gestation and Growth [Gen3G] and Hyperglycemia and Adverse Pregnancy Outcome [HAPO]) to test whether genetic risk scores for fasting glucose, fasting insulin, insulin secretion, and insulin sensitivity discovered outside of pregnancy influence GDM risk. In a study published in Diabetes (10) they found substantial genetic overlap, laying the foundation for elucidating the heterogeneity of GDM and implementing precision medicine in this condition (9).

In the **Division of Rheumatology, Allergy & Immunology** and the **Center for Immunology & Inflammatory Diseases**, Caroline Sokol and Andrew Luster addressed the question of how allergic responses to innocuous environmental antigens develop. Immune responses start when activated dendritic cells – innate immune cells that surveil the body for signs of damage or infection – move to the lymph node to activate the antigen-specific adaptive immune response. This movement of dendritic cells, from the peripheral tissues to the lymph node, has long been thought to be solely controlled by activation-induced dendritic cell upregulation of the chemokine receptor CCR7. This paradigm was established in models of bacterial and viral infection, but it did not explain the observations that allergens induce dendritic cell migration to the lymph nodes without dendritic cell upregulation of CCR7. This apparent contradiction was addressed in a recent study published in Immunity (10) showing that the migration of allergen-activated dendritic cells is actually a two-step process. The first step, which consists of activated dendritic cells exiting the peripheral tissues and flowing through lymphatic vessels to the lymph node, is mediated by relatively low-level expression of CCR7. The second step, which was previously undescribed, occurs when these dendritic cells reach the border of the lymph node – the subcapsular sinus space. Here, dendritic cells must await a second chemokine signal CCL8, produced by allergen-activated macrophages that reside on the floor of the subcapsular sinus. This CCL8 signals through CCR8, which is specifically expressed on dendritic cells involved in allergic immune responses, to promote their entry into the lymph node parenchyma where they can initiate T helper cell activation and differentiation. These observations define a new, previously undescribed step in dendritic cell migration to allergens and reveal a role for lymph node resident macrophages in controlling



Allergen-activated CD301b+ dendritic cells pass across the floor of the lymph node subcapsular sinus space in wild type, but not Ccr8-/- mice. The subcapsular sinus space is outlined by gp38+ lymphatic endothelium (green) and CD169+ macrophages (white). CD11c+ dendritic cells (blue) migrate from the periphery via the afferent lymphatics and enter the lymph node by crossing the subcapsular sinus floor. Allergen-responsive CD11c+CD301b+ (blue & red) dendritic cells require CCR8 to cross the floor of the subcapsular sinus and become stuck in the subcapsular sinus in Ccr8-/- mice.

the subset-specific entry of dendritic cells into the lymph node. Future study will reveal whether similar two-step pathways involving other chemokine ligands and receptors are involved in the subset-specific migration of various dendritic cell subsets. Regardless, this study reveals the CCL8/CCR8 pathway to be a possible therapeutic target to treat or prevent allergic diseases while keeping other immune responses intact and unaffected.

Kim Blumenthal published a population-based analysis in the British Medical Journal (11) of outpatient records of a large number of British patients that revealed that those believed to be allergic to penicillin had significantly increased risks of contracting the dangerous infections MRSA (methicillin-resistant Staphylococcus aureus) and Clostridium difficile (C. difficile). The study found that much of that increased risk can be attributed to the use of broad-spectrum alternative antibiotics after documentation of a penicillin allergy. MRSA and C. difficile are major health risks worldwide. According to the Centers for Disease Control and Prevention, 2 million people are infected with resistant bacteria every year and at least 23,000 people die each year as a direct result. C. difficle is considered one of the three most serious threats ("urgent") by the Centers for Disease Control and Prevention. C. difficile causes over a half a million infections in the US per year and over 30,000 patients die within 30 days of the initial diagnosis. This paper elucidated a pathway between a newly documented penicillin allergy, which results in alternative antibiotic exposure, which then results in MRSA and/or C. difficile. Because 95% of the 32 million US patients with a penicillin allergy in their medical record are found not to be truly allergic, this study identifies appropriate penicillin allergy evaluations – which is done in less than 1% of patients with recorded penicillin allergy – as an essential contributor to the globally important outcomes of antibiotic stewardship, reducing antibiotic resistance and health-care-associated infections.

Shariq Usmani and Thorsten Mempel in a study published in Cell Host Microbe (12) identified a specific function for the Nef protein found in HIV and related viruses that appears to slow down viral spread in the earliest stages of infection but help the virus survive later on by evading the immune response. Recent studies by Mempel's team have suggested that – in contrast to the conventional view that HIV spreads throughout the body as free viral particles – the virus can be transported by infected T cells that travel through tissues and the circulatory system and then spread the infection by direct contact with uninfected cells.

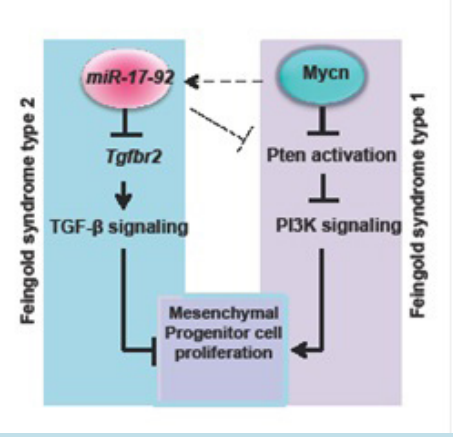
In **Infectious Disease**, with global goals of providing HIV treatment to over 25 million people in sub-Saharan Africa, it is critical to clarify the toxicity profiles of regimens commonly used in that region. Although efavirenz is widely used as a first-line therapy in Africa, it has been removed from this status in the United States and Europe, in part because of its association with depression and suicidal ideation in Caucasian populations. In a prospective cohort study of approximately 700 individuals starting HIV treatment in Uganda, Mark Siedner and colleagues compared the incidence of suicidal ideation and depressive symptoms in those taking efavirenz to those taking other HIV-related therapies. They found no evidence of increased suicidal ideation in people taking efavirenz and a signal for decreased incidence of depressive symptoms. These results offer reassuring data for efavirenz use in sub-Saharan Africa and reinforce the importance of the study of therapeutics in the sub-populations in which they are used. Oral cholera vaccines are promising tools for global cholera control but little is known about their effectiveness outside the historically cholera-endemic areas of Asia. In this four-year study, Louise Ivers and colleagues measured the long-term effectiveness of oral cholera vaccine in two regions of rural Haiti, where a massive cholera outbreak began in 2010. The results demonstrated high levels of protection from the vaccine used. These findings are already being incorporated into global policy on cholera control and prevention (13). Many bacterial pathogens use nanomachines to inject molecules into human cells. Understanding how these molecules alter human cells is key to gaining insights into how these bacteria cause infections. Because these molecules often display functions that are redundant with other molecules delivered by these pathogens, it can be difficult to decipher the function of the molecules using loss of function mutations. To address this limitation, Cammie Lesser and colleagues developed an approach to study these molecules on their own, by introducing them and a nanomachine into non-pathogenic bacteria. Their research uncovered new functions for several molecules using this approach, thus demonstrating its utility (14). Global typhoid control programs are being seriously hampered by the absence of accurate diagnostics, especially in endemic zones where it is difficult to distinguish current from previous infection. Using proteoimmunomics and machine learning approaches, Richelle Charles and colleagues discovered that assessing serum IgA responses against two Salmonella Typhi antigens (Hemolysin E and Salmonella Typhi lipopolysaccharide) accurately identifies febrile patients with typhoid fever. They performed discovery analysis using samples from patients with typhoid fever in Bangladesh and validated the approach using samples from febrile patients with typhoid fever in Nepal (15). Erica Shenoy and colleagues report the transmission of Klebsiella pneumonia carrying mcr-1, a recently identified plasmid-mediated mobile colistin resistance gene, via duodenoscope. This is the first documented nosocomial transmission of mcr-1-harboring bacteria in the United States. Two patients had highly related mcr-1-positive K. pneumonia isolated from clinical cultures; a duodenoscope was the only identified epidemiological link. Flaws in duodenscopy design leading to transmission of multidrug-

resistant organisms persist despite recent initiatives to improve device safety (16). Public health detailing is a quality improvement strategy in which governmental or public health organizations use the marketing methods of pharmaceutical companies to educate clinicians about best practices. This report by Kevin Ard and colleagues examines public health detailing programs designed to improve prescribing of HIV pre-exposure prophylaxis in New England and New York City and outlines strategies to increase the effectiveness of public health detailing for pre-exposure prophylaxis (17).

In the **Vaccine and Immunotherapy Center (VIC)**, Dr. Ruxandra Sîrbulescu published a study showing that purified mature naive B lymphocytes can be used as a novel cell-based immunotherapy to improve healing of acute and diabetic wounds after a single topical application (18). Chronic wounds affect 12-15% of patients with diabetes and are associated with a drastic decrease in their quality of life. This study showed that B cell treatment accelerated acute and chronic wound closure by approximately 25% in an obese diabetic mouse model of wound healing developed in his laboratory,

In the **Division of General Internal Medicine**, Chana Sacks analyzed Medicare Part D spending suggests $925 million is the difference between what Medicare reported spending in 2016 for 29 brand-name combination drugs and what the estimated spending would have been if generic components had been used for the same number of doses. Prescriber education and more rational substitution policies may help promote generic substitution and therapeutic interchange to save money in the Medicare drug benefit program (19). In a prospective study, Karen Sepucha and colleagues measured the percentage of patients who were well-informed and received treatments that matched their preferences. Overall about one third of the sample facing decisions about common, elective orthopedic procedures met these criteria for informed, patient-centered (IPC) decisions. Regardless of whether the patient had surgery or not, patients who made IPC decisions had better overall and disease-specific quality of life compared to those who did not. In addition, patients who made IPC decisions reported significantly less regret and more satisfaction with their symptoms and treatment. The study provides important new evidence of the relationship between shared decision making and health outcomes, suggesting that how we make decisions with our patients may impact how well they do (20).

In the **Endocrine Unit**, Murat Bastepe and his group developed a mouse model to understand the role of the Gsp oncogene (Gsα-R201H), a mutant of the stimulatory G protein alpha-subunit (Gsα), in various tissues. Using this mouse model, they investigated the developmental effects of stimulatory G protein (Gs) signaling in the growth plate. They revealed that a tight control of Gs signaling is critical for long bone growth and provided novel insights into the pathophysiology of skeletal disorders caused by aberrant cAMP signaling, such as McCune-Albright Syndrome and Albright's Hereditary Osteodystrophy. The findings were published in Bone earlier in the year. In other work, they determined that the extra-large variant of the Gsα subunit, i.e. XLαs, regulates skeletal production of the phosphaturic hormone FGF23. Their results indicate that XLαs mediates FGF23 synthesis by promoting signaling downstream of a distinct class of heterotrimeric G proteins, namely Gq/11. These findings have important implications in human diseases caused by dysregulated FGF23 actions. While investigating the skeletal disorder Feingold syndrome, Dr. Tatsuya Kobayashi and his group uncovered key molecular mechanisms leading to reduced proliferation of mesenchymal progenitors. Feingold syndrome, which is characterized by microcephaly, short stature, and brachysyndactyly, is caused by a mutation in MYCN, a member of the Myc family of proto-oncogenes (type 1), or by a mutation in the microRNA-17-92 (type 2). Traditional perspectives suggested that both types of the disease are caused by a direct interaction of the microRNA with Myc. However, using rigorous in vitro and in vivo studies in mice, Dr. Kobayashi demonstrated that aberrations in two distinct signaling pathways cause these syndromes; the Pten/PI3K pathway plays the major role in Feingold syndrome type 1, and the TGF-β pathway in type 2. This study was published in Nature Communications (21).



In **Nephrology,** Andrew Allegretti identified angiopoietin-2 as a novel marker of worsening kidney function and death among individuals with severe liver disease (22). The association between serum angiopoiein-2 levels and mortality was significant even after adjusting for other known risk factors in this context, including the MELD score. In addition to highlighting a promising biomarker with potential clinical utility, this study enhances interest in endothelial function and vascular permeability as a key pathway in hepatorenal syndrome and ultimately as a potential therapeutic target for what is currently a highly fatal condition with minimal therapeutic options short of liver transplantation. In collaboration with basic scientists in the Gastroenterology Division, Dr. Allegretti is pursuing these questions in model systems. Although acute kidney injury

(AKI) with recovery is often assumed to be of no long-term consequence, Jessica Tangren found that a prior episode of AKI warrants careful consideration in women of child bearing age (23). More specifically, in a retrospective study of MGH records dating back to 1998, she found that a prior episode of AKI was significantly associated with the risk of future preeclampsia and with the delivery of infants that are small for gestational age. Thus history of AKI before pregnancy, despite apparent full recovery, mandates enhanced surveillance during pregnancy. Acidosis is an important complication of AKI and CKD attributable in large part to the loss of kidney acid excretion. Current treatment approaches are limited to exogenous base supplementation and approaches to enhancing acid excretion are lacking. Sylvie Breton outlined a novel approach to this problem, showing that adenosine or other agonists of ADORA2A and ADORA2B purinergic P1 receptors increase kidney acid excretion by inducing vacuolar H+ ATPase membrane accumulation in medullary type A intercalated cells in a cAMP/PKA pathway-dependent mechanism (24).

In **Pulmonary and Critical Care**, David Lagares published a high impact paper in Science Translational Medicine (25) demonstrating that fibroblast-to-myofibroblast differentiation driven by matrix stiffness increases the mitochondrial priming (proximity to the apoptotic threshold) of these activated cells. Persistent myofibroblast activation distinguishes pathological fibrosis from physiological wound healing, suggesting that therapies selectively inducing myofibroblast apoptosis could prevent progression and potentially reverse established fibrosis in diseases such as scleroderma, a heterogeneous autoimmune disease characterized by multiorgan fibrosis. Mitochondria in activated myofibroblasts, but not quiescent fibroblasts, are primed by death signals such as the proapoptotic BH3-only protein BIM, which creates a requirement for tonic expression of the antiapoptotic protein BCL-XL to sequester BIM and ensure myofibroblast survival. Myofibroblasts become particularly susceptible to apoptosis induced by "BH3 mimetic" drugs inhibiting BCL-XL such as ABT-263. ABT-263 displaces BCL-XL binding to BIM, allowing BIM to activate apoptosis on stiffness-primed myofibroblasts. Therapeutic blockade of BCL-XL with ABT-263 (navitoclax) effectively treats established fibrosis in a mouse model of scleroderma dermal fibrosis by inducing myofibroblast apoptosis. Using a BH3 profiling assay to assess mitochondrial priming in dermal fibroblasts derived from patients with scleroderma, he demonstrated that the extent of apoptosis induced by BH3 mimetic drugs correlates with the extent of their mitochondrial priming, indicating that BH3 profiling could predict apoptotic responses of fibroblasts to BH3 mimetic drugs in patients with scleroderma. Together, his findings elucidate the potential efficacy of targeting myofibroblast antiapoptotic proteins with BH3 mimetic drugs in scleroderma and other fibrotic diseases. Jay Rajagopal studied the cellular composition and hierarchy of the mouse tracheal epithelium by single-cell RNA-sequencing (scRNA-seq) and in vivo lineage tracing in a study published in Nature (26). They identify a rare cell type, the Foxi1+ pulmonary ionocyte; functional variations in club cells based on their location; a distinct cell type in high turnover squamous epithelial structures that we term 'hillocks'; and disease-relevant subsets of tuft and goblet cells. We developed 'pulse-seq', combining scRNA-seq and lineage tracing, to show that tuft, neuroendocrine and ionocyte cells are continually and directly replenished by basal progenitor cells. Ionocytes are the major source of transcripts of the cystic fibrosis transmembrane conductance regulator in both mouse (Cftr) and human (CFTR). Knockout of Foxi1 in mouse ionocytes causes loss of Cftr expression and disrupts airway fluid and mucus physiology, phenotypes that are characteristic of cystic fibrosis. By associating cell-type-specific expression programs with key disease genes, we establish a new cellular narrative for airways disease.

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26. Nature. 2018 Aug;560(7718):319-324. doi: 10.1038/s41586-018-0393-7. Epub 2018 Aug 1. Montoro DT1,2,3,4, Haber AL4, Biton M4,5, Vinarsky V1,2,3, Lin B1,2,3, Birket SE6,7, Yuan F8, Chen S9, Leung HM10,11, Villoria J1,2,3, Rogel N4, Burgin G4, Tsankov AM4, Waghray A1,2,3,4, Slyper M4, Waldman J4, Nguyen L4, Dionne D4, Rozenblatt-Rosen O4, Tata PR12,13,14,15, Mou H16,17, Shivaraju M1,2,3, Bihler H18, Mense M18, Tearney GJ10,11, Rowe SM6,7, Engelhardt JF8, Regev A19,20, Rajagopal J21,22,23,24.

Molecular Biology

Department Report

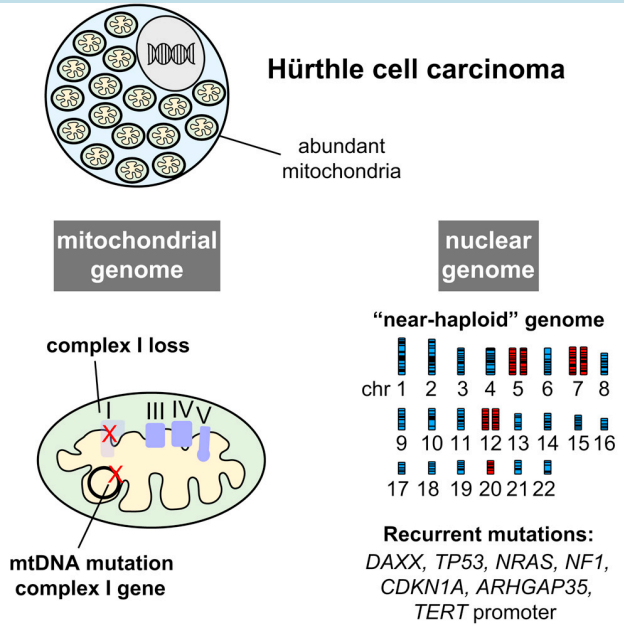
Robert E. Kingston, PhD, Chief

The Department of Molecular Biology at Massachusetts General Hospital is a part of both the research community of the hospital and the Division of Medical Sciences of the Harvard Graduate School of Arts and Sciences. We also have a strong connection with the Department of Genetics at HMS, where most of our scientists hold concurrent appointments. Members of the Department carry out fundamental studies in bioinformatics, genetics, molecular biology, and related disciplines, on a variety of topics at the cutting edge of science and medicine. Our mission is to propel scientific breakthroughs for the benefit of MGH's patients and the worldwide community. Our central priority is to hire the best early-career scientists and help them to develop the next-generation science that will advance biomedicine.

At present, approximately 225 people, including 18 faculty, about 166 postdoctoral fellows and graduate students, and about 41 staff members, comprise the Department of Molecular Biology. Our areas of excellence include:

- Chromatin remodeling, long noncoding RNAs, X-chromosome inactivation (Kingston, Lee), epigenetics, (Hochedlinger, Kingston, Lee), reprogramming & pluripotency (Hochedlinger).
- Human genetics, mitochondrial physiology and disease (Mootha), and mitochondrial membrane structure and proteins (Mootha, Chao).
- Plant biology, signaling, and pathogen defense. Innate immune signaling pathways (Ausubel, Sheen).
- Bacterial pathogenesis (Ausubel, Hung) and fungal pathogenesis (Ausubel).
- Cytoskeletal assembly, dynamics, and transport (Blower, Subramanian), macromolecular assembly dynamics (Chao).
- Chemical biology (Hung, Szostak). Synthetic biology, chemical evolution, and protocells (Szostak).
- Insulin signaling (Avruch, Ruvkun). Kinase/GTPase mediation of mitogen and stress signaling (Avruch).
- V(D)J recombination (Oettinger), innate and adaptive immunity (Xavier).
- Synapse formation, transmission, and trafficking (Kaplan).
- miRNA and RNAi pathways; aging in C. elegans; search for extraterrestrial life (Ruvkun).
- Clinical gastroenterology, inflammatory bowel disease, Crohn's disease, celiac disease and ulcerative colitis, gut microbiome (Xavier).
- Pathophysiology and somatosensory defects in Autism Spectrum Disorder (Orefice).

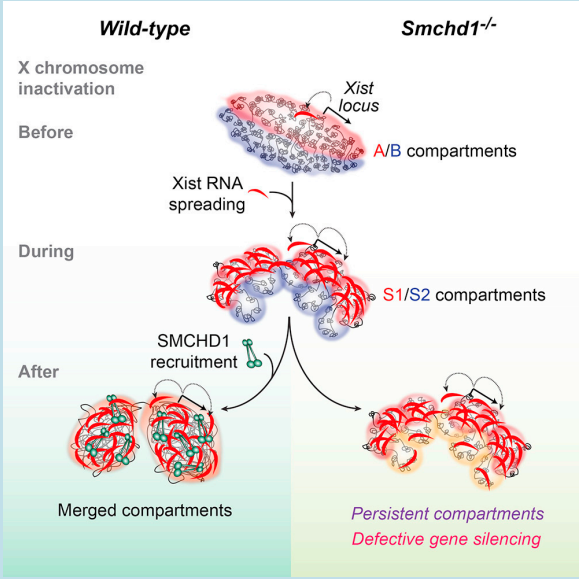
The Department of Molecular Biology is happy to welcome Ramnik Xavier and Lauren Orefice as its newest faculty members. Dr. Xavier has been a long-standing affiliate of the Department throughout his time at MGH. He officially joined the Department in January 2018. Dr. Orefice comes to us from Harvard Medical School, where she built a cutting-edge research platform focused on the pathophysiology of Autism Spectrum Disorder. She launched her laboratory at MGH in January 2019. We are excited to have Drs. Xavier and Orefice, and look forward to helping them advance their research programs.



Work from the Mootha lab, done in collaboration with several investigators at MGH, characterized dramatic genome-wide changes in Hürthle cell carcinoma (Gopal et al, Cancer Cell. 2018 Aug 13;34(2):242-255).

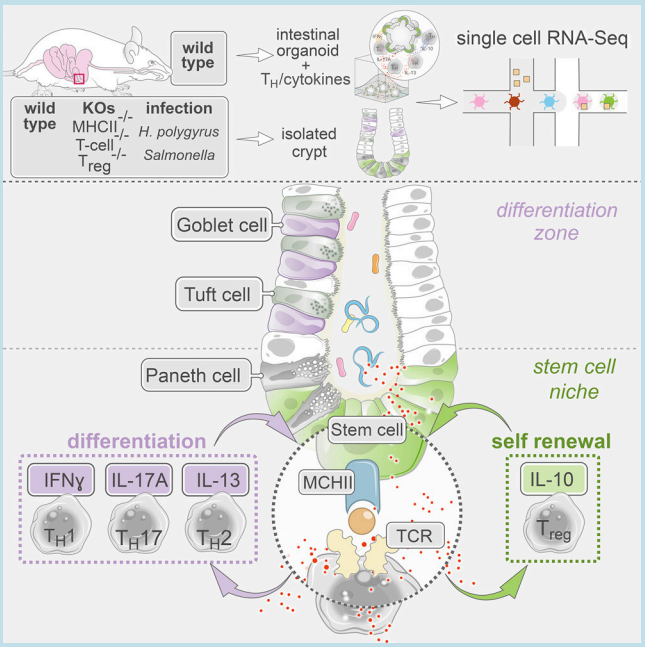
Our laboratories focus on enhancing the understanding of biology and disease through the pursuit of fundamental and translational research. In one recent example of our work, the Mootha lab (with colleagues from MGH and elsewhere) turned their attention to Hürthle cell carcinoma (HCC), a form of thyroid cancer with an extraordinary accumulation of mitochondria and a tendency for clinically aggressive behavior (Gopal et al, Cancer Cell. 2018 Aug 13;34(2):242-255). This highly collaborative effort utilized whole exome sequencing to perform a joint analysis of the nuclear and mitochondrial genomes of HCC primary tumors, locoregional recurrences, and distant metastases. The study revealed unique driver events that were maintained during tumor evolution, including disruptive mitochondrial DNA mutations in complex I subunits (the first step in aerobic respiration) as well as widespread loss of multiple chromosomes culminating in a "near-haploid" state. These sequence and copy number alterations in the mitochondrial and nuclear genomes of HCC and its metastases spotlight the molecular underpinnings of this cancer and provide inspiration for novel therapeutic strategies that may leverage these changes.

Jeannie Lee's laboratory recently published a study that illuminates the role of a protein called SMCHD1 ("structural-maintenance-of-chromosomes hinge domain containing 1") in X chromosome inactivation, the process by which mammals ensure proper X chromosome gene dosage in females (Wang et al, Cell. 2018 Jul 12;174(2):406-421). The X inactivation process depends on a stepwise folding of the X chromosome, with distinct intermediates, each having a particular structure. Unlike other chromosomes, the inactive X chromosome (Xi) lacks structural features called "A/B compartments", and mostly lacks "topologically associated domains" (TADs). By ablating SMCHD1, the Lee lab reveal a hidden layer of intermediate chromosomal structure, the "S1/S2" compartments, in Xi. Formation of S1/S2 depends on Xist ("X-inactive specific transcript") – a long noncoding RNA that coats Xi as part of the gene silencing mechanism. Xist spreads over gene-rich regions of Xi and causes restructuring of initially-present A/B compartments to form S1/S2. SMCHD1 then merges S1/S2 to create a compartment-less organization. Unexpectedly, TADs persist on the Xi, albeit in a weakened state. Ablating Smchd1 causes persistence of S1/S2 structures, strengthening of TADs, regional Xist spreading defects, and failure of Xi silencing. The Lee lab describes this stepwise structural rearrangement, in which S1/S2 is eliminated and TADs are attenuated, as an "Origami Model" – one where incremental folding steps eventually lead to a substantial change in overall structure.



Jeannie Lee's lab showed that the architectural protein SMCHD1 is necessary for X chromosome inactivation (Wang et al, Cell. 2018 Jul 12;174(2):406-421).

Showcasing another thematic strength in our department – molecular mechanisms of innate and adaptive immunity – Ramnik Xavier's lab published a report on interactions of intestinal stem cells (ISCs) and T helper (Th) cells, demonstrating the existence of a key signaling process necessary for maintenance of healthy intestinal tissue (Biton et al, Cell. 2018 Nov 15;175(5):1307-1320). At the core of this process are two phenomena: first, ISCs were found to contain a surface protein called MHC II, the "Major Histocompatibility Complex II", which is generally associated with immune system cells (cells expressing MHC II are able to present antigens to Th cells, thereby activating the production of signaling proteins called cytokines). Second, the fate of ISCs – whether they self-renew or differentiate to specific intestinal epithelial cell types – was found to be influenced by different cytokines produced by Th cells. Regulatory cytokines were found to favor self-renewal, whereas inflammatory cytokines promoted differentiation. Further work needs to be done to clarify these interactions, but it is plausible that ISCs present antigens directly to nearby Th cells, which then produce the signals necessary to maintain gut tissue homeostasis.



Ramnik Xavier's lab published a report on interactions of intestinal stem cells (ISCs) and T helper (Th) cells, demonstrating the existence of a key signaling process necessary for tissue homeostasis (Biton et al, Cell. 2018 Nov 15;175(5):1307-1320).

Neurology

Department Report

Merit Cudkowicz, MD, MSc, Chief

Guided by the needs of our patients, the mission of the Department of Neurology is to be the preeminent academic neurology department in the US by providing outstanding clinical care while rapidly discovering new treatments to reduce and eliminate the devastating impact of neurological disorders; training the very best neurologists and scientists of the future; and improving the health and well-being of the diverse communities we serve. Our core values are excellence in service, innovation, education and neuroscience research in the field of neurology.

Mass General hosts the nation's largest hospital-based neuroscience research program (ranked #1 in NIH funding for hospital-based neurology programs). Our greatest asset in achieving our research goals is our faculty, whose numbers continue to grow (with six strategic recruits in the past three years and more on the horizon). Several faculty members are serving on NIH councils and are leaders of major disease consortiums (e.g. amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's, adrenoleukodystrophy, and Alzheimer's), members of the National Academy, and members of the National Alzheimer Prevention Act national council. Despite a challenging federal funding environment, the Department of Neurology research revenue continues to increase over prior years, bringing in over $115M in total research revenue and maintains an average NIH success rate of 28%.

Departmental Strategic Research Priorities

1. Unite department around a common vision: leadership in therapeutic research to better understand/treat diseases
2. Build cohesive community and partnerships, within and beyond department, that fosters collaboration and innovation
3. Target investment in a few key areas where we are best positioned to have significant impact
4. Develop a strong pipeline of faculty / develop the next generation of leaders
5. Provide resources to allow all faculty to be more productive in their research
6. Diversify and expand revenue streams through more strategic pursuit of philanthropy and other funding sources

A Sample of New Strategic Initiatives in 2018

- Biobank: >5500 Neurology patients enrolled to date
- FY18 Philanthropic Initiatives surpassed goals by 67%- over $54M raised!
- New Biostatistics Consultative Service Offered (internal service that provides biostatistical assistance with data analysis). The results, after 4 months, were 17 grants submitted, 1 funded project, and 1 paper accepted to Annals of Neurology
- Proposal Library of successful grant submissions created to provide guidance to Faculty when writing and submitting grants

Breakthroughs in Research and Therapeutics

Integrated magnetic resonance imaging and [11 C]-PBR28 positron emission tomographic imaging in amyotrophic lateral sclerosis

To characterize [11 C]-PBR28 brain uptake using positron emission tomography (PET) in people with amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS). We have previously shown increased [11 C]-PBR28 uptake in the precentral gyrus in a small group of ALS patients. Herein, we confirm our initial finding, study the longitudinal changes, and characterize the gray versus white matter distribution of [11 C]-PBR28 uptake in a larger cohort of patients with ALS and PLS. Eighty-five participants including 53 with ALS, 11 with PLS, and 21 healthy controls underwent integrated [11 C]-PBR28 PET-magnetic resonance brain imaging. Patients were clinically assessed using the Upper Motor Neuron Burden (UMNB) and the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). [11 C]-PBR28 uptake was quantified as standardized uptake value ratio (SUVR) and compared between groups. Cortical thickness and fractional anisotropy were compared between groups and correlated with SUVR and the clinical data. [11 C]-PBR28 uptake and ALSFRS-R were compared longitudinally over 6 months in 10 ALS individuals. Whole brain voxelwise, surface-based, and region of interest analyses revealed increased [11 C]-PBR28 uptake in the precentral and paracentral gyri in ALS, and in the subcortical white matter for the same regions in PLS, compared to controls. The increase in [11 C]-PBR28 uptake colocalized and correlated with cortical thinning, reduced fractional anisotropy, and increased mean diffusivity, and correlated with higher UMNB score. No significant changes were detected in [11 C]-PBR28 uptake over 6 months despite clinical progression. Glial activation measured by in vivo [11 C]-PBR28 PET is increased in pathologically relevant regions in people with ALS and correlates with clinical measures. Ann Neurol 2018; 83:1186-1197.

Alshikho MJ, Zurcher NR, Loggia ML, Cernasov P, Reynolds B, Pijanowski O, Chonde DB, Izquierdo Garcia D, Mainero C, Catana C, Chan J, Babu S, Paganoni S, Hooker JM, Atassi N. Integrated magnetic resonance imaging and [(11) C]-PBR28 positron emission tomographic imaging in

amyotrophic lateral sclerosis. Ann Neurol. 2018;83(6):1186-1197. Epub 2018/05/10. doi: 10.1002/ana.25251. PubMed PMID: 29740862; PMCID: PMC6105567.

Tau impairs neural circuits, dominating amyloid-β effects, in Alzheimer models in vivo
The coexistence of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the neocortex is linked to neural system failure and cognitive decline in Alzheimer's disease. However, the underlying neuronal mechanisms are unknown. By employing in vivo two-photon Ca2+ imaging of layer 2/3 cortical neurons in mice expressing human Aβ and tau, we reveal a dramatic tau-dependent suppression of activity and silencing of many neurons, which dominates over Aβ-dependent neuronal hyperactivity. We show that neurofibrillary tangles are neither sufficient nor required for the silencing, which instead is dependent on soluble tau. Surprisingly, although rapidly effective in tau mice, suppression of taugene expression was much less effective in rescuing neuronal impairments in mice containing both Aβ and tau. Together, our results reveal how Aβ and tau synergize to impair the functional integrity of neural circuits in vivo and suggest a possible cellular explanation contributing to disappointing results from anti-Aβ therapeutic trials.

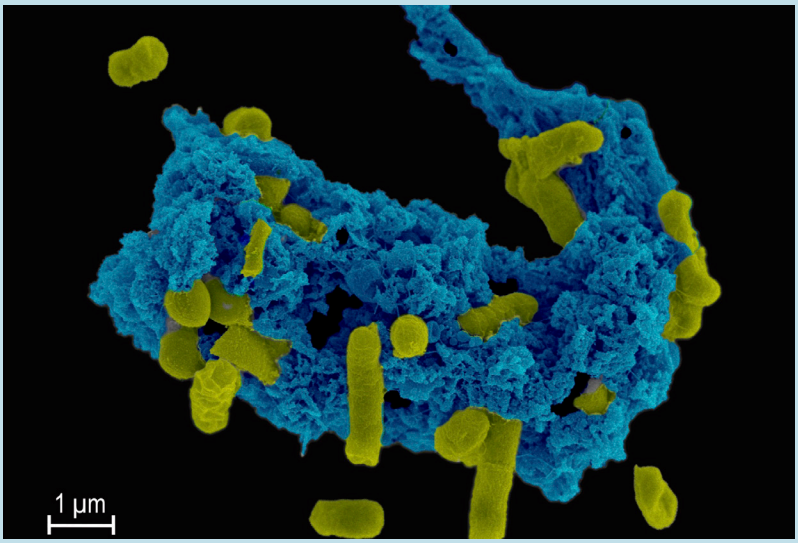
Busche MA, Wegmann S, Dujardin S, Commins C, Schiantarelli J, Klickstein N, Kamath TV, Carlson GA, Nelken I, Hyman BT. Tau impairs neural circuits, dominating amyloid-beta effects, in Alzheimer models in vivo. Nat Neurosci. 2019;22(1):57-64. Epub 2018/12/17. doi: 10.1038/s41593-018-0289-8. PubMed PMID: 30559471.

Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model
Adult hippocampal neurogenesis (AHN) is impaired before the onset of Alzheimer's disease (AD) pathology. We found that exercise provided cognitive benefit to 5×FAD mice, a mouse model of AD, by inducing AHN and elevating levels of brain-derived neurotrophic factor (BDNF). Neither stimulation of AHN alone, nor exercise, in the absence of increased AHN, ameliorated cognition. We successfully mimicked the beneficial effects of exercise on AD mice by genetically and pharmacologically inducing AHN in combination with elevating BDNF levels. Suppressing AHN later led to worsened cognitive performance and loss of preexisting dentate neurons. Thus, pharmacological mimetics of exercise, enhancing AHN and elevating BDNF levels, may improve cognition in AD. Furthermore, applied at early stages of AD, these mimetics may protect against subsequent neuronal cell death.

Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, Kim E, Rompala A, Oram MK, Asselin C, Aronson J, Zhang C, Miller SJ, Lesinski A, Chen JW, Kim DY, van Praag H, Spiegelman BM, Gage FH, Tanzi RE. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. Science. 2018;361(6406). Epub 2018/09/08. doi: 10.1126/science.aan8821. PubMed PMID: 30190379; PMCID: PMC6149542.

Efficient Gene Transfer to the Central Nervous System by Single-Stranded Anc80L65
Adeno-associated viral vectors (AAVs) have demonstrated potential in applications for neurologic disorders, and the discovery that some AAVs can cross the blood-brain barrier (BBB) after intravenous injection has further expanded these opportunities for non-invasive brain delivery. Anc80L65, a novel AAV capsid designed from in silico reconstruction of the viral evolutionary lineage, has previously demonstrated robust transduction capabilities after local delivery in various tissues such as liver, retina, or cochlea, compared with conventional AAVs. Here, we compared the transduction efficacy of Anc80L65 with conventional AAV9 in the CNS after intravenous, intracerebroventricular (i.c.v.), or intraparenchymal injections. Anc80L65 was more potent at targeting the brain and spinal cord after intravenous injection than AAV9, and mostly transduced astrocytes and a wide range of neuronal subpopulations. Although the efficacy of Anc80L65 and AAV9 is similar after direct intraparenchymal injection in the striatum, Anc80L65's diffusion throughout the CNS was more extensive than AAV9 after i.c.v. infusion, leading to widespread EGFP expression in the cerebellum. These findings demonstrate that Anc80L65 is a highly efficient gene transfer vector for the murine CNS. Systemic injection of Anc80L65 leads to notable expression in the CNS that does not rely on a self-complementary genome. These data warrant further testing in larger animal models.

Hudry E, Andres-Mateos E, Lerner EP, Volak A, Cohen O, Hyman BT, Maguire CA, Vandenberghe LH. Efficient Gene Transfer to the Central Nervous System by Single-Stranded Anc80L65. Mol Ther Methods Clin Dev. 2018; 10:197-209. Epub 2018/08/16. doi: 10.1016/j.omtm.2018.07.006. PubMed PMID: 30109242; PMCID: PMC6083902.



Bacteria entrapped in β-amyloid. Transfected H4 cell cultures expressing human Aβ were infected with Salmonella bacteria. Following incubation (1 hr), insoluble aggregates were pelleted from culture media and analyzed by scanning electron microscopy. In the model for Aβ microbial entrapment, soluble oligomers first bind bacterial cell wall carbohydrates. Bound oligomers provide a nidus and anchor for amyloid fibril propagation that mediates the rapid capture, agglutination, and permanent entrapment of bacterial cells. Presented is a pseudo color micrograph showing entrapped bacterial cells (Green) and entrapping β-amyloid fibrils (Blue). (Image by Dr Deepak Kumar Vijaya Kumar)

Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, Washicosky KJ, Gyorgy B, Breakefield XO, Tanzi RE, Moir RD. Alzheimer's Disease-Associated beta-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection. Neuron. 2018;100(6):1527-32. Epub 2018/12/21.

Alzheimer's Disease-Associated b-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection

Amyloid-β peptide (Aβ) fibrilization and deposition as β-amyloid are hallmarks of Alzheimer's disease (AD) pathology. We recently reported Aβ is an innate immune protein that protects against fungal and bacterial infections. Fibrilization pathways mediate Aβ antimicrobial activities. Thus, infection can seed and dramatically accelerate β-amyloid deposition. Here, we show Aβ oligomers bind herpesvirus surface glycoproteins, accelerating β-amyloid deposition and leading to protective viral entrapment activity in 5XFAD mouse and 3D human neural cell culture infection models against neurotropic herpes simplex virus 1 (HSV1) and human herpesvirus 6A and B. Herpesviridae are linked to AD, but it has been unclear how viruses may induce β-amyloidosis in brain. These data support the notion that Aβ might play a protective role in CNS innate immunity, and suggest an AD etiological mechanism in which herpesviridae infection may directly promote Aβ amyloidosis.

Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, Washicosky KJ, Gyorgy B, Breakefield XO, Tanzi RE, Moir RD. Alzheimer's Disease-Associated beta-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection. Neuron. 2018 Jul 11;99(1):56-63.e3. doi: 10.1016/j.neuron.2018.06.030. PMID: 30001512. PMCID: PMC6075814.

Antisene oligonucletoides extend survival and reverse decrement in muscle response in ALS models

Mutations in superoxide dismutase 1 (SOD1) are responsible for 20% of familial ALS. Given the gain of toxic function in this dominantly inherited disease, lowering SOD1 mRNA and protein is predicted to provide therapeutic benefit. An early generation antisenseoligonucleotide (ASO) targeting SOD1 was identified and tested in a phase I human clinical trial, based on modest protection in animal models of SOD1 ALS. Although the clinical trial provided encouraging safety data, the drug was not advanced because there was progress in designing other, more potent ASOs for CNS application. We have developed next-generation SOD1 ASOs that more potently reduce SOD1 mRNA and protein and extend survival by more than 50 days in SOD1G93A rats and by almost 40 days in SOD1G93A mice. We demonstrated that the initial loss of compound muscle action potential in SOD1G93A mice is reversed after a single dose of SOD1 ASO. Furthermore, increases in serum phospho-neurofilament heavy chain levels, a promising biomarker for ALS, are stopped by SOD1 ASO therapy. These results define a highly potent, new SOD1 ASO ready for human clinical trial and suggest that at least some components of muscle response can be reversed by therapy.

McCampbell A, Cole T, Wegener AJ, Tomassy GS, Setnicka A, Farley BJ, Schoch KM, Hoye ML, Shabsovich M, Sun L, Luo Y, Zhang M, Thankamony S, Salzman DW, Cudkowicz M, Graham DL, Bennett CF, Kordasiewicz HB, Swayze EE, Miller TM, Comfort N, Wang B, Amacker J. Antisense oligonucleotides extend survival and reverse decrement in muscle response in ALS models. J Clin Invest. 2018 Aug 1;128(8):3558-3567. doi: 10.1172/JCI99081. Epub 2018 Jul 16. PMID: 30010620, PMCID: PMC6063493.

Impact of Antiretroviral Regimens on Cerebrospinal Fluid Viral Escape in a Prospective Multicohort Study of Antiretroviral Therapy-Experienced Human Immunodeficiency Virus-1–Infected Adults in the United States

Cerebrospinal fluid (CSF) viral escape occurs in 4%-20% of human immunodeficiency virus (HIV)-infected adults, yet the impact of antiretroviral therapy (ART) on CSF escape is unclear. A prospective study of 1063 participants with baseline plasma viral load (VL) ≤400 copies/mL between 2005 and 2016. The odds ratio (OR) for ART regimens (protease inhibitor with nucleoside reverse transcriptase inhibitor [PI + NRTI] vs other ART) and CSF escape was estimated using mixed-effects models. Baseline mean age was 46 years, median plasma VL, and CD4 count were 50

copies/mL, and 424 cells/μL, respectively. During median follow-up of 4.4 years, CSF escape occurred in 77 participants (7.2%). PI + NRTI use was an independent predictor of CSF escape (OR, 3.1; 95% confidence interval, 1.8-5.0) in adjusted analyses and models restricted to plasma VL ≤50 copies/mL (P < .001). Regimens that contained atazanavir (ATV) were a stronger predictor of CSF viral escape than non-ATV PI + NRTI regimens. Plasma and CSF M184V/I combined with thymidine-analog mutations were more frequent in CSF escape vs no escape (23% vs 2.3%). Genotypic susceptibility score-adjusted central nervous system (CNS) penetration-effectiveness (CPE) values were calculated for CSF escape with M184V/I mutations (n = 34). Adjusted CPE values were low (<5) for CSF in 27 (79%), indicating suboptimal CNS drug availability. PI + NRTI regimens are independent predictors of CSF escape in HIV-infected adults. Reduced CNS ART bioavailability may predispose to CSF escape in patients with M184V/I mutations.

Mukerji SS, Misra V, Lorenz DR, Uno H, Morgello S, Franklin D, Ellis RJ, Letendre S, Gabuzda D. Impact of Antiretroviral Regimens on Cerebrospinal Fluid Viral Escape in a Prospective Multicohort Study of Antiretroviral Therapy-Experienced Human Immunodeficiency Virus-1-Infected Adults in the United States. Clin Infect Dis. 2018;67(8):1182-90. Epub 2018/04/05. doi: 10.1093/cid/ciy267. PubMed PMID: 29617912; PMCID: PMC6160603.

Neurogenetic contributions to amyloid beta and tau spreading in the human cortex

Tau and amyloid beta (Aβ) proteins accumulate along neuronal circuits in Alzheimer's disease. Unraveling the genetic background for the regional vulnerability of these proteinopathies can help in understanding the mechanisms of pathology progression. To that end, we developed a novel graph theory approach and used it to investigate the intersection of longitudinal Aβ and tau positron emission tomography imaging of healthy adult individuals and the genetic transcriptome of the Allen Human Brain Atlas. We identified distinctive pathways for tau and Aβ accumulation, of which the tau pathways correlated with cognitive levels. We found that tau propagation and Aβ propagation patterns were associated with a common genetic profile related to lipid metabolism, in which APOE played a central role, whereas the tau-specific genetic profile was classified as 'axon related' and the Aβ profile as 'dendrite related'. This study reveals distinct genetic profiles that may confer vulnerability to tau and Aβ in vivo propagation in the human brain.

Sepulcre J, Grothe MJ, d'Oleire Uquillas F, Ortiz-Teran L, Diez I, Yang HS, Jacobs HIL, Hanseeuw BJ, Li Q, El-Fakhri G, Sperling RA, Johnson KA. Neurogenetic contributions to amyloid beta and tau spreading in the human cortex. Nat Med. 2018;24(12):1910-18. Epub 2018/10/29. doi: 10.1038/s41591-018-0206-4. PubMed PMID: 30374196.

Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis

There are limited treatments for progressive multiple sclerosis. ibudilast inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4 and can cross the blood-brain barrier, with potential salutary effects in progressive multiple sclerosis. We enrolled patients with primary or secondary progressive multiple sclerosis in a phase 2 randomized trial of oral ibudilast (≤100 mg daily) or placebo for 96 weeks. The primary efficacy end point was the rate of brain atrophy, as measured by the brain parenchymal fraction (brain size relative to the volume of the outer surface contour of the brain). Major secondary end points included the change in the pyramidal tracts on diffusion tensor imaging, the magnetization transfer ratio in normal-appearing brain tissue, the thickness of the retinal nerve-fiber layer, and cortical atrophy, all measures of tissue damage in multiple sclerosis. Of 255 patients who underwent randomization, 129 were assigned to ibudilast and 126 to placebo. A total of 53% of the patients in the ibudilast group and 52% of those in the placebo group had primary progressive disease; the others had secondary progressive disease. The rate of change in the brain parenchymal fraction was -0.0010 per year with ibudilast and -0.0019 per year with placebo (difference, 0.0009; 95% confidence interval, 0.00004 to 0.0017; P=0.04), which represents approximately 2.5 ml less brain-tissue loss with ibudilast over a period of 96 weeks. Adverse events with ibudilast included gastrointestinal symptoms, headache, and depression. In a phase 2 trial involving patients with progressive multiple sclerosis, ibudilast was associated with slower progression of brain atrophy than placebo but was associated with higher rates of gastrointestinal side effects, headache, and depression. (Funded by the National Institute of Neurological Disorders and Stroke and others; NN102/SPRINT-MS ClinicalTrials.gov number, NCT01982942 .).

Fox RJ, Coffey CS, Conwit R, Cudkowicz ME, Gleason T, Goodman A, Klawiter EC, Matsuda K, McGovern M, Naismith RT, Ashokkumar A, Barnes J, Ecklund D, Klingner E, Koepp M, Long JD, Natarajan S, Thornell B, Yankey J, Bermel RA, Debbins JP, Huang X, Jagodnik P, Lowe MJ, Nakamura K, Narayanan S, Sakaie KE, Thoomukuntla B, Zhou X, Krieger S, Alvarez E, Apperson M, Bashir K, Cohen BA, Coyle PK, Delgado S, Dewitt LD, Flores A, Giesser BS, Goldman MD, Jubelt B, Lava N, Lynch SG, Moses H, Ontaneda D, Perumal JS, Racke M, Repovic P, Riley CS, Severson C, Shinnar S, Suski V, Weinstock-Guttman B, Yadav V, Zabeti A, Investigators NS-MT. Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis. N Engl J Med. 2018;379(9):846-55. Epub 2018/08/30. doi: 10.1056/NEJMoa1803583. PubMed PMID: 30157388; PMCID: PMC6172944.

Tau Protein Disrupts Nucleocytoplasmic Transport in Alzheimer's Disease
Tau is the major constituent of neurofibrillary tangles in Alzheimer's disease (AD), but the mechanism underlying tau-associated neural damage remains unclear. Here, we show that tau can directly interact with nucleoporins of the nuclear pore complex (NPC) and affect their structural and functional integrity. Pathological tau impairs nuclear import and export in tau-overexpressing transgenic mice and in human AD brain tissue. Furthermore, the nucleoporin Nup98 accumulates in the cell bodies of some tangle-bearing neurons and can facilitate tau aggregation in vitro. These data support the hypothesis that tau can directly interact with NPC components, leading to their mislocalization and consequent disruption of NPC function. This raises the possibility that NPC dysfunction contributes to tau-induced neurotoxicity in AD and tauopathies.

Eftekharzadeh B, Daigle JG, Kapinos LE, Coyne A, Schiantarelli J, Carlomagno Y, Cook C, Miller SJ, Dujardin S, Amaral AS, Grima JC, Bennett RE, Tepper K, DeTure M, Vanderburg CR, Corjuc BT, DeVos SL, Gonzalez JA, Chew J, Vidensky S, Gage FH, Mertens J, Troncoso J, Mandelkow E, Salvatella X, Lim RYH, Petrucelli L, Wegmann S, Rothstein JD, Hyman BT. Tau Protein Disrupts Nucleocytoplasmic Transport in Alzheimer's Disease. Neuron. 2018;99(5):925-940 e7. Epub 2018/09/05. doi: 10.1016/j.neuron.2018.07.039. PubMed PMID: 30189209; PMCID: PMC6240334.

A 3D human triculture system modeling neurodegeneration and neuroinflammation in Alzheimer's disease
Alzheimer's disease (AD) is characterized by beta-amyloid accumulation, phosphorylated tau formation, hyperactivation of glial cells, and neuronal loss. The mechanisms of AD pathogenesis, however, remain poorly understood, partially due to the lack of relevant models that can comprehensively recapitulate multistage intercellular interactions in human AD brains. Here we present a new three-dimensional (3D) human AD triculture model using neurons, astrocytes, and microglia in a 3D microfluidic platform. Our model provided key representative AD features: beta-amyloid aggregation, phosphorylated tau accumulation, and neuroinflammatory activity. In particular, the model mirrored microglial recruitment, neurotoxic activities such as axonal cleavage, and NO release damaging AD neurons and astrocytes. Our model will serve to facilitate the development of more precise human brain models for basic mechanistic studies in neural-glial interactions and drug discovery.

Park J, Wetzel I, Marriott I, Dreau D, D'Avanzo C, Kim DY, Tanzi RE, Cho H. A 3D human triculture system modeling neurodegeneration and neuroinflammation in Alzheimer's disease. Nat Neurosci. 2018;21(7):941-951. Epub 2018/06/27. doi: 10.1038/s41593-018-0175-4. PubMed PMID: 29950669.

New Interdisciplinary Centers

Sean M. Healey & AMG Center for ALS at Mass General
Director: Merit Cudkowicz, MD
A recent philanthropic gift helped launch the new Healey Center for ALS at Mass General. The Healey Center unites the world's leading experts to revolutionize how treatments are developed for people with amyotrophic lateral sclerosis (ALS). We support and accelerate groundbreaking, innovative global clinical trials for all people with ALS. With a host of new tools and technologies available today, our scientists are actively translating basic ALS research into new treatments and therapies. The Center will also support, through endowed chairs, the work of Mass General scientists working to understand the biology of ALS and to develop treatments.

The Henry and Allison McCance Center for Brain Health
Co-Directors: Jonathan Rosand, MD; Rudy Tanzi, PhD; Greg Fricchione, MD
Our goal is to maximize human potential through brain health by developing tools to measure and quantify brain health; identifying risk factors for brain deterioration; quantifying the impact of lifestyle changes; and developing and delivering new treatments. We aim to develop tools and therapies for brain health that can be integrated into primary care and wellness practices.

Interdisciplinary Brain Center (IBC)
Neurology Executive Leadership: Steve Arnold, MD; Brad Hyman, MD, PhD
As an interdisciplinary collaboration of the Departments of Neurology, Psychiatry and the Martinos Center, our mission is to synergize research for the discovery and development of promising diagnostics and therapeutics for brain disorders affecting cognition, emotion and behavior.

Gaurdia Banister PhD, RN, NEA-BC, FAAN, Executive Director

The past year has been one of further development and advancement for the Yvonne L. Munn Center for Nursing Research. Nurse Scientists working in the Center along with nurse scholars across the MGH and Partners locally and nationally, have collaborated to promote inquiry designed to enhance patient care outcomes and improve the work environment for all who care for patients.

Over the year, Nurse Scientists explored symptom science especially around pain management and skin breakdown, evaluated the professional practice work environment, and studied patient response to disease and the experience of patients and families living with illness. In addition, nurse researchers have been the recipients of internal and external funding, disseminated their research findings nationally and internationally in presentations and high impact journals. The work of the nurse scientists over the past year has expanded nursing knowledge and provided new understandings about how patients experience illness. Through research and translation of evidence into practice, nurses have affected the delivery of safe, effective, high quality of care to patients and families at the MGH.

Welcome to our newest Nurse Scientist: Jennifer Cahill RN, PhD

Jennifer Cahill RN, PhD

Dr. Jennifer Cahill completed her undergraduate education at the University of Connecticut, pre-doctoral training at the National Cancer Institute and doctoral study at the University of Texas. Additionally, she has a Master of Science degree in clinical investigation from the MGH Institute of Health Professions. Dr. Cahill has broad practice and research experience in the care of adults and children with solid and liquid tumors. As a nurse scientist in the Yvonne L. Munn Center for Nursing Research, Dr. Cahill will bring comprehensive training in both basic and clinical research methods to the MGH. To date her research interests focus on clinical trials outcome assessment, biologic basis of symptoms and toxicity in the treatment of cancer, testing interventions for symptom management, patient use of electronic medical record, and survivorship. She has presented her research nationally and disseminated her results in nursing, medical and other interdisciplinary journals. We are delighted that she has joined our team!

American Nurses Credentialing Center (ANCC) Magnet Redesignation

In January 2018, MGH Nursing received confirmation of its fourth magnet redesignation. Magnet designation is considered the gold standard of nursing excellence, focusing on multiple criteria that address excellence in nursing. The redesignation application is grounded in a professional practice model, provides examples of distinguished nursing care and is supported by research and evidence that describes high quality patient and family outcomes. In 2003, the MGH became the first hospital in Massachusetts to receive this recognition from the American Nurses Credentialing Center (ANCC). Since then, the hospital has successfully been Magnet designated every four years. This year, the report submitted to the ANCC prominently featured nursing research and evidence, viewed by reviewers as integral components of the magnet redesignation process. To this end, the Munn Center Staff and Nurse Scholars across the MGH community provided research and relevant evidence that supported magnet criteria and highlighted how nursing knowledge, discovery and a creative spirit of inquiry are fully embedded within the culture of MGH Nursing.

The Connell Fellowship for Postdoctoral Study in Nursing Research

The Munn Center is currently recruiting early career nurse researchers to participate in an innovative opportunity to complete postdoctoral training in an academic medical center setting. Through the generous support of the William F. Connell family, funders of numerous opportunities to develop nurse researchers in the past, this current funded initiative will now support the postdoctoral preparation for nurses. The goal of the program is to develop the research competence of a cohort of novice nurse scientists by providing advanced research training around research that addresses research foci of importance to Patient Care Services and the Munn Center. Attention to research design, methodology as well as intervention and outcome evaluation will be included in this mentored experience. The program's overall objective is to cultivate expertise among nurses in the conduct of clinical studies that will improve patient care delivery in this ever-changing healthcare environment. There will be up to two postdoctoral nursing research fellows selected early next year.

2018 Nursing Research Grand Rounds

Nursing grand rounds are presented to the MGH community on a quarterly basis. This year rounds included research that focused on topics such as "Understanding the Influence of Nurses on Cesarean Delivery Rates, A Nurse-Driven Model to Improve Retention in Care of High-Risk HIV

Nursing

Department Report

2018 Jeanette Ives Erickson Research Award recipient
Dr. Jeanette Ives Erickson RN, Dr. Harry Orf, Dr. Sue Slaugenhaupt, Dr. Maurizio Fava, Dr. Virginia Capasso RN (recipient)

Patients", "Validating a Functional Pain Scale for Hospitalized Adults", and "Evaluating the Impact of Speak Up for Safety Training and African American Nurses' Perceptions of a Leadership Development Program".

2018 Research Awards Supported Through the Munn Center

Last year, Gaurdia Banister RN, PhD, NEA- BC, FAAN became the first recipient of the newly developed Connell-Jones Endowed Chair in Nursing and Patient Care Research to advance her research related to interprofessional collaborative practice and diversity due to the generosity of the William F. Connell family. Dr. Banister and her team received Honorable Mention/Program on the Move for the Interprofessional Dedicated Education Units from the National Center for Interprofessional Practice and Education. They have a publication under review and another publication regarding the results of this work in development. Dr. Banister submitted a final report to the American Nurses Foundation for a funded research project entitled, "An Exploration of the Sustained Impact of the Clinical Leadership Collaborative for Diversity in Nursing (CLCDN) Program among African American Nurse Participants". A publication is currently in development and the study will be featured as an exemplar in an upcoming issue of upcoming issue of American Nurse Today, the official Journal of the American Nurses Association, currently distributed to 175,000 dedicated nurses across a multitude of clinical specialties and practice settings.

The Jeanette Ives Erickson Research Award, funded by the MGH Research Institute, is presented annually to a mid-career, doctorally prepared nurse researcher with a dedication and passion for inquiry that improves patient and family care outcomes. In 2018 this award was presented to Virginia Capasso, PhD, ANP-BC, ACNS-BC, CWS. Dr. Capasso is a Clinical Nurse Specialist and Nurse Scientist in The Institute of Patient Care. Her funding will support a pilot study of the Evaluation of the EdemaWear to Reduce the Lower Extremity Edema in Patients with Chronic Venous Insufficiency.

2018 The Connell Nurse-Led Research Team Award recipients
Gail Alexander RN, Dr. Brian French RN, Dr. Colleen Syndeman RN

Another exciting development this year has been the creation of the Connell Nurse–Led Research Team Award. The William F. Connell family, sponsors of this award, promotes research led by a nurse scientist and an interdisciplinary team of nurses and scholars from other disciplines, interested in addressing a clinical problem of significance to improving patient care outcomes. The inaugural recipient of this award is Colleen Snydeman, PhD, RN, NE-BC, the Director of the PCS Office of Quality & Safety. Her team members include Robert Kacmarek, PhD, RRT, Brian M. French, PhD, RN, Gail Alexander, RN, Jeanne McHale, RN, and Beth Nagle, RN. Their study is entitled: "Evaluating the Impact of Speak Up for Safety Training: A Randomized Controlled Trial Simulation Intervention with an Interdisciplinary Team".

Recipient and principal investigator: Courtney Balliro, RN, and her team, Mallory Hillard, RN; and Mary Larkin, RN, of the Diabetes Research Center, and mentor, Dr. Diane Carroll, RN, of the Munn Center for Nursing Research

2018 Yvonne L. Munn Center Nursing Research Award Recipients

Over the past year, many nurse scholars have been the recipient of grants to support their work. In addition, many scholars have disseminated their research findings in journals with international impact. The list below provides examples of recipients so recognized.

Grant Funding:

Principal Investigator: Courtney Balliro, BS, RN, CDE
Team: Mallory A. Hillard, BS, RN; Mary E. Larkin, MS, RN, CDE
Unit: Diabetes Research Center
Mentor: Diane Carroll, PhD, ACNS-BC, FAAN, Yvonne L. Munn Center for Nursing Research
Project: *Empowering the Patient Voice: Analysis of Patient Satisfaction Data to Inform Future Development of a Bionic Pancreas*

2018 Yvonne L. Munn Center Nursing Research Award Recipient
Recipient and principal investigator: Christina Burke, RN, of the Lunder 10 Hematology Oncology Unit, and mentor, Dr. Anne-Marie Barron, RN

Principal Investigator: Christina Burke, BSN, RN, OCN
Unit: Lunder 10 Hematology Oncology
Mentor: Anne-Marie Barron, PhD, RN, PMHCNS-BC, Simmons College/Mass General
Project: *Exploring the Experiences and Perspectives of Bone Marrow Transplant Nurses in Relation to Integrating Humor in Their Practice*

Nursing

Department Report

Recipient and principal investigator: Stephanie Qualls, RN, and her team, Laura Jones, RN; MaiAnh Tran-Allen, RN; Tara Tehan, RN; and Mary Guanci, RN, of the Lunder 6 Neuroscience ICU, with their mentor, Dr. Colleen Snydeman, RN, of the Nursing & PCS Office of Quality and Safety

Principal Investigator: Stephanie Qualls, BSN, RN
Team: Laura Jones, BSN, RN; MaiAnh Tran-Allen, BSN, RN; Tara Tehan, MSN, MBA, RN; Mary Guanci, MSN, RN, CNRN
Unit: Lunder 6 Neuroscience ICU
Mentor: Colleen Snydeman, PhD, RN, NE-BC, Nursing & PCS Office of Quality and Safety
Project: *A Comparative Study of Oral Endotracheal Tube Securing Methods and the Impact on Skin and Mucosal Membrane Integrity*

Publications

Dolan, J., Determinants of Nurses' Use of Physical Restraints in Surgical Intensive Care Unit Patients. Am J Critical Care. (2017) Sep 26 (5):373-379. doi: 10.4037/ajcc2017244.

Erickson, J. I., Duffy, M. E., Ditomassi, M., & Jones, D. (2017). Development and Psychometric Evaluation of the Professional Practice Work Environment Inventory. Journal of Nursing Administration, 47(5), 259-265.

Milotte, H. Carroll, D.L., Coakley, A. (2018). The effect of a therapeutic pillow on pain following Nephrectomy: A randomized clinical trial. Urologic Nursing, 38(3), 137-143. doi:10.7257/1053-816X.2018.38.3.137

Simonelli MC, Doyle LT, Columbia M, Wells PD, Benson KV, Lee CS. (2018). Effects of Connective Tissue Massage on Pain in Primiparous Women after Cesarean Birth. J Obstetric Gynecology Neonatal Nursing. (2018 (5):591-601. Doi 10.1016/j.jogn.2018.07.006. Epub 2018 Aug 11.

Jeffrey L. Ecker, MD, Chief

Research in Obstetrics and Gynecology at MGH

The Massachusetts General Hospital (MGH), Department of Obstetrics & Gynecology is the third-largest admitting service at MGH with a faculty of more than fifty. Our clinical and research teams are leaders in advancing such health concerns as gynecologic oncology (including cancers of the ovary, cervix and endometrium), menopause, high-risk obstetrics, infertility and reproductive medicine and urogynecology.

The **Vincent Center for Reproductive Biology (VCRB)** consists of basic and clinical scientists whose primary research emphasis includes infertility, maternal-fetal interaction, aging and gynecologic cancers. The center provides an optimal environment for individuals who are interested in integrating clinical, translational and basic sciences and have a strong desire to pursue a career in academic research. Our overall research mission is to overcome infertility, improve health care for both non-pregnant and pregnant women, combat gynecologic cancers, and ease the menopausal transition in women through basic, translational, and clinical research. A major step in realizing this goal was achieved in June of 1995 with the formal creation of the Vincent Center for Reproductive Biology - a state of the art research facility developed to serve as the center of our department's scientific endeavors. Since its inception, the VCRB has been successfully nurtured into the department's cornerstone for basic and translational research related to reproductive and women's health.

The Vincent Center for Reproductive Biology (VCRB) Research team. The VCRB was founded in 1995 and has a mission to overcome infertility, improve health care for both non-pregnant and pregnant women, combat gynecologic cancers, and ease the menopausal transition in women through basic, translational, and clinical research. Pictured are the VCRB Faculty, Associate Faculty and Staff.

The **Deborah Kelly Center for Outcomes Research** has been garnering attention in its effort to facilitate exemplary obstetrical and gynecologic outcomes-based research in women's health care. Outcomes research encompasses investigative efforts of women's health conditions valued by patients, providers and clinical and translational research scientists. Collectively, the data derived are expected to help guide clinical care. These accomplishments, paired with strengths in research found in other divisions within our department, have combined to make our research enterprise a critical component of the OB/GYN service.

Concomitant with these goals, we strive to provide "real time" training opportunities in female reproductive and cancer biology for undergraduate and graduate students, postdoctoral fellows, residents, clinical fellows, and junior faculty. To this end, we have established and maintained highly successful integrative and collaborative basic/translational and outcomes-based research training programs.

Achievements:

Dr. Caroline Mitchell and her lab team in the Vincent Center for Reproductive Biology. From Left to Right, Laura Yockey, Alissa Mitchell, Agnes Bergerat-Thompson, Caroline Mitchell, MD.

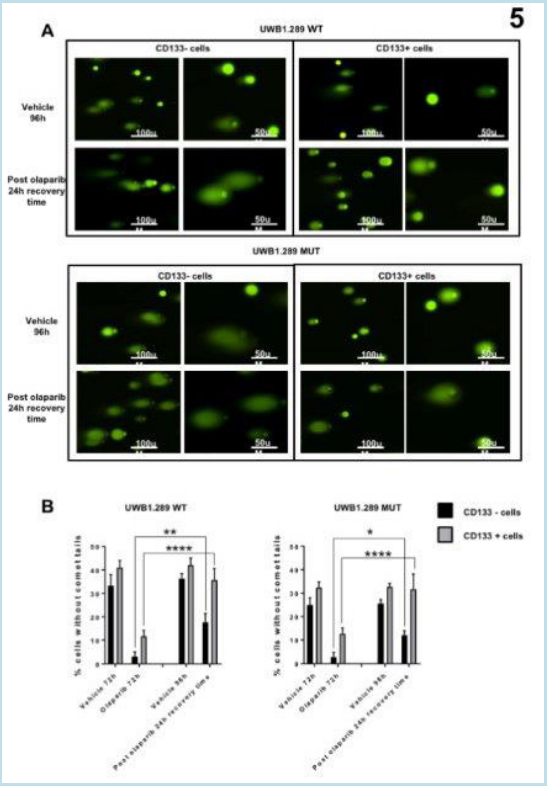
Mitchell C, Reed SD, Diem S, Larson JC, Newton KM, Ensrud KE, LaCroix AZ, Caan B, Guthrie KA. Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs. Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. JAMA Intern Med. 2018 May 1;178(5):681-690. PMID: 29554173

This 12-week, multicenter, randomized clinical trial enrolled postmenopausal women with moderate to severe symptoms of vulvovaginal itching, pain, dryness, irritation, or pain with penetration. The main outcome was decrease in severity (0-3) of most bothersome symptom (MBS) between enrollment and 12 weeks. Additional measures included a composite vaginal symptom score, Female Sexual Function Index (FSFI) score (2-36), modified Female Sexual Distress Score-Revised item 1, treatment

satisfaction and meaningful benefit, Vaginal Maturation Index, and vaginal pH. Our results suggest that neither prescribed vaginal estradiol tablet nor over-the-counter vaginal moisturizer provides additional benefit over placebo vaginal tablet and gel in reducing postmenopausal vulvovaginal symptoms.

Bellio C, DiGloria C, Foster R, James K, Konstantinopoulos PA, Growdon WB, Rueda BR.PARP inhibition induces enrichment of DNA repair proficient CD133 and CD117 positive ovarian cancer stem cells. Mol Cancer Res. 2018 Nov 6. pii: molcanres.0594.2018. doi: 10.1158/1541-7786.MCR-18-0594. [Epub ahead of print] PMID:30401718.

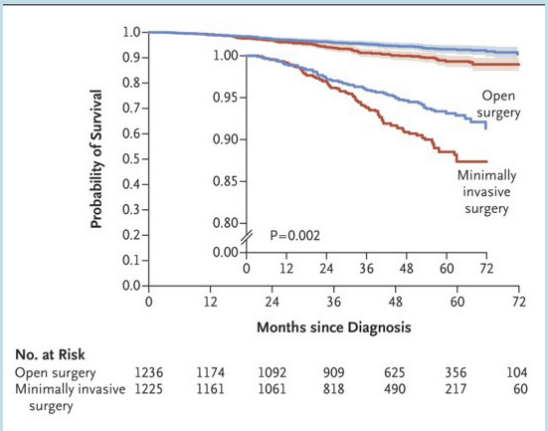
Poly (ADP-ribose) polymerase inhibitors (PARPi) are FDA approved monotherapy agents for the treatment of recurrent ovarian cancer (OvCa) in patients with and without a BRCA mutation. Despite promising response rates, not all patients derive benefit and the majority develop resistance. PARPi treatment in vitro and in vivo induced an enrichment of CD133+ and CD117+ ovarian cancer stem cells (CSCs). This effect was not impacted by BRCA mutation status. In the CSC fractions, PARPi induced cell cycle arrest in G2/M with a consequent accumulation of yH2AX, RAD51 and uniquely DMC1 foci. DNA damage and repair monitoring assays demonstrated that CSCs display more efficient DNA repair due, in part, to activation of embryonic repair mechanisms which involved the RAD51 homologue, DMC1 recombinase. Preserved and induced homologous repair (HR) could be a mechanism of an inherent resistance of CSCs to the synthetic lethality of PARPi that likely promotes disease recurrence. Implications: Treatment with PARPi fails to significantly impact OvCa CSC populations, likely contributing to recurrent disease. OvCa CSCs stabilize genomic integrity post PARPi treatment, due to a more efficient inherent DNA-repair capacity. PARPi induced DMC1 recombinase and HR-proficiency provide CSCs the opportunity to repair DNA damage more efficiently.



CD133+ cells show enhanced DNA repair efficiency. A, UWB1.289 WT (upper panel) and UWB1.289 MUT (lower panel) cells were analyzed 96 hours after treatment with vehicle or 72 hours post treatment with 10 mM olaparib followed by a 24 hour no treatment recovery period and then subjected to magnetic bead separation to isolate CD133+ and CD133- cells. DNA damage in the purified cell fractions was assessed by the comet assay. Representative results are shown. B, Quantitation of the comet assay results (see details in Methods) determined that the DNA repair efficiency of CD133+ cells is ignificantly enhanced compared to their CD133- counterparts (n=3, mean + SEM, p-value < 0.0001). (Bellio et al Mol Cancer Res. 2018)

Melamed A, Margul DJ, Chen L, Keating NL, Del Carmen MG, Yang J, Seagle BL, Alexander A, Barber EL, Rice LW, Wright JD, Kocherginsky M, Shahabi S, Rauh-Hain JA. Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. N Engl J 2018 Nov 15;379(20):1905-1914. doi: 10.1056/NEJMoa1804923. Epub 2018 Oct 31.

Minimally invasive surgery was adopted as an alternative to laparotomy (open surgery) for radical hysterectomy in patients with early-stage cervical cancer before high-quality evidence regarding its effect on survival was available. We sought to determine the effect of minimally invasive surgery on all-cause mortality among women undergoing radical hysterectomy for cervical cancer. We performed a cohort study involving women who underwent radical hysterectomy for stage IA2 or IB1 cervical cancer during the 2010-2013 period at Commission on Cancer-accredited hospitals in the United States. The study used inverse probability of treatment propensity-score weighting. We also conducted an interrupted time-series analysis involving women who underwent radical hysterectomy for cervical cancer during the 2000-2010 period, using the Surveillance, Epidemiology, and End Results program database. In the primary analysis, 1225 of 2461 women (49.8%) underwent minimally invasive surgery. Women treated with minimally invasive surgery were more often white, privately insured, and from ZIP Codes with higher socioeconomic status, had smaller, lower-grade tumors, and were more likely to have received a diagnosis later in the study period than women who underwent open surgery. Over a median follow-up of 45 months, the 4-year mortality was 9.1% among women who underwent minimally invasive surgery and 5.3% among those who underwent open surgery (hazard ratio, 1.65; 95% confidence interval [CI], 1.22 to 2.22; P=0.002 by the log-rank test). Before the adoption of minimally invasive radical hysterectomy (i.e., in the 2000-2006 period), the 4-year relative survival rate among women who underwent radical hysterectomy for cervical cancer remained stable (annual percentage change, 0.3%; 95% CI, -0.1 to 0.6).



Inverse Probability of Treatment-Weighted Survival Curves among Women with Stage IA2 or IB1 Cervical Cancer, According to Type of Surgery. Shaded bands represent the 95% confidence interval. Women who underwent minimally invasive surgery had shorter overall survival than those who underwent open surgery (P=0.002 by the log-rank test). The at-risk table shows the actual number of patients at risk. The inset shows the same data on an enlarged y axis. (Melamed et al, NEJM 2017)

The adoption of minimally invasive surgery coincided with a decline in the 4-year relative survival rate of 0.8% (95% CI, 0.3 to 1.4) per year after 2006 (P=0.01 for change of trend). In an epidemiologic study, minimally invasive radical hysterectomy was associated with shorter overall survival than open surgery among women with stage IA2 or IB1 cervical carcinoma. (Funded by the National Cancer Institute and others.).

Clapp MA, James KE, Kaimal AJ. The effect of hospital acuity on severe maternal morbidity in high-risk patients. Am J Obstet Gynecol. 2018 Jul;219(1):111.e1-111.e7. doi: 10.1016/j.ajog. 2018.04.015. Epub 2018 Apr 16. PubMed PMID: 29673571.

The majority of the 4 million deliveries per year in the United States occur at facilities that deliver less than 650 women per year, and delivery volume has been associated with maternal outcomes. Furthermore, many types of providers, including midwives, family practitioners, and obstetricians, oversee and manage prenatal and intrapartum care. In 2015, the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists published guidelines that established levels of maternal care. These guidelines outlined the nursing, provider, and facility requirements for hospitals to be designated a birthing center or 1 of 4 levels of care. To date, these levels of maternal care have not been adopted widely; currently, no data exist on how these designations may affect maternal or neonatal outcomes. Because the levels of maternal care attempt to reflect a hospital's ability to treat patients with certain conditions that are associated with increased risk of complications, our objective was to use the Nationwide Readmission Database to compare outcomes among high- and low-risk patients between high- and low-acuity hospitals. In the adjusted analysis, we found that intermediate-risk patients had a slightly increased risk of morbidity in both low-acuity and high-acuity centers compared with low-risk patients (adjusted risk ratios, 1.53 [95% confidence interval, 1.33-1.77] vs 1.57 [95% confidence interval, 1.49-1.65]). However, there was a notable difference in the adjusted risk ratios for severe maternal morbidity in the high-risk population: the adjusted risk ratio was 9.55 (95% confidence interval, 6.83-13.35) in low-acuity hospitals compared with 6.50 (95% confidence interval, 5.94-7.09) in high-acuity hospitals. High-risk patients have a higher risk of severe maternal morbidity at low-acuity hospitals compared with high-acuity centers. These findings support the concept of regionalization of maternity care to improve outcomes for high-risk patients.

The Levels of Maternal Care aim to ensure high-risk patients are referred to appropriate providers and hospitals, but currently there are limited methods available to objectively quantify risk and determine the appropriate level of care for a patient. Commonly, risk is subjectively assigned by providers, introducing the inadvertent effects of anecdotes and biases in clinical judgment and the possibility of disparate provisions of care if risk status is incorrectly assigned. Dr. Clapp was awarded a career development award from the American Association of Obstetricians and Gynecologists/American Board of Obstetrics and Gynecology Foundation for his project to utilize electronic health record data to address the current need for accurate, equitable risk stratification in obstetrics, with the goal of improving provider awareness of risk. This information could be used to guide decisions to consult, refer, or transfer a patient's care to a provider or facility with the appropriate resources to manage high-risk patients.

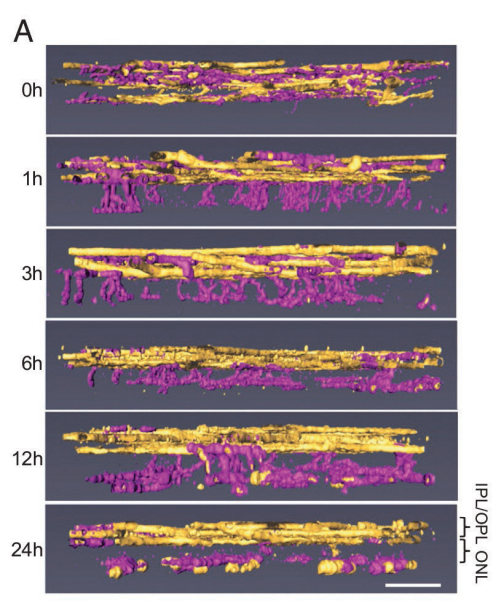
Ophthalmology

Department Report

Joan W. Miller, MD, Chief

The research mission of the Mass. Eye and Ear/MGH Department of Ophthalmology is focused on eliminating blinding diseases and disorders of the eye and visual system. Tackling blinding diseases using a multifaceted, multidisciplinary approach has been the mainstay of the Department's past success in translational medicine. This approach has led to advancements such as proton beam irradiation, photodynamic therapy, anti-VEGF therapies, and the Boston Keratoprosthesis, which have saved sight or improved vision for millions of people worldwide. The Department pursues a programmatic research strategy focused on areas of greatest unmet medical need, including inherited retinal degenerations and age-related macular degeneration (AMD), diabetic eye disease, and optic neuropathies, particularly glaucoma. Our largest investment has been directed toward developing our genetics and genomics programs—with significant emphasis and support in the areas of retina and glaucoma; we believe that leveraging genetic information will accelerate our understanding of diseases and help identify therapeutic targets. At the same time, we are maintaining our commitment to other programs, including, cornea and ocular surface, oncology, immunology, infectious disease, vision rehabilitation and perception.

Moving forward, the goal of the Department is to build and support our research enterprise by continued emphasis on the basic science and translational research programs of our faculty, and to support clinical research that will result in the design, testing and translation of novel treatments to patients with blinding diseases. Our experience, knowledge, and drive to succeed continue to propel our efforts forward and we are very optimistic that significant treatment breakthroughs and cures for many blinding diseases are imminent.



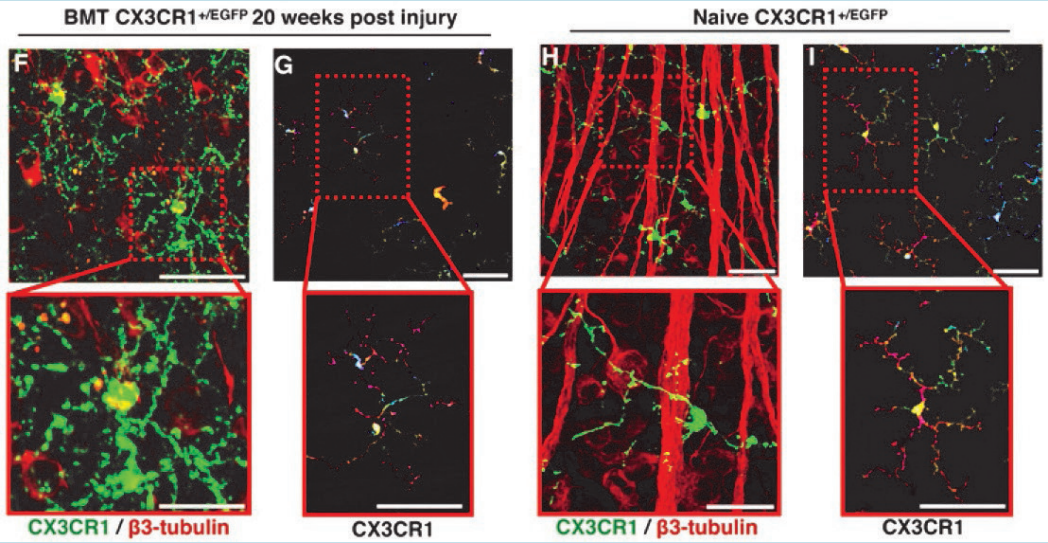
Microglia change location and morphology within 24h post- retinal detachment (RD). Retinas at various time points after detachment were whole-mount stained with microglia marker anti-P2ry12 antibody (magenta) and lectin (yellow). Side view of retinas shows the time-course change of microglia location and their processes in the outer nuclear layer of the retina.

Figure adapted from Microglia inhibit photoreceptor cell death and regulate immune cell infiltration in response to retinal detachment. PNAS. 2018; 115(27): E6264-E6273. Copyright 2018 National Academy of Sciences.

Defining the function of microglia in retinal function and disease

Researchers at Mass Eye and Ear have shown that microglia, the primary immune cells of the brain and retina, play an important role in regulating the response to retinal injury and disease. A research team led by Kip M. Connor, PhD, demonstrated the beneficial role of microglial cells in the eye after retinal detachment. Retinal detachment and subsequent degeneration of the retina can lead to progressive visual decline due to photoreceptor death, the major light-sensing cells in the eye. The study, published in the Proceedings of the National Academy of Sciences (July 2018), describes morphological changes in microglia in response to retinal detachment using a preclinical model. In response to retinal detachment, microglia rapidly respond, migrating in a uniform pattern toward the affected area where they phagocytose injured or dying photoreceptors, possibly protecting surrounding photoreceptors from further damage or injury. Depletion of the microglia in the model led to the occurrence of more photoreceptor death. These studies point to a new therapeutic approach targeting the modulation of microglia to prevent photoreceptor loss, provide an extended window for surgery, and preserve vision longer after retinal detachment

Another study led by Eleftherios Paschalis, PhD, demonstrated a role for microglia in the neuroglial remodeling process that occurs after injury, and how this may contribute to retinal degeneration. Published in the Proceedings of the National Academy of Sciences (November 2018), the results describe a mechanism by which patients with acute ocular injuries become susceptible to progressive neurodegeneration long after the injury has taken place. In this process, bone-marrow-derived peripheral monocytes infiltrate into the retina after acute injury, where they adopt a microglia-like morphology and contribute to progressive loss of retinal ganglion cells. These microglia become engrafted into the retina and remain in a continuously reactive inflammatory state—expressing high levels of major histocompatibility complex class II (MCH-II), interleukin 1-β (IL-1 β), and tumor necrosis factor-α (TNFα)—for prolonged periods after the initial injury. These findings have therapeutic implications in progressive neuroretinal diseases where inflammation has a significant role.

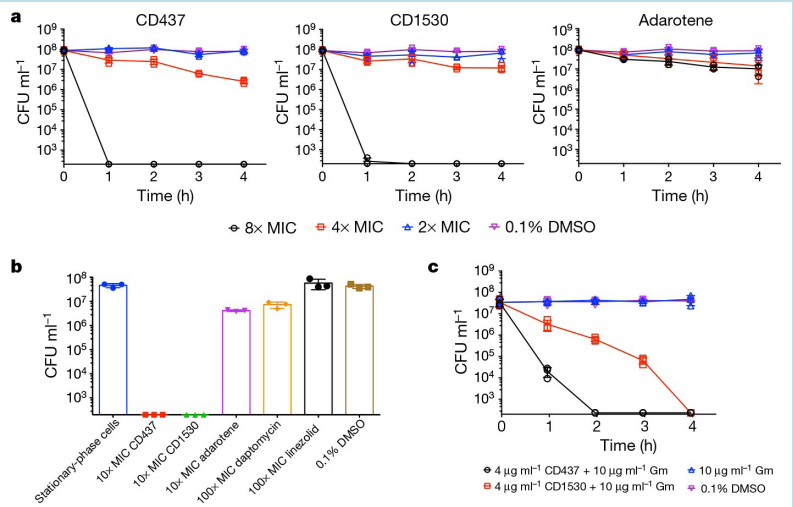


Engrafted peripheral CX3CR1+ cells remain active despite morphometric quiescence. F and G: Twenty weeks after injury, peripheral CX3CR+ monocytes appear to frequently interact with and engulf β3 tubulin+ neuronal tissue (F), despite their otherwise ramified and quiescent morphology (G). H and I: In contrast, in naïve eyes, although ramified CXCR1+ monocytes come into contact with β3 tubulin+ neuronal tissue, they do not internalize it.

Figure adapted from Permanent neuroglial remodeling of the retina following infiltration of CSF1R inhibition-resistant peripheral monocytes. PNAS. 2018; 115(48): E11359-E11368. Copyright 2018 National Academy of Sciences.

Researchers identify new class of synthetic antibiotics shown to be effective against Staphylococcus aureus and Enterococcus

In a significant advance against drug-resistant superbugs, investigators within the Harvard-wide Program on Antibiotic Resistance, a program administered by Mass. Eye and Ear, have identified a new class of synthetic antibiotics that effectively target two of the most virulent, multi-drug resistant pathogens, Staphylococcus aureus and Enterococcus. As these pathogens are responsible for thousands of deaths each year, the newly discovered antibiotics could one day help treat deadly infections caused by these superbugs. The result of a collaboration among a multidisciplinary group of researchers from Mass. Eye and Ear, Mass General Hospital, Brown University, and Emory University, a new screening technology using C. elegans was employed to screen for potential antibiotics and novel compounds that can safely distinguish and rupture bacterial membranes, while sparing human cells. More than 82,000 compounds were screened, leading to the identification of two synthetic retinoids that were able to kill MRSA (methicillin-resistant Staphylococcus aureus), a staph bacteria that is highly resistant to several antibiotics. The investigators also identified the genes that mediate the effect of these drugs and showed that the retinoid compounds weaken the bacterial cell membranes. They also demonstrated that the new compounds were especially effective when paired with the existing antibiotic, gentamicin. These finding were published in Nature (April, 2018). According to Michael Gilmore, PhD—Co-director of the Infections Disease Institute, a Mass. Eye and Ear researcher, and the founder and director of the Harvard-wide consortium—these results are meaningful, as antibiotic resistance is a leading public health concern that threatens everyone, especially patients who undergo complex surgeries.

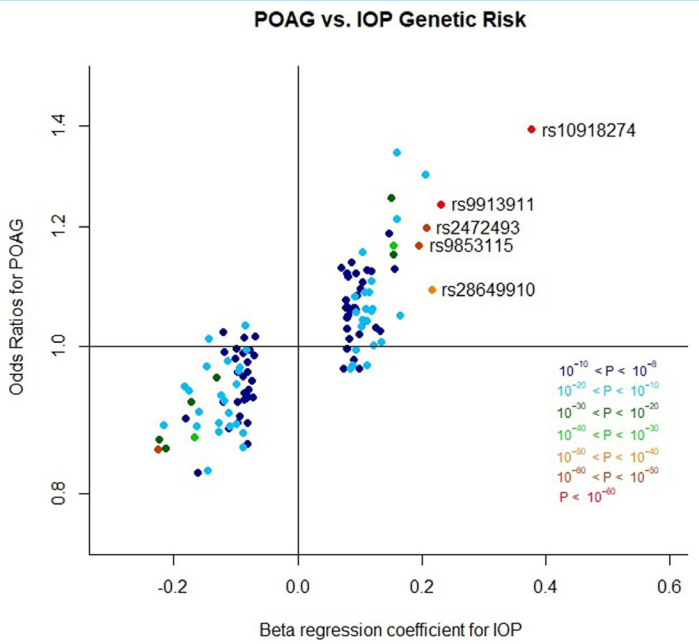


CD437 or CD1530 alone or in combination with gentamicin are effective against persisters. A and B: Viability of stationary-phase S. aureus (a) or S. aureus VRS1 (b) when treated with the indicated concentrations of each retinoid for 4 hours. C: Viability upon treatment of S. aureus MW2 persisters with the indicated concentrations of retinoids in combination with gentamicin (Gm).

Figure from A new class of synthetic retinoid antibiotics effective against bacterial persisters. Nature. 2018; 556(7699):103-107.

Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma (POAG)

Identification of novel genetic variants could pave the way for a genetic-based screening program (GWAS) to help identify glaucoma, the world's leading cause of incurable blindness. Led by Mass. Eye and Ear investigator and Co-director of the Glaucoma Center of Excellence Janey Wiggs, MD, PhD, and scientists from King's College London and University College London, the study published in Nature Genetics (June 2018) investigated genetic determinants for intraocular pressure (IOP), a major risk factor for glaucoma, in approximately 140,000 people drawn from the UK Biobank, EPIC-Norfolk, and the previously



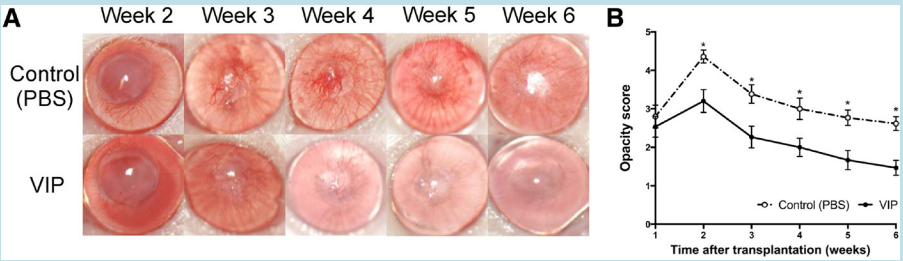
Scatter plot demonstrating correlation effect estimates for SNP associations with IOP in GWAS meta-analysis with effect estimates for SNP associations with POAG. Each point represents one SNP from the 120 independent IOP-associated SNPs. Color of each point represents the statistical significance of the SNP association with IOP.

Figure from Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. Nat Genet. 2018; 50(6): 778-782

reported combined results from 14 European studies in the International Glaucoma Genetics Consortium (IGGC). Meta-analysis of the participants revealed genome-wide significant associations for 112 unique autosomal genetic regions, of which 68 were novel. The identified loci suggest a strong role for angiopoietin-receptor tyrosine kinase signaling, lipid metabolism, mitochondrial function, and developmental processes underlying risk for elevated IOP. Additionally, the genetic variations were able to predict with 75% accuracy whether someone might develop glaucoma. The overall results also show that IOP risk is highly correlated with disease (primary open angle glaucoma (POAG)) risk, further supporting a role for IOP in disease development. As the underlying mechanisms of disease are better defined, it is hoped that clinicians can offer improved therapy for both those living with the disease and those who may develop it.

Vasoactive Intestinal Peptide (VIP) injection may improve corneal transplant survival

Corneal transplantation is the most prevalent form of tissue transplantation, and successful outcome mainly relies on the density and function of corneal endothelial cells (CEnCs), which keep the graft transparent. Injection of vasoactive intestinal peptide (VIP) directly into the eyes of mice is able to enhance corneal graft survival, according to a manuscript published in the American Journal of Pathology (September, 2018). The research team, led by Co-director of the Cornea Center of Excellence Reza Dana, MD, MPH, MSc, evaluated the effects of VIP on corneal tissue in cell culture and in living animals receiving corneal transplants. VIP, a 28 amino acid neuropeptide, is recognized as an immunoregulatory and protective factor in various organ systems. Results from the study showed numerous ways in which VIP may exert beneficial effects. In cell cultures of human CEnCs, VIP accelerated wound healing compared to controls. When CEnCs were exposed to interferon-γ or tumor necrosis factor-α—substances known to induce apoptotic cell death—VIP showed a dose-dependent protective effect. In live mice that underwent corneal transplantation, grafts were more transparent in VIP-treated mice compared to controls four to eight weeks after transplantation. Eight weeks after transplantation, 85% of VIP-treated grafts survived compared to 0% of control grafts, and CEnC density was higher in VIP-treated corneas compared to controls. Although it was known that VIP could help preserve the integrity of CEnCs and may be used by eye banks to improve the survival of donor corneas, this study demonstrates that administration of VIP in vivo after corneal transplantation can help improve graft survival. If confirmed by further clinical studies, the use of VIP could increase the number of donated corneas suitable for transplantation and improve the outcome of corneal transplantation.



VIP treatment decreases graft opacity in a murine model of corneal transplantation with endothelial injury. A: Representative photos showing corneas at week 2 to 6 after transplantation. B: Graft opacity scores are significantly decreased in VIP-treated group from week 2 to 6 after transplantation compared to controls.

Figure adapted from Vasoactive Intestinal Peptide Promotes Corneal Allograft Survival. Am J Path. 2018; 188(9):2016-2024.

Cultivated Stem Cells for Reconstruction of the Ocular Surface

In April of 2018, a team from Mass. Eye and Ear led by Co-director of the Cornea Center of Excellence Ula Jurkunas, MD, used a technique called cultivated autologous limbal stem epithelial cell transplantation (CALEC) to restore a healthy eye surface to a patient with a chemical burn to one eye using adult stem cells from the unaffected eye. Limbal stem cells, located in the outer border of the cornea, function to maintain the barrier between the cornea and the conjunctiva. This barrier may be disrupted if limbal stem cells are absent or dysfunctional, allowing the

conjunctiva to grow over the cornea causing vision loss. In the CALEC procedure, a small biopsy of stem cells was removed from the limbus of the patient's healthy eye, where a high number of stem cells are produced, and taken to a laboratory where they are expanded into hundreds of cells prepared on a graft of amniotic membrane. Once the graft is ready for transplant, scar tissue is cleared away in the damaged eye and the graft is sutured in. The goal of CALEC is to rebuild a healthy surface for the damaged eye using healthy limbal stem cells from the other, non-affected eye. Thus, CALEC can only help patients with limbal stem cell deficiency in one eye. Once a healthy surface has been restored, the patient could receive conventional corneal transplants—an outcome not possible without CALEC as limbal stem cells are needed to support corneal graft tissue. In some patients, CALEC alone is enough to restore full sight and a corneal transplant is unnecessary. With CALEC, there is no risk of transplant rejection, as the cells are taken from the patient's own body and patients who receive CALEC do not need to take immunosuppressive medications to support the transplant tissue.

First FDA-approved Gene Therapy Procedure for Inherited Disease

Mass. Eye and Ear made medical history in March 2018 by performing the first FDA-approved gene therapy for patients with a form of inherited blindness. This is the first time any FDA-approved gene therapy has been given to a patient for any inherited retinal disease. The treatment, trade name Luxturna™, was developed by Spark Therapeutics and approved in December by the Food and Drug Administration (FDA) for patients aged 12 months and older. Luxturna™ has been shown to improve visual function in children and adults with inherited retinal disease caused by mutations in the gene RPE65. The landmark procedure, performed on a 13-year-old patient by Jason Commander, MD, PhD, involves injected a modified virus into a patient's eyes to correct a deficiency caused by mutations in the RPE65 gene. These mutations prevent the production or function of a protein needed for proper functioning of the retina, the light-sensitive tissue in the back of the eye that initiates vision. After having both eyes treated, the patient has noted vision improvement and is most excited to be able to ride his bike at dusk. The culmination of decades of work by many individuals, including researchers led by Jean Bennett, MD, and Al Maguire, MD at the University of Pennsylvania, Luxturna™ represents a pivotal moment in medicine, holding an exciting promise that precision-based medicine may become an integral and routine component of patient care.

Links to videos detailing Luxturna™ treatment and follow-up:
https://focus.masseyeandear.org/making-gene-therapy-history/#.XD0zUDmJVuQ.email
https://focus.masseyeandear.org/two-months-after-gene-therapy-jack-sees-a-little-brighter-more-clearly/#.XD0ydP4r8kc.email

Oral & Maxillofacial Surgery

Department Report

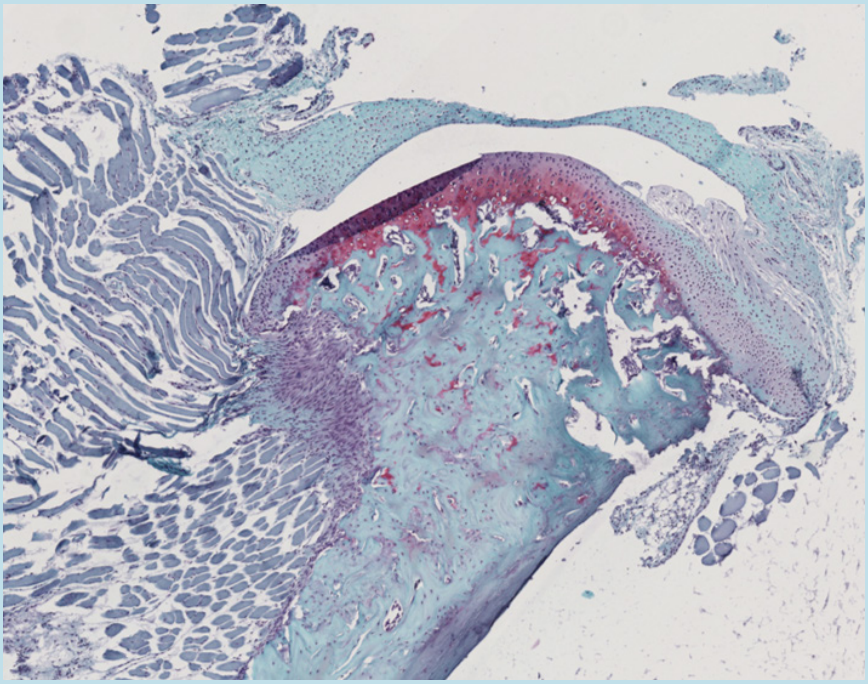
Maria J. Troulis, DDS, MSc, FACS, Chief

The focus of our department's research continues to be a thematically driven translational research program that is intimately integrated with our clinical program(s). We have organized the research into two centers: The Skeletal Biology Research Center (SBRC) and The Center for Applied Clinical Investigation (CACI). Both centers promote the introduction to research of trainees at all levels (high school to post-docs).

Skeletal Biology Research Center (SBRC), is located in the Thier 5 Laboratory (approx.1500sq ft.). The translational science performed focuses on bone biology and rare tumor biology (giant cell tumor and clear cell odontogenic carcinoma). Another area of study is metabolic/inflammatory bone disorders (MRONJ, microbiology-sterile osteomyelitis/necrosis, synovial chondromatosis). In addition, there is also an emphasis on in-vivo tissue engineering (distraction osteogenesis) and ex-vivo tissue engineering (bone, cartilage and joint). We have developed a standard minipig model for the study of the biology of bone. We have started work on osteoarthritis, with newly recruited Dr. Joe McCain. This team is working on developing a mouse model for cartilage repair/generation. Other components of the program include distracter device design, 3D imaging/ treatment planning, navigation and minimally invasive technologies.

Center for Applied Clinical Investigation (CACI), directed by Dr M. August, plays a significant role in evidence-based studies related to the diagnosis, management and outcomes of common problems within our specialty, such as wisdom teeth extraction, dental implantology and medication related osteonecrosis of the jaws (MRONJ), maxillofacial pathology (pediatric jaw tumors, rare jaw tumors), facial pain, minimally invasive surgery and, temporomandibular joint surgery outcomes. The center serves to study outcomes (retrospective and prospective) on treatment protocols developed in the Department. We have initiated QI/Safety/Service improvement (Dr. Ed Lahey) and Education/Simulation research (Dr. John Tannyhill).

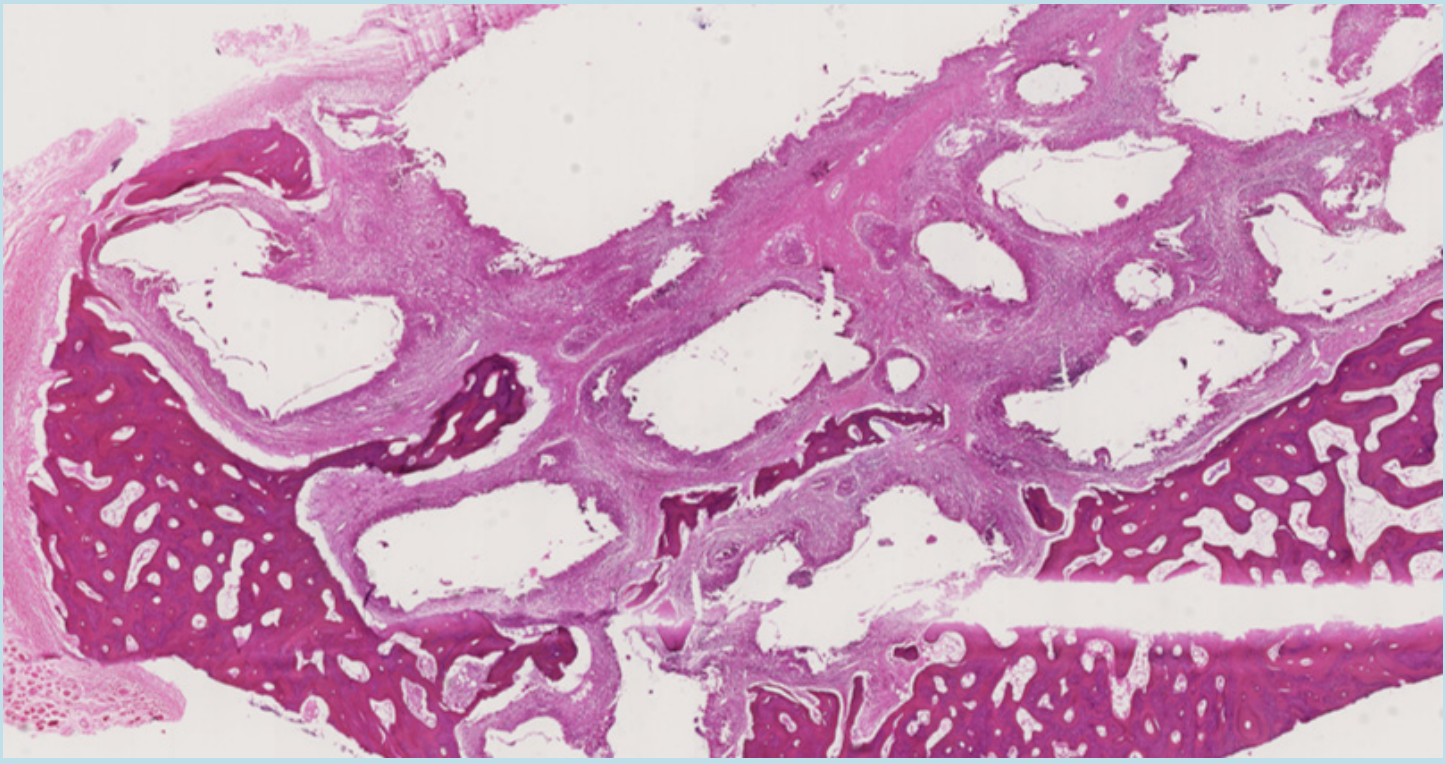
This year was used to continue to promote and nuture our studies in tissue engineering, TMJ repair/generation. collaborations include the Department of Pathology, Drs. Iafrate, Faquin and Rivera (Genetics of Clear Cell Odontogenic Carcinoma) and Oncology, Dr. Raje (Genetics of Bone Metabolism and MRONJ). New collaborations include Dr Vicki Rosen and Dr Joe McCain in Temporomandibular Joint Repair; Drs Yakir Levine and Rox Andersen in attached ginigva reconstruction. Dr Klein has been leading the study of the effect of marijuana on tooth movements.



Mice healthy temporomandibular joint anatomy (Safranin O staining).

The Center for Applied Clinical Investigation (CACI)
A select few ongoing outcomes, retrospective and prospective studies include the study of jaw osteomyelitis; risk factors of suamous intraepithelial lesions undergoing malignant transformation; skeletal relapse following reconstructive jaw surgery; facial dog bites and how they can be prevented; heterotopic ossification of the temporomandibular joint; rare jaw lesions adult and pediatric population; brain absess as a sequela of odontogenic infection.

Skeletal Biology Research Center (SBRC)
Tissue-engineered mandible with three-dimensionally printed polycaprolactone and beta-tricalcium phosphate scaffolds in a porcine model (Postdoctoral Research Fellow, Dr Fernando Guastaldi).
Bioengineering of autologous bone is an exciting minimally invasive alternative to bone harvesting techniques to replace lost bone. The aim of this study is to reconstruct porcine mandibular critical-sized bone defects by combining autologous progenitor cells, 3D CAD/CAM printing of scaffolds, and short pre-implantation times.



Reconstruction of porcine mandibular critical-sized bone defect. H&E section showing good integration of the construct (3D printed ß-TCP/PCL scaffold + porcine bone marrow stem cells) and bone formation inside the construct at 8 weeks post-implantation.

Intra-articular delivery of therapeutic hydrogel for temporomandibular joint regeneration in mice.
Tissue engineering and stem cell based therapies have become an alternative approach for the treatment of joint disorders. The goals of this study are to stablish a surgical approach and develop a model for inducing injury to the TMJ of mice and to develop a nano-carrier system capable of modulating the recruitment of cells and serve as a regenerative matrix for articular tissue.

We hope that these strong foundations will result in another productive research year, with the development of new researchers and which will translate into improved patient care.

Otolaryngology

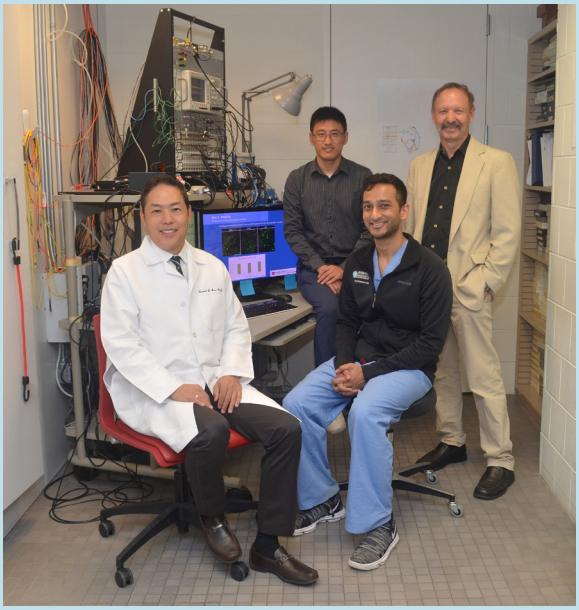
Department Report

D. Bradley Welling, MD, PhD, FACS, Chief

Driven by a mission to find better treatments and cures for otolaryngology conditions, including deafness and diseases of the head and neck, the Department of Otolaryngology at Massachusetts Eye and Ear/Harvard Medical School is committed to moving science in these areas forward. Being home to a large and productive community of otolaryngology researchers, as well as a rich landscape of collaborators, positions us to accelerate the science necessary for the prevention, management, and rehabilitation of human communication disorders. From advancements in using optogenetics to one day improve auditory implants to using facial reanimation techniques to treat corneal nerve damage, we strive to always be at the forefront of medicine in order to ensure the best care possible for our patients.

Researchers use optogenetics to transform cells in the inner ear to respond to light

Best known for research applications in the brain, optogenetics is a technology that uses light-sensitive proteins (known as "opsins") to change the properties of a cell so that it becomes photoactive. This allows for the photoactive cells in living organisms to be controlled with pulses of visible light, which investigators can use to directly activate or suppress a particular group of cells with millisecond precision. Optogenetics has been proposed as a means to improve auditory implant outcomes by reducing channel interaction and increasing electrode density, but the introduction of opsins into cochlear spiral ganglion neurons (SGNs) in vivo has been challenging. A research team at Mass. Eye and Ear, led by Daniel J. Lee, MD, and M. Christian Brown, PhD, showed that cells in the inner ear can become photoactive through the use of optogenetics by using a synthetically developed ancestral adeno-associated virus vector called Anc80 to deliver the opsins. This study is the first to describe robust SGN transduction, opsin expression, and optically evoked auditory electrophysiology in neonatal mice. Ultimately, this work may provide the basis for a new generation of cochlear implants based on light.



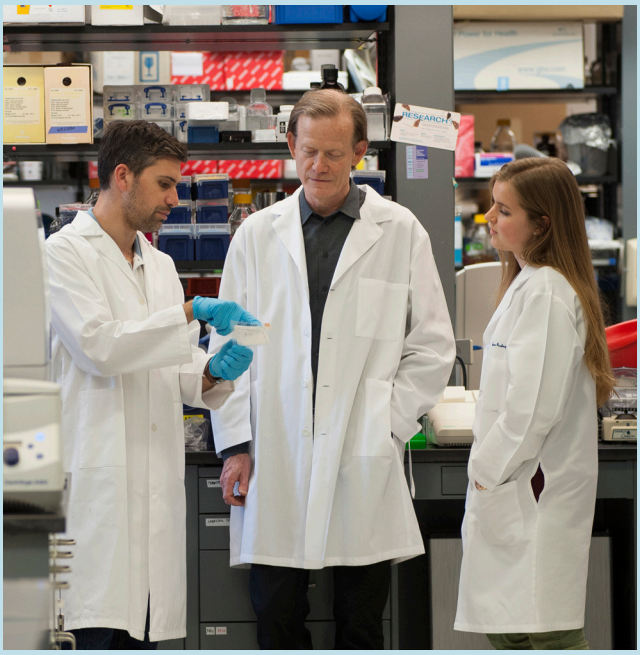
The Auditory Brainstem Implants and Optical Stimulation Laboratory at Mass. Eye and Ear. From left to right: Daniel Lee, Xiankai Meng, Vivek Kanumuri, and M. Christian Brown. Photo by Garyfallia Pagonis.

In vivo base editing of post-mitotic sensory cells

Programmable nucleases can introduce precise changes to genomic DNA through homology-directed repair (HDR). Unfortunately, HDR is largely restricted to mitotic cells and is typically accompanied by an excess of stochastic insertions and deletions (indels). In a study led by Albert Edge, PhD, of the Eaton-Peabody Laboratories at Mass. Eye and Ear, a team of investigators presented an in vivo base editing strategy that addresses these limitations. The team used nuclease-free base editing to install an S33F mutation in β-catenin that blocks β-catenin phosphorylation, impedes β-catenin degradation, and upregulates Wnt signaling. In vitro, base editing installs the S33F mutation with a 200-fold higher editing:indel ratio than HDR. In post-mitotic cells in mouse inner ear, injection of base editor protein:RNA:lipid installs this mutation, resulting in Wnt activation that induces mitosis of cochlear supporting cells and cellular reprogramming. In contrast, injection of HDR agents does not induce Wnt upregulation. These results establish a strategy for modifying posttranslational states in signaling pathways and an approach to precision editing in post-mitotic tissues.

Sensory neuron diversity in the inner ear is shaped by activity

In the auditory system, type I spiral ganglion neurons (SGNs) convey complex acoustic information from inner hair cells (IHCs) to the brainstem. Although SGNs exhibit variation in physiological and anatomical properties, it is unclear which features are endogenous and which reflect input from synaptic partners. Using single-cell RNA sequencing, a research team including Sharon G. Kujawa, PhD, and M. Charles Liberman, PhD, of the Eaton-Peabody Laboratories at Mass. Eye and Ear, derived a molecular classification of mouse type I SGNs comprising three subtypes that express unique combinations of Ca2+ binding proteins, ion channel regulators, guidance molecules, and transcription factors. Based on connectivity and susceptibility to age-related loss, these subtypes correspond to those defined physiologically. Additional intrinsic differences among subtypes and across the tonotopic axis highlight an unexpectedly active role for SGNs in auditory processing. SGN identities emerge postnatally and are disrupted in a mouse model of deafness that lacks IHC-driven activity. These results elucidate the range, nature, and origins of SGN diversity, with implications for the treatment of congenital deafness.



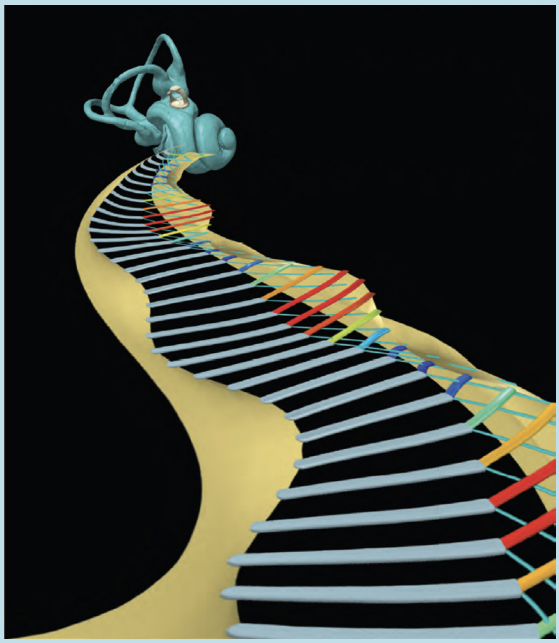
Albert Edge in his laboratory based at Mass. Eye and Ear, having a discussion with research fellows. Photo by John Earle.

Head and neck surgeon develops a new procedure to circumvent corneal nerve damage

A rare disorder known as neurotrophic keratitis can leave patients at risk of losing their eyesight. This degenerative disease results from impaired sensory innervation to the cornea due to injury to the nerve that powers it, the trigeminal nerve. Without sensory input, most interventions to restore vision in these patients, including corneal transplants, aren't likely to succeed. Nate Jowett, MD, FRCSC, an expert in head and neck reconstruction and reinnervation at Mass. Eye and Ear, developed a novel nerve transfer technique to restore sensory input to the cornea. Similar to how a less critical motor nerve may be used to reanimate a smile in patients with facial palsy, this technique involves the transfer of a less-critical regional sensory nerve to restore sensory input to the cornea through an ingrowth of fibers that originally supplied sensation to the earlobe. With sensation re-established, the cornea may begin to heal and restoration of sensory feedback can prevent further damage.

Cochlear amplification and tuning depend on the cellular arrangement within the organ of Corti

The field of cochlear mechanics has been undergoing a revolution due to recent findings made possible by advancements in measurement techniques. While it has long been assumed that basilar-membrane (BM) motion is the most important determinant of sound transduction by the inner hair cells (IHCs), a recent study led by Sunil Puria, PhD, of the Eaton-Peabody Laboratories at Mass. Eye and Ear, showed that other parts of the sensory epithelium close to the IHCs, such as the reticular lamina (RL), move with significantly greater amplitude for weaker sounds. With a computational-model of the mouse cochlea, he showed that individual outer hair cells (OHCs) can work together to produce high hearing sensitivity and frequent selectivity because of the overlapping asymmetrical Y-shaped structures that they form with the Deiters' cells (DCs) and phalangeal processes (PhPs). Altering the geometry and material properties of these structures reveals that all three components have a profound effect on BM and reticular-lamina amplification and tuning. These results imply that the DCs and PhPs must be properly accounted for in emerging OHC regeneration therapies.



A depiction of the inner ear, with a stylized glimpse inside at the vibrating lattice of 'Y-shaped' cellular architecture, found within the organ of Corti. Image courtesy of Hamid Motallebzadeh, Garyfallia Pagonis, Peter Gottlieb, Haobing Wang, and Sunil Puria.

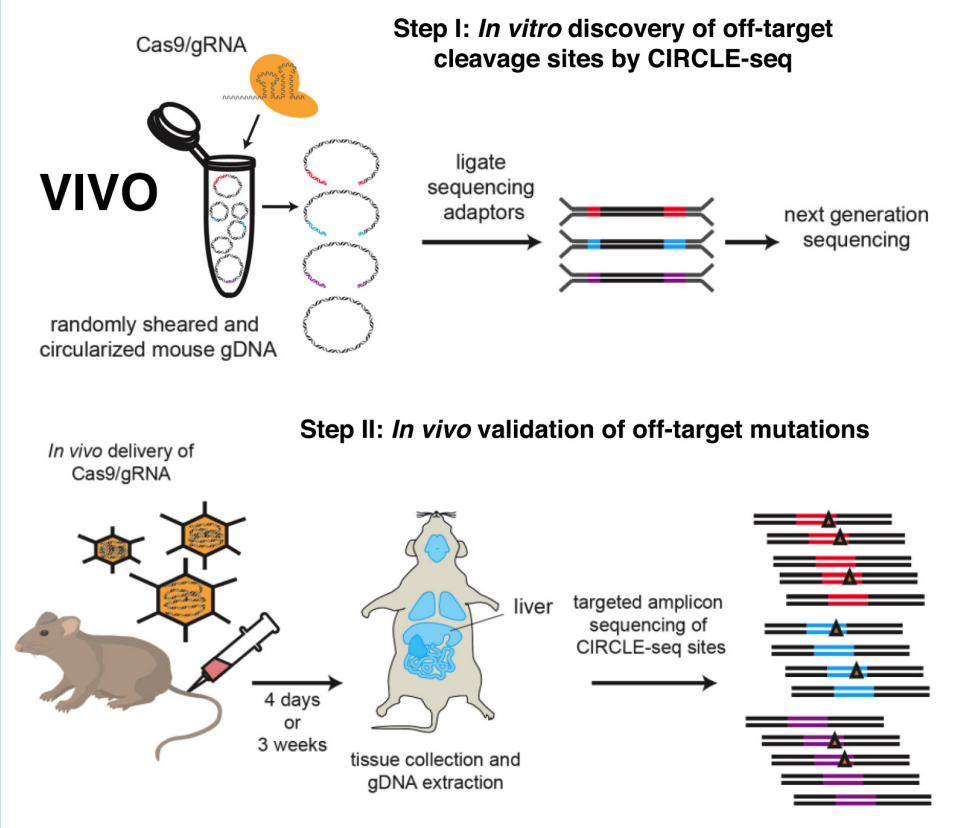
David N. Louis, MD, Chief

Pathology plays a critical and substantial role in academic medicine, as a natural connection between the diagnosis of human disease and experimental biomedical investigation. Major advances in molecular pathology and pathology informatics continue to accelerate the pace of diagnostic and translational research. In turn, the rapidity and frequency of interactions between clinical and scientifc areas makes this an exciting time in the field of pathology. Laboratory-based scientifc research is a major component of MGH Pathology, and is complemented by productive clinical research activities. As a result, MGH Pathology provides an exciting stage for basic and translational research.

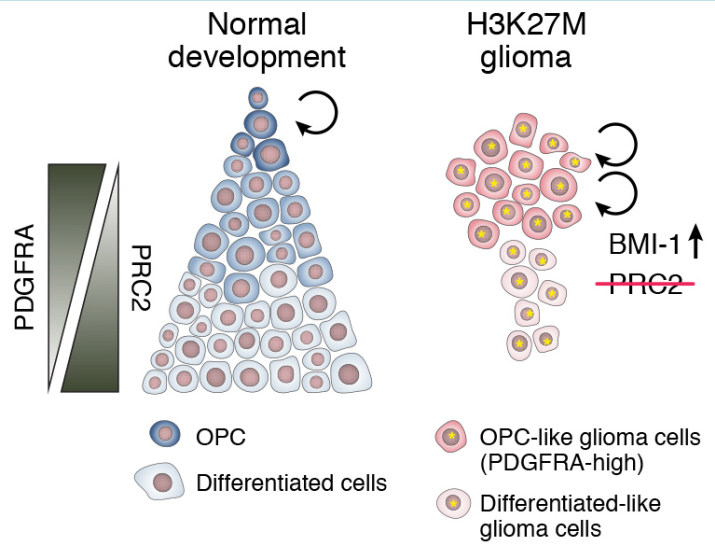
MGH Pathology Research has grown considerably over the past two decades, building an exceptional and well-funded group of basic science and translational investigators with particular strengths and expertise in cancer biology, genomics, and epigenetics as well as with single-cell and genome editing technologies. Over the past several years, we have implemented initiatives identifed from our departmental strategic planning process: leveraging our world-class expertise in genome editing and clinical genome sequencing to expand our understanding of the functional signifcance of DNA sequence variants; expanding computational biology and bioinformatics faculty, personnel, and infrastructure to accelerate the development of the novel discipline of Computational Pathology; and building collaborations and interactions throughout the MGH through our Center for Integrated Diagnostics. We believe that these efforts will help to ensure that MGH Pathology faculty remain at the forefronts of their felds, enabling them to continue advancing our understanding and diagnosis of human diseases.

In vivo CRISPR editing with no detectable genome-wide off-target mutations.
Akcakaya P, Bobbin ML, Guo JA, Malagon-Lopez J, Clement K, Garcia SP, Fellows MD, Porritt MJ, Firth MA, Carreras A, Baccega T, Seeliger F, Bjursell M, Tsai SQ, Nguyen NT, Nitsch R, Mayr LM, Pinello L, Bohlooly-Y M, Aryee MJ, Maresca M, Joung JK. Nature. 2018;561(7723):416-419.

CRISPR-Cas nucleases permit the targeted editing of genes and hold great promise for developing therapeutics to address a wide range of human diseases. Yet, an important concern for therapeutic applications is the potential to generate unwanted DNA changes at "off-target" sites. To address this significant limitation, the Joung lab at MGH developed the Verification of In Vivo Off-targets (VIVO) method to robustly detect off-target effects in vivo in mice. This work uncovered the first convincing evidence that appropriately designed CRISPR-Cas nucleases can alter their intended on-target sites efficiently without inducing any detectable off-target mutations. Taken together, these results define a broadly applicable approach to define CRISPR-Cas nucleases off-targets in any organism in vivo and show the feasibility of obtaining a high therapeutic index with respect to unwanted off-target changes.



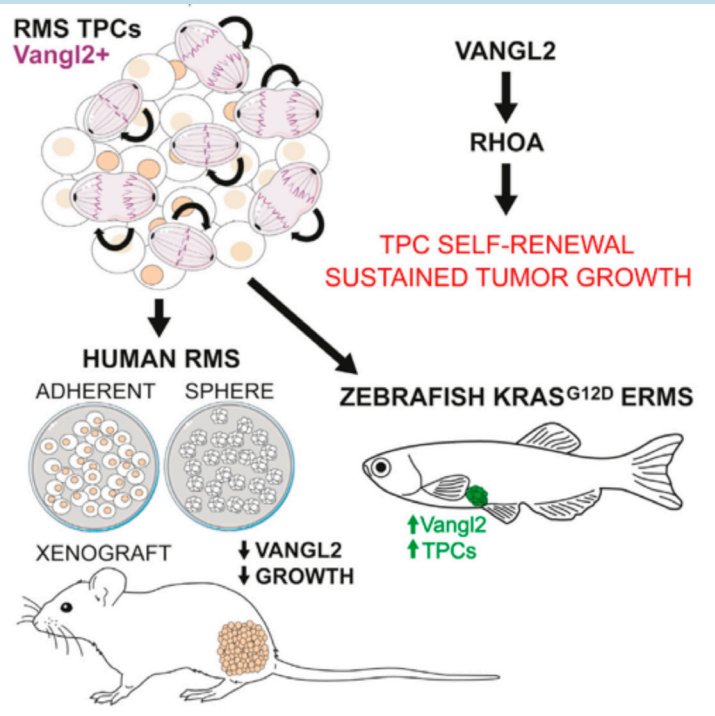
VIVO (Verification of In Vivo Off-Targets): A highly sensitive method for detection and quantification of CRISPR-Cas nuclease off-target mutations in vivo (Akcakaya P et al., Nature 2018).



Cellular architecture of Histone H3 lysine27-to-methionine (H3K27M) mutated gliomas derived from single-cell RNA-sequencing. Normal development (left) compared with H3K27M-gliomas (right). As compensation mechanism, malignant H3K27M-glioma cells over-express BMI-1 to drive growth and self-renewal (Filbin MG et al., Science 2018).

Developmental and oncogenic programs in H3K27M gliomas dissected by single-cell RNA-seq.
Filbin MG, Tirosh I, Hovestadt V, Shaw ML, Escalante LE, Mathewson ND, Neftel C, Frank N, Pelton K, Hebert CM, Haberler C, Yizhak K, Gojo J, Egervari K, Mount C, van Galen P, Bonal DM, Nguyen QD, Beck A, Sinai C, Czech T, Dorfer C, Goumnerova L, Lavarino C, Carcaboso AM, Mora J, Mylvaganam R, Luo CC, Peyrl A, Popovic M, Azizi A, Batchelor TT, Frosch MP, Martinez-Lage M, Kieran MW, Bandopadhayay P, Beroukhim R, Fritsch G, Getz G, Rozenblatt-Rosen O, Wucherpfennig KW, Louis DN, Monje M, Slavc I, Ligon KL, Golub TR, Regev A, Bernstein BE, Suvà ML. Science. 2018;360(6386):331-335.

Gliomas harboring mutation in histone H3 lysine 27 (H3K27M-gliomas) occur primarily in the midline of the brainstem in young children and are invariably fatal within one year of diagnosis. Using single-cell RNA-sequencing, Suva and colleagues uncovered that H3K27M-gliomas are driven by a stem/progenitor subpopulation that recapitulates oligodendrocyte-progenitor cells (OPC-like). These cells compensate for H3K27M-regulated epigenetic dysfunction by expressing a unique molecular program driven by the epigenetic stem cell regulator BMI1. Importantly, these stem/progenitor cells can be also be targeted by inhibition of the OPC-lineage factor PDGFRA. In total, this work is the first to characterize any pediatric cancer by single-cell genomic techniques and has redefined many key aspects of the pathogenesis of histone mutant gliomas.



The non-canonical WNT signaling molecule Vangl2 drives self-renewal of cancer stem cells in both zebrafish and human rhabdomyosarcoma through downstream regulation of RhoA (Hayes et al., Cell Stem Cell 2018).

Vangl2/RhoA Signaling Pathway Regulates Stem Cell Self-Renewal Programs and Growth in Rhabdomyosarcoma.
Hayes MN, McCarthy K, Jin A, Oliveira ML, Iyer S, Garcia SP, Sindiri S, Gryder B, Motala Z, Nielsen GP, Borg JP, van de Rijn M, Malkin D, Khan J, Ignatius MS, Langenau DM. Cell Stem Cell. 2018;22(3):414-427.

Tumor growth and relapse are driven by rare cell types that display similarities to normal tissue stem cells. Yet, identification of these cells and key pathways that drive their survival has been elusive. This is especially true for rhabdomyosarcoma – a pediatric tumor of the muscle. Work from Langenau and colleagues recently identified the non-canonical WNT signaling molecule Van Gogh-like 2 (Vangl2) as a marker of tumor stem cells in rhabdomyosarcoma and uncovered that the VANGL2/RHOA axis directly regulates tumor growth and the survival of rare relapse driving cell types. This work is important because it now allows for identification of human cells that sustain rhabdomyosarcoma tumor growth and provides novel therapeutic targets for treatment of this disease.

Artificial Intelligence Approach for Variant Reporting.
Zomnir MG, Lipkin L, Pacula M, Meneses ED, MacLeay A, Duraisamy S, Nadhamuni N, Al Turki SH, Zheng Z, Rivera M, Nardi V, Dias-Santagata D, Iafrate AJ, Le LP, Lennerz JK. JCO Clin Cancer Inform. 2018;2018.

Next-generation sequencing is a technology to efficiently decipher genetic code and identify genetic changes that cause disease. Yet, current approaches for calling meaningful mutations requires detailed analysis and sign off by a board-certified pathologist or geneticist. Here, Lennerz and colleagues used artificial intelligence (AI) and machine learning to aid in identifying meaningful mutations for the clinical care of patients. Using these approaches, they have built a decision support tool for variant reporting. The authors employed over 9 million datapoints in the training set where the model had a sensitivity of >93%. The laboratory implemented the decision-support tool clinically in 2016, and it has significantly decreased the burden of human analysis of complex data sets by supplementing clinical decision making with a robust artificial intelligence model.

Ronald E. Kleinman, MD, Chief

The research mission of the Department of Pediatrics is to advance translational basic, clinical and population science related to the health and development of infants, children, and adolescents. Research at MGHfC recognizes the challenges and opportunities for child health research dictated by the changing social, economic and health care policy landscape in the US, including the shift toward Precision Medicine. Across the Department, our research integrates multidisciplinary clinical and scientific expertise with local, regional, national and international collaborations.

With the appreciation that biological events beginning during gestation and continuing into childhood can strongly influence disease onset during childhood and beyond, we intend to expand our integrated models focused on pre-clinical/early and translational clinical studies to provide the rationale for possible therapeutic and/or preventive interventions. Our overarching goal is to improve the lives of children and families through science. A current strategic priority is to develop new effective personalized and preventive strategies for disorders starting in childhood by integrating multi-level, multisystem data ranging from the molecular to the whole child in order to prevent or reverse development of disease. To better coordinate our effort and to integrate our scientific mission within the MGH Research Institute we have established the Pediatric Translational Research Center (PTRC) in which basic, translational, clinical, and community-based research are blended to deliver state-of-the-art clinical care, to provide superb training opportunities, and foster cutting-edge discoveries to achieve our mission. We are currently focused on the following specific research missions:

Allergy & Immunology

The research mission for Pediatric Allergy & Immunology is to partner with our patients to advance new therapeutic, preventative and educational interventions for the millions of children affecting by the spectrum of allergic disease including both IgE- and non IgE-mediated forms of food allergy and asthma. A major research focus within the Division is on the mechanisms of immune-mediated food hypersensitivities including IgE-mediated food allergy, chronic gastrointestinal inflammatory diseases related to food allergy such as eosinophilic esophagitis and allergic proctocolitis. To advance this research effort, The Food Allergy Center at Massachusetts General Hospital (FAC@MGH) was established in 2010 as a multi-disciplinary research and clinical care virtual center with the recruitment of Dr. Shreffler to provide leadership, and the core participation of clinicians and investigators from Allergy / Immunology, Rheumatology, Gastroenterology, Dermatology, Pathology, Psychology, Nutrition, Child Life and the Harvard CTSA-supported, MGH Clinical Research Center (CRC). At the time of its inception, there were no clinical trials, interventional or otherwise, focused on food allergy at MGH. To date, the FAC@MGH has initiated than 40 IRB-approved studies on food allergy. These studies represent almost 3,000 research participants in total, more than 2,000 of whom have undergone oral food provocation tests (food challenges). These include randomized interventional trials for food allergy, including two studies funded by NIAID – (NCT01750879, NCT02698033), enrolling 100s of patients and conducting 1000s of study visits, demonstrating the capacity to carry out randomized interventional trials for the food allergic population, including the necessary regulatory compliance (cGCP and ICH), pediatric and adult patient recruitment, data management and all other necessary requirements.

The Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) study has demonstrated our capacity to also carry out larger population cohort / low risk interventional trials: GMAP is an observational healthy newborn cohort study that has enrolled >1000 newborns from a single multi-provider general pediatrics site since May 1, 2014. The study aims to identify risk factors for the development of food allergy – allergic proctocolitis (AP) primarily, but immediate hypersensitivity as well – and collects maternal breast milk, infant stool (at <1 week, 2 weeks, 1, 2, 4, 6, 9, 12, 18, 24 months) and blood (at 1, 2 and 3 years of age).

To complement the discovery efforts, Dr. Michael Pistiner leads our program on Prevention, Education and Advocacy. This program is one of the largest in the country targeting high risk infants by collaborating with primary care pediatricians in the MGH/Partners network to lower the barriers of access in order to expand the early childhood diet to include common allergens – the most effective means of allergy prevention currently proven – and to develop a national model for doing this in other settings. Because of Dr. Pistiner's efforts, effective Dec 2018, we have also become the second site for an NIAID-funded prevention study, led by our colleagues at Johns Hopkins University and have attracted other new extramural funding for education and prevention as well.

In 2016, the FAC@MGH was awarded a seven-year UM1 award by NIAID to be part of the Consortium for Food Allergy Research (CoFAR), the first time for any center in New England and only one of six in the US. The Division enjoys strong collaborations with academic and industry groups at

BWH (The Channing Laboratory), BCH, MIT, The Broad Institute, Sanofi and others.

Cardiology

The Pediatric/Congenital Cardiology division is involved in research in basic science and health services research to understand the causes of congenital heart disease and to study clinical interventions to improve the provision of pediatric cardiovascular care and foster a patient centered environment. We are fortunate to have a robust clinical and academic environment to promote these research endeavors. Members of our service are engaged in basic science research understanding the genetic etiologies of vascular pathology such as aortopathies (e.g. Marfan and Loeys Dietz syndromes). We are also involved in health services research specifically in the area of patient safety and quality as it pertains to pediatric cardiology. We have ongoing investigations evaluating diagnostic accuracy of cardiac imaging, investigations evaluating of parental health literacy among congenital heart disease families, and studies of resource use among patients undergoing congenital heart surgery. Our preventative cardiology service has collaborated with the Harvard T.H. Chan School of Public Health on projects to examine outpatient and wireless means to track physical activity and caloric intake.

Critical Care Medicine

A major focus of the division of Pediatric Critical Care Medicine is preventing and understanding mechanisms of pediatric traumatic brain injury. Our neurocritical care research efforts include basic science and translational studies to understand cellular and molecular events that occur following brain trauma, with the goal of finding new therapies that mitigate specific maladaptive responses and improve outcome. We also conduct clinical research to better understand classification systems for pediatric traumatic brain injury and use of propensity matching to determine risk factors for poor outcome as a site in the multicenter ADAPT study (Sarah Murphy, site PI). In addition, we seek to inform public health trauma prevention strategies to reduce pediatric traumatic brain injury through our Trauma and Injury Prevention Outreach Project (TIPOP). This multidisciplinary group focuses on research, community outreach, and education on the most common areas of pediatric injury leading to emergency department visits and PICU admissions including motor vehicle crashes, window falls, and recreational-related trauma. Lastly, our division is dedicated to the exploration of bioethical considerations that arise when caring for critically ill and injured children.

Endocrinology

The focus of research in the Division of Endocrinology is to enhance the understanding of endocrine systems and endocrine disease during the childhood, adolescent and transition years. Areas of particular interest include investigations into the biology of conditions that span the nutritional spectrum from obesity to the female athlete triad to anorexia nervosa, utilizing state-of-the-art neuroimaging techniques coupled with investigations of circulating hormones important in appetite regulation, and carbohydrate, fat and bone metabolism, studies of the immunology of diabetes, and investigations of novel technologies related to diabetes care. We will continue to foster an environment of inquiry and investigation among our faculty and fellows, work on optimizing funding opportunities to maintain a strong research base within the division. This includes intra- and extra-mural collaborations with other laboratories actively engaged in these areas to create a rich and interactive reinforcing environment that will lead to changes in medical care paradigms for children with endocrine disorders.

Gastroenterology, Hepatology & Nutrition/ Mucosal Immunology and Biology Research Center

Our mission is to expand clinical, basic and translational research in pediatric gastroenterology and nutrition to provide better outcomes for pediatric patients. Using a multidisciplinary approach, our major basic research mission is to characterize the role of the enteric mucosa and its mucosal barrier function at the interface between microbial luminal stimuli and lymphoid effector responses. We focus on the enterocyte and its involvement in microbial "crosstalk," lymphoid-nerve-epithelial interactions and inappropriate developmental responses secondary to epigenetic pressure by the gut microbiota during the first 1000 days of life. We also look at host-pathogen interactions during infection as well as how the enterocyte functions both as a barrier to antigen trafficking and as a site for the beneficial effects of probiotics in chronic inflammation. Finally, we are interested in the gut-brain axis, particularly as concerns small intestinal and blood brain barriers in the contest of neuroinflammatory diseases. Our researchers examine strategies used by gut microbiota to affect the host and how these interactions lead to both local and systemic chronic inflammation and autoimmunity in the Mucosal Immunology and Biology Research Center. In addition, active clinical and translational research to implement personalized and primary preventive medicine is carried out in our Airway, Voice and Swallowing Center for Children; the Center for Celiac Research and Treatment; the Center for Diagnostic, Therapeutic and Interventional Endoscopy; the Center for Inflammatory Bowel Disease; the Center for Nutrition; the Center for Pediatric Hepatobiliary and Pancreatic Disease; the Food Allergy Program; the Liver Transplantation Program; the Lurie Center for Autism Pediatric Gastroenterology Program; the Neurogastroenterology Program and the Pediatric Weight Center.

General Academic Pediatrics

Our research mission remains dedicated to improving the health of children and adolescents through research on prevention and reduction of the burden of chronic disease among children; reduction and elimination of disparities in children's health and healthcare; evaluating the costs and cost-effectiveness of interventions and screening guidelines; and improving the health of populations across the lifecourse through innovations in research, patient care, education, and community advocacy. We also conduct research to prepare and support primary care pediatricians in the delivery of health care innovations, leveraging clinical and community partnerships to implement and sustain effective interventions.

Division faculty have a wide variety of research specialties, including:

- Childhood obesity prevention and treatment, including understanding the role physical activity and other health behaviors play in chronic disease prevention, the development of new, innovative childhood obesity interventions, and the dissemination and implementation of proven-effective programs.
- Providing comprehensive, high quality care to children with special health care needs, including autism spectrum disorder through collaborations such as the Autism Intervention Research Network on Physical Health (AIR-P), Autism Speaks Autism Treatment Network (ATN), and the newly created Autism Learning Health Network (ALHN).
- Strategies to address tobacco use and exposure in families, including the development of the Clinical Effort Against Secondhand Smoke Exposure (CEASE), a free program available in all 50 states, thirdhand smoke, electronic cigarettes, regulating smoking in multiunit housing, and raising the purchase age of tobacco to 21.
- Maternal-child health throughout the life course, including how substance use in pregnant and parenting women impacts the health of children and families, obesity prevention efforts beginning pre-conception and in pregnancy, and the role and influence of fathers in the early life period.
- How the built environment, such as architecture and urban planning, can affect individual and population health.
- Health outcomes of HIV-infected adolescents and adolescents at risk for HIV infection.

Genetics and Metabolism

The Division of Medical Genetics and Metabolism at MGHIC is actively engaged in basic science research at the cellular and sub-cellular level and as well in translational and clinical studies. We perform counseling, diagnostic and management services helping patients and physicians to better understand the genetic contributions to their health and disease and to diagnose and treat a wide variety of genetic/metabolic conditions. We have established specialty clinics in Metabolism, Lysosomal Storage Diseases, Mitochondrial disease, Turner Syndrome, William syndrome, 22q Deletion Syndrome, Stickler Syndrome, Klinefelter syndrome, Hereditary Hemorrhagic Telangiectasia, CHARGE syndrome, a multidisciplinary Sensorineural Hearing Loss Clinic at the MEEI, an Autism Genetics Clinic at the Lurie Center, Pitt Hopkins Syndrome Clinic and Pediatric Cancer Predisposition Clinic. Our multidisciplinary Down Syndrome Clinic is leading the way in care and research including participation in groundbreaking clinical therapeutic trials of agents to improve cognitive function in people with Down syndrome. Our Williams syndrome and Pitt Hopkins syndrome clinics are world renown, with the largest experience with these patients of any site in the world and regularly have international referrals seeking our expertise. Active clinical trials are also underway with lysosomal storage and mitochondrial diseases. The MGH Genetics Division has been at the forefront of applying clinical whole exome sequencing for diagnosis and new gene discovery in selected patients and participates in the NIH sponsored Undiagnosed Diseases Network. Our services impact every field of pediatric and adult medicine. We have active engagement throughout the hospital in advisory and teaching capacities assisting other providers and committees in the implementation of genetics in medicine.

Global Health

The Division of Global Health at MassGeneral Hospital for Children was founded in 2010 and includes faculty, research fellows and staff with diverse experience and interests but a shared objective. Our goal is to build and foster strong partnerships for interdisciplinary research, education and clinical care aimed at improving the health of the most vulnerable children in our global community. Our work builds upon MassGeneral Hospital for Children's long-standing commitment to scientific and clinical innovation as our faculty and staff work on solutions to prematurity, birth asphyxia, neonatal sepsis, childhood pneumonia, cholera transmission, and HIV at several low resource sites across the globe.

Hematology/Oncology

The physician scientists and clinical investigators in the Division of Pediatric Hematology-Oncology work tirelessly to explore the causes of cancer and to develop better treatments for cancer and nonmalignant hematologic illnesses. Together with our pediatric subspecialists we have developed multi-disciplinary programs and clinics for children with brain tumors, sarcomas, survivors of childhood cancer, stroke, and Hemophilia. In addition to our therapeutic clinical trials we also have important companion studies examining quality of life and neurocognitive sequelae for the survivors of childhood cancer. We are active members of an international clinical research group known as the Childrens Oncology Group as well as members of a Neuroblastoma and Medulloblastoma Translational Research Consortium. These groups give us access as participants or co-principal investigators to novel Phase 1,2, and 3 clinical trials. We have ongoing research projects with our colleagues in Radiation oncology, Pathology, the MGH Cancer Center, and Oral and Maxillofacial Surgery. Dr. Miguel Rivera is using epigenome editing tools to examine the genetic drivers in Ewing's sarcoma and medulloblastoma. We are in the second year of an exciting project with Dr. Shannon Stott in the Cancer Center. Her lab is isolating exosomes and circulating tumor cells("liquid biopsy") from the peripheral blood of patients with brain tumors and sarcomas as both a diagnostic assay and a noninvasive method to monitor response to therapy. Dr. Kaban's team has been evaluating the molecular genetics and use of adjuvant anti-angiogenic treatment for giant cell lesions of the maxillofacial and axial/appendicular skeleton.

Infectious Disease

The Pediatric Infectious Disease Unit has been active in both basic science and in translational/clinical research. Dr. Harris's externally funded cholera research efforts encompass investigation of the immune response to Vibrio cholerae infection with an emphasis on vaccine response and development, and exploration of the molecular epidemiology and ecology of V. cholerae. Dr. Warren's pivotal discovery over the past several years of the differential genomic responses between humans and mice to sepsis and inflammation has led to the establishment of a large multicenter project to investigate mechanisms responsible for species-specific sensitivity to inflammation and to develop novel therapies to treat human sepsis. Dr. El Saleeby has been developing refined vancomycin dosing algorithms for hospitalized children. Dr. Pasternack has been part of a clinical and research consortium focused on the study of children with PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection). Dr. Pierce is engaged in the development of novel molecular diagnostic tools for the clinical microbiology laboratory.

Lurie Center

At the Lurie Center for Autism, the primary focus is to partner with individuals and families to incorporate groundbreaking research into the practice of clinical medicine. The integration of clinical care and clinical research through the initiation of clinical treatment trials continues to be a focus. Our collaborative research project with Drs. Jacob Hooker and Nicole Zurcher (Martinos Center), aims to identify an "inflammatory subtype" of autism and has produced very exciting preliminary findings. To identify inflammation within the brains of patients with autism spectrum disorder (ASD), we are assessing translocator protein 18 kDA (TSPO) expression in individuals using [11C]PBR28 positron emission tomography (PET) imaging. Preliminary results show a striking decrease in the expression of this protein in males with ASD compared to age- and gender-matched typically developing controls, indicating a change in neuroimmune activity within the brains of patients (see #1 below). Second, our ongoing work in this model aims to incorporate females in these studies based on evidence in mice and in postmortem human brains that immune system function within the brain differs between males and females (see #2 below), which we believe has relevance for the sex bias in ASD (4:1 males to females). Our ongoing work is to develop an animal model to determine the function of TSPO protein changes, both in the brain and in the peripheral (blood) cells of males and females, and these studies are underway in Dr. Staci Bilbo's lab (see #3 below). Finally, the pre-clinical arm of the Lurie Center (Bilbo lab) and the clinical arm (researchers and clinicians) have established a monthly "think tank" for consistent interaction and cross-fertilization of ideas.

Neonatology and Newborn Medicine

The research efforts in the Neonatology and Newborn Medicine Unit are multifaceted and range from basic science to epidemiology. All research projects share a common mission, which is to advance scientific knowledge aimed at improving the care and treatment of our very vulnerable patients and their families. Reflective of the broad clinical spectrum of issues in our patient population: from extremely low birth-weight infants and the myriad medical issues they face, to full-term infants with various congenital anomalies or those born with physiologic dependence to opioids due to in-utero exposure, we have the following main research foci: 1. Developmental biology approaches to study how prematurity affects human development and to create new strategies and treatment to mitigate the negative impact of prematurity; 2. Neuroprotection strategies, including an examination of those factors that affect neurodevelopmental outcomes following perinatal neurological insults; 3.

interventions to mitigate the effects of substance abuse disorders pre and postnatally.

Nephrology

The Nephrology Division has a significant focus on the discovery of molecular defects that cause rare genetic disorders affecting the regulation of mineral ion homeostasis; particularly on the identification of genetic mutations leading to different forms of pseudohypoparathyroidism and hypoparathyroidism, as well as on the molecular definition of disorders affecting the regulation of phosphate homeostasis. Thus, we reported the first large outcome study on Jansen's metaphyseal chondrodysplasia, which is caused by activating mutations in the PTH/PTHrP receptor leading to hypercalcemia, hypophosphatemia, and severe growth plate abnormalities. These retrospective analyses revealed that patients affected by this disease are extremely short as adults and have extensive medical problems, partly because of hypercalcemia and hypercalciuria/phosphaturia, which invariably causes nephrocalcinosis and appears to lead to chronic kidney disease in older adults. In addition to these genetic studies, we started collaborative work several years ago to screen for effective inhibitors of the major sodium-dependent phosphate transporter, NPT2a, in the proximal renal tubules. Since hyperphosphatemia is a major problem in all patients with advanced chronic kidney disease (CKD), such an inhibitor, if given early during the CKD course, could be highly beneficial for preventing hyperphosphatemia, vascular calcifications, and elevations in FGF23 levels, which are all causes of kidney disease progression and premature mortality. These efforts resulted in the discovery of the first orally active small molecule that effectively lowers blood phosphate levels in wild-type rodents by increasing urinary phosphate excretion. We have furthermore indicated through in vivo studies that the inhibitor is indeed specific for NPT2a and that it can induce urinary phosphate-wasting in mouse models of tumoral calcinosis and chronic kidney disease. In addition to these efforts on disorders affecting calcium and phosphate homeostasis, Dr. Tan's research has made major contributions to the identification of the molecular defects underlying steroid-resistant nephrotic syndrome (SRNS). He documented in numerous families known causative mutations in 20 different genes and identified novel candidate genes through the analysis of additional consanguineous and non-consanguineous families. These efforts to identify the underlying genetic defects will allow disease-specific interventions using established medications and will help in the search for novel therapies.

Pulmonary

The research focus of the Pulmonary Division encompasses 6 areas. The first area of research, led by Drs. Bernard Kinane and Lael Yonker, is the genetic basis of lung disease including interstitial lung disease and non-cystic fibrosis bronchiectasis. In collaboration with the Partners Center for Personalized Medicine, we have developed novel whole exome and genetic panel approaches, which allow for rapid and multiple gene analysis. The second area, led by Dr. Lael Yonker, is an effort to develop new models of the cystic fibrosis (CF) airway. This year Dr. Yonker established a cellular model of this airway and has defined how bacteria interact with this model system thus broadening our understanding of airway inflammation. Specifically, she has shown that neutrophil-derived cPLA2α contributes to bacterial-induced neutrophil transepithelial migration. The third area, led by Drs Lael Yonker and Shannon Fracchia, is clinical research looking at the use of correctors and potentiators of CFTR to treat cystic fibrosis. This year they were key participants in the clinical trial for the next-generation cystic fibrosis transmembrane conductance regulator corrector VX-659, in triple combination with tezacaftor and ivacaftor (VX-659-tezacaftor-ivacaftor) to treat cystic fibrosis patients with the most common mutation. The fourth area lead by Drs Lael Yonker and Bethany Bartley focuses on CF palliative care and this year they were able to define novel CF advance care planning protocols and assessed the preferences of patients with CF. The fifth area, led by Dr. Kinane, focuses on genetic correctors for Duchenne's muscular dystrophy (DMD). Dr. Kinane has now demonstrated that eteplirsen reduces pulmonary function decline in patients with DMD. In the next year, he will extend this work for other novel correctors of DMD.
Finally in the area of education research, Dr. Ben Nelson established a novel mentor program for residents and fellows and is assessing the utility and feasibly of such programs.

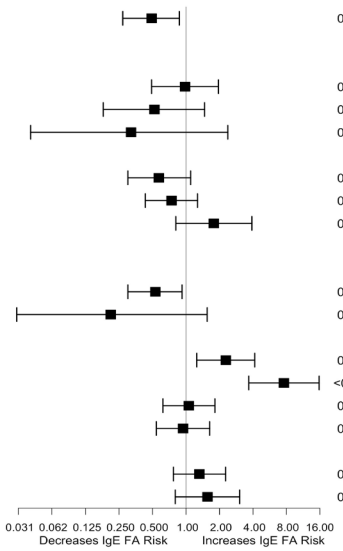
Notable Achievements 2018

Allergy & Immunology

Prospective Identification of Risk Factors for the Development of Food Allergy Early in Life

From the Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) cohort, we have for the first time prospectively defined the cumulative one-year incidence of food protein induced allergic proctocolitis (FPIAP) in a U.S. suburban cohort to be 17% and we have evaluated risk factors for the development of this early form of food allergy, predominantly triggered by cow's milk allergen.

	Cohort: n (%)	IgE FA: n (%)	Unaffected: n (%)	Odds Ratio [95% CI]	p-value
	903	56	847		
Demographics					
Female	417 (46)	17 (30)	400 (47)	0.49 [0.27, 0.87]	0.016
Race					
White	601 (69)	41 (73)	560 (68)	*	
Asian	164 (19)	11 (20)	153 (19)	0.98 [0.49, 1.96]	0.959
Other	110 (13)	4 (7)	106 (13)	0.52 [0.18, 1.47]	0.215
Hispanic or Latino	41 (6)	1 (2)	40 (6)	0.32 [0.04, 2.38]	0.265
Delivery Characteristics					
C-section	286 (32)	12 (21)	274 (32)	0.57 [0.3, 1.1]	0.093
Maternal Antibiotics at Delivery	449 (50)	24 (43)	425 (50)	0.74 [0.43, 1.27]	0.275
Infant Perinatal Antibiotics	80 (9)	8 (14)	72 (9)	1.78 [0.81, 3.91]	0.151
Diet through 4 months					
Breastmilk	370 (41)	32 (57)	338 (40)	*	
Mixed	481 (53)	23 (41)	458 (54)	0.53 [0.3, 0.92]	0.025
Formula	52 (6)	1 (2)	51 (6)	0.21 [0.03, 1.55]	0.125
Other Characteristics					
FPIAP	153 (17)	17 (30)	136 (16)	2.28 [1.25, 4.15]	0.007
Eczema	365 (44)	47 (84)	318 (41)	7.6 [3.67, 15.73]	<0.001
First child	423 (47)	27 (48)	396 (47)	1.06 [0.62, 1.82]	0.838
Pets	333 (41)	22 (39)	311 (41)	0.94 [0.54, 1.63]	0.816
Family History (1st Degree Relative)					
Family History of Atopy	409 (45)	29 (52)	380 (45)	1.32 [0.77, 2.27]	0.315
Family History of Food Allergies	138 (15)	12 (21)	126 (15)	1.56 [0.8, 3.04]	0.190



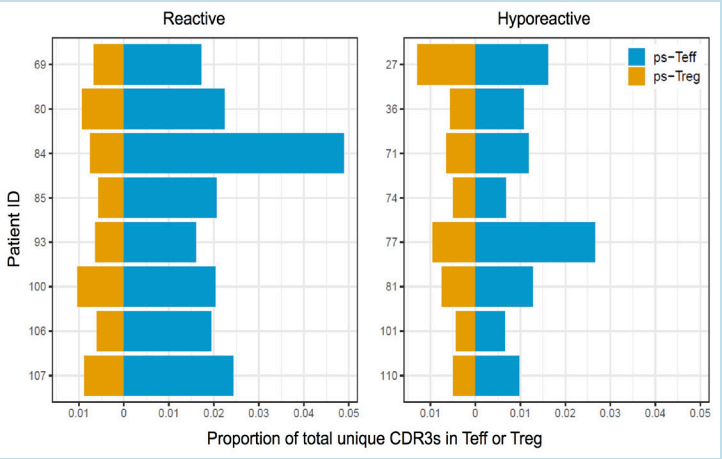
Breastfeeding from the time of initial feeding when combined with formula was associated with almost half the rate of AP ($p<0.05$). Mode of delivery, perinatal antibiotic exposure, and presence of siblings were not associated with AP (not shown), however eczema as well as a family history of food allergies, bloody stools or diet intolerance/feeding difficulties all were significantly associated with infant AP ($p<0.05$, not shown).
It remains unclear if FPIAP increases the risk of developing IgE-mediated food allergies (FA); it is additionally unclear if FPIAP is part of the atopic march or if the food avoidance necessary to treat AP predisposes to FA by preventing early food introduction.

We used a prospective observational cohort of 903 healthy newborn infants to evaluate the rates of FPIAP and FA in young children. FPIAP was diagnosed by the treating physician with diagnosis requiring blood in the stool. FA was determined by independent agreement of two allergist reviewers based on clinical reactivity and documented IgE sensitivity.

Of 903 infants analyzed, 153 (16.9%) children were diagnosed with FPIAP and 56 (6.2%) children were diagnosed with FA. Seventeen (11% of FPIAP; 1.9% of whole cohort) children with FPIAP were diagnosed with FA, while 39 (5%) children without FPIAP developed FA ($p=0.099$). Children with FPIAP were significantly more likely than healthy controls to develop FA to milk (3.9% v. 0.5%, $p<0.001$) and egg (5.9% v. 2.5%, $p<0.04$). There were non-significant trends toward higher rates of FA to peanut as well.

Infants with FPIAP were significantly more likely to develop IgE-mediated food allergies to milk and egg, with trends toward higher rates of FA to other foods. FPIAP may represent an early step on the atopic march, possibly compounded by subsequent allergen avoidance, to potentially increase the risk of developing some IgE-mediated food allergies.

Longitudinal evaluation of microbiota composition continues in collaboration with Ramnik Xavier as part of the newly established Food Allergy Science Initiative at the Broad Institute.



Peanut Allergy Phenotypes

Peanut allergy is an IgE-dependent condition, however, the clinically observed variability in clinical sensitivity is not adequately explained by assays of peanut allergen-specific IgE. We hypothesize that characterizing differences in the antigen-specific CD4+ T cell phenotypes and the TCR repertoire within various T cell compartments – given their role in disease pathogenesis – may be useful biomarkers of the differences in clinical sensitivity and help meet this important clinical issue. Using an assay to identify antigen specific T cells (CD154 expression after in vitro stimulation), we evaluated the TCR repertoire diversity and size within effector (Teff) or regulatory (Treg) CD4 T cell compartments. Using this approach, we found that the relative expansion of the Teff compartment was associated with greater clinical sensitivity to peanut exposure – defined by the gold standard, double

blind placebo controlled food challenges. This phenotypic difference is now being tracked longitudinally as patients undergo immunotherapy to peanut (i.e., desensitization).

Critical Care

Dr. Whalen and collaborators demonstrated for the first time that three-dimensional brain-like tissue cultures with human endothelial cells subjected to controlled cortical impact or a concussion TBI mouse model recapitulated biochemical responses of mouse brain endothelium seen in controlled cortical impact and concussion traumatic brain injury models1. This study is the first to establish feasibility of using human cultured brain cells in vitro to directly study responses of human cells to traumatic injury, address the lack of human experimental data, and validate the relevance of mouse TBI models. Dr. Whalen also published the longest follow up study of a preclinical adolescent concussion model2. This study showed that neurological deficits can be permanent in adulthood after repetitive concussive TBI in adolescent mice, and that new hyperactivity can emerge over time (akin to ADHD that occurs in adolescents after concussions). Importantly, IL-1 emerged as a causal mechanism of neurological dysfunction in that model, whereas IL-1 receptor played a protective role in a cerebral contusion model, highlighting the importance of stratifying TBI based on pathological definitions rather than Glasgow Coma Scale scores1.

Dr. Lok participated in a study examining the protective effects against oxidative damage of a free radical scavenger in oligodendrocyte precursor cells (OPCs)3. OPCs are important as a source of new oligodendrocytes, the cells that produce the myelin sheath around axons. In the setting of brain injury, it is important to find ways to rescue OPCs and to promote their differentiation into mature new oligodendrocytes so that the conduction of nerve impulses can continue along myelinated axons. Dr. Lok and collaborators also examined the role of AKAP12 in the process of myelination in the central nervous system4. The findings in this study are significant as they advance the understanding of OPC differentiation and provided evidence that suggests that pericytes are required for this process.

Dr. Murphy led an analysis on the efficacy of the GCS score, the most widely used head trauma assessment score and the de facto classification system for TBI severity5. The GCS score had not been previously validated in children younger than 5 years. The impact of this analysis was to establish a more refined classification of injury severity among patients in the larger category of "severe TBI" that will be used in the subsequent analyses to compare the therapeutic effect of treatment strategies between patients with similar mortality risk.

Lastly, Dr. Cummings led bioethical discussions around the care of medically-complex, co-joined twins culminating in a publication in the New England Journal of Medicine6. This garnered significant attention in the media and resulted in multiple downstream articles examining bioethical considerations surrounding the separation of co-joined twins.

References:

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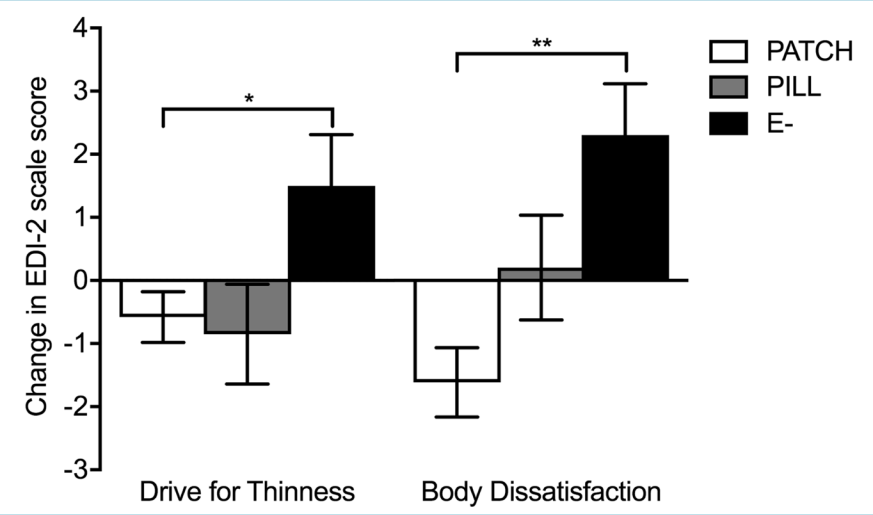
3. Takase et al., 2018 Neurosci Lett: Protective effects of a radical scavenger edaravone on oligodendrocyte precursor cells against oxidative stress
4. Maki et al., 2018 Stem Cells: A-Kinase anchor protein 12 is required for oligodendrocyte differentiation in adult white matter.
5. Murphy et al., 2017 J Neurotrauma: Tripartite Stratification of the Glasgow Coma Scale in Children with Severe Traumatic Brain Injury and Mortality: An Analysis from a Multicenter, Comparative Effectiveness Study
6. Cummings et al., 2017 N England J Med: Case 33-2017. 22-Month-Old Conjoined Twins.

Endocrinology

In the past year, Dr. Misra's laboratory reported data from a randomized controlled trial of transdermal 17-β estradiol vs. oral ethinyl estradiol vs. no estrogen (Psychoneuroendocrinology in press) in 14-25-year-old oligoamenorrheic athletes (a population at high risk of disordered eating behavior). The study showed improved trajectories for drive for thinness (DT) and body dissatisfaction (BD) scores on the Eating Disorders Inventory-2 (EDI-2) in those who received estrogen therapy vs. those that did not. Further, in 3-group comparisons, those randomized to the transdermal estradiol patch outperformed those who received no estrogen for decreases in EDI-2 DT and BD scores (Figure 1) and outperformed those who received oral estrogen for measures of uncontrolled eating on the TFEQ-R18. These data demonstrated for the first time that estrogen

replacement may improve eating disorder pathology in oligoamenorrheic athletes, emphasizing the importance of normalizing estrogen levels in conditions associated with disordered eating behavior.



Changes in EDI-2 Drive for Thinness and Body Dissatisfaction scores in oligo-amenorrheic athletes randomized to transdermal 17β-estradiol with cyclic progesterone (PATCH), oral ethinyl estradiol and desogestrel (PILL), or no estrogen (E-). *p < .05, **p < .01. Accepted in Psychoneuroendocrinol 2018.

Drs. Braun and Stanley recently published a description of the effects of pitavastatin on glucose homeostasis and liver fat content in men at risk of diabetes. Whereas many statins increase the risk of diabetes, pitavastatin is proposed to be neutral to glucose homeostasis, although this hypothesis had not previously been tested using the gold standard euglycemic hyperinsulinemic clamp. In addition, small studies have suggested that statins may reduce liver fat content, but this also had not been investigated in a larger randomized controlled trial. Drs. Braun and Stanley demonstrated that pitavastatin is indeed neutral to glucose homeostasis, compared to identical placebo, with a trend toward reduction in fasting insulin and HOMA-IR. They showed that pitavastatin has no effect on liver fat content, suggesting that investigation of other agents for treatment of nonalcoholic fatty liver disease is needed (J Clin Endocrinol Metab. 2018).

Further, Dr. Whooten published data from a non-randomized trial of 707 children in kindergarten through eighth grade who participated in a 1-hour before school physical activity program, compared to non-participating control students. The study showed the students who participated in the program 3 days/week had improvement in BMI as well as increased odds of being in a lower BMI category at 12 -week follow-up, compared to students participating 2 days/week and controls. Children who participated in both 2 and 3 days/week programming had improvements in social-emotional wellness compared to controls. These findings support a potential role for before-school physical activity programs in improving child physical and behavioral health. The paper was published in the American Journal of Preventive Medicine.

Gastroenterology, Hepatology & Nutrition / Mucosal Immunology and Biology Research Center

Celiac Disease, Genomic, Environmental, Microbiome and Metabolomic (CDGEMM) Study

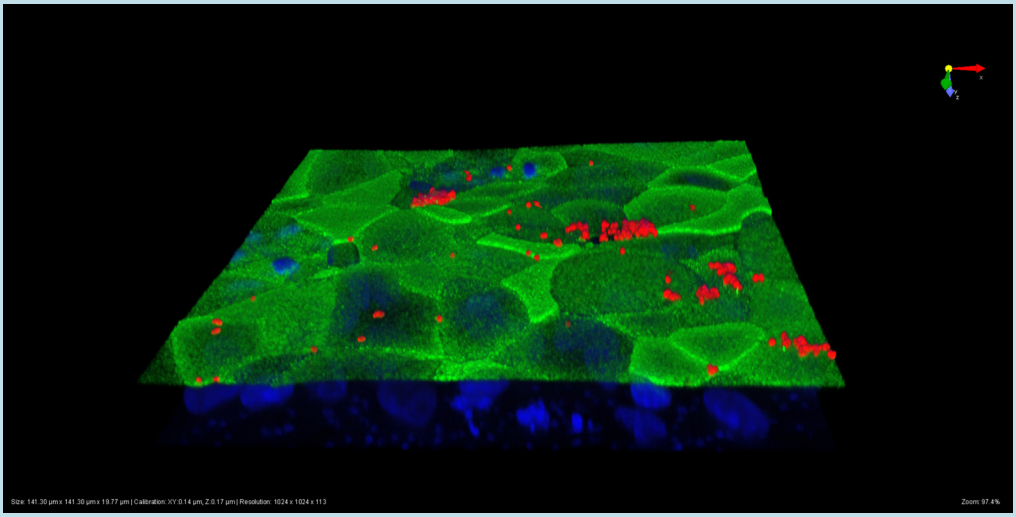
The Celiac Disease, Genomic, Environmental, Microbiome and Metabolomic (CDGEMM) Study is an international, observational study of approximately 500 infants. By studying infants with a first-degree relative with celiac disease, we are examining environmental factors – such as method of birth delivery, use of antibiotics and breast or formula feeding – as well as the genetic makeup of the infants and their microbial "signature." Using blood, stool, and tissue samples from the mothers as well as the children, along with extensive food and antibiotic use diaries, demographic data, and microbial sequencing data, we are amassing an enormous amount of data to study celiac disease development with the goal of preventing the disease before it occurs.

We developed the CDGEMM study following the results of a pilot study of 47 infants, which investigated the timing of introducing gluten into the diet and the resulting changes in the microbiota during the introduction of solid food. Findings from the pilot suggested that understanding how the microbiota of infants with a genetic predisposition to celiac disease differ from infants without the predisposition might help predict celiac disease or another autoimmune disorder. We have enrolled more than 370 infants in Boston, Italy and Spain. Preliminary data from a small number of infants who have gone on to develop celiac disease show interesting differences in the development of the microbiome of at-risk celiac disease infants and healthy controls. Results from our recently concluded pilot study include:

- Colonization of the microbiome of infants at risk of developing celiac disease is influenced by underlying genetics at the species level.
- We identified significantly different microbial species in infants based on birthing delivery mode, feeding practices, and exposure to antibiotics at birth between from 7 days after birth to 6 months of age
- Even before exposure to solid foods, including gluten, early environmental factors may predispose the microbiome of infants at risk of celiac disease toward inflammation and autoimmunity or toward immune tolerance and pathogen protection.

Development and Validation of Human Gut Organoids for the Development of Novel Therapeutic Strategies for Celiac Disease, Necrotizing Enterocolitis and Enteropathogens Infection

In the last year, we have made great strides in an innovative technique using intestinal tissue from people who have undergone clinically indicated endoscopies. By using this tissue, we have developed gut organoids, which are powerful tools to study the interaction between the gut tissue and the complex bacterial ecosystem in our intestine. Human intestinal organoids are part of a repository that counts now about 50 samples, derived from multiple regions of the small and large intestine. Based on our own and other studies, organoids express a gene profile that recapitulates the developmental stage and/ or the disease state of the tissue of origin. They can be stored frozen virtually endlessly and resuscitated and handled similarly to cell lines.



We have used organoids to derive high throughput assays to study the effect of environmental factors on innate immune response and barrier function of the gut. Our work has generated significant advancement in understanding S. Typhi pathogenesis We have also shed light on some important functional differences in the development of fetal intestine, which could be crucial in the development of necrotizing enterocolitis (NEC). We have also leveraged the organoids to study alternative strategies for enteropathogens that develop antibiotic resistance. Finally, we have used the organoids platform to study the intestinal epithelium of celiac patients. Our next step is to leverage this model from proof-of-concept to develop new strategies for the treatment of celiac disease, NEC and enteropathogens' vaccine development.

Studying the Microbiome of the Blood

With the advent of microbiome studies, we are revisiting the idea that blood is sterile. Studies show that, even in healthy controls, microbial communities inhabit the blood. With new genetic sequencing techniques, we have been able to view bacteria in the blood as well as DNA. In this project, we are looking at how bacteria move into the blood under conditions of increased intestinal permeability found in individuals with active celiac disease. Increased intestinal permeability could play a role in the transport of bacteria found in the blood to other parts of the body.

We are looking for differences in the microbial component of blood and how this might be expressed in healthy controls, people with celiac disease in remission, and people with active celiac disease. By using stool samples as well as blood samples to measure microbial communities, we can look for correlations in the microbial composition of blood and stool in the three different patient populations. Our pilot study shows that the blood microbiome of active celiac patients has a different composition and microbial diversity as compared to healthy controls and celiac patients in remission. The comparison between the fecal and hematic microbiomes highlights the differences between the two environments in terms of microflora composition and function. A better understanding of the hematic microflora could not only provide new insights into the onset of celiac disease, but also could be instrumental in the development of new therapies and diagnostic tools for this autoimmune disease.

General Academic Pediatrics

Mental Health and Payments for Children with Chronic Medical Conditions

More and more children and youth experience chronic health conditions. This new study examines a sample of 6.6 million children and youth ages 0-26 years and 5.8 million of their parents, all of them with commercial health insurance. In this group, patients with a chronic medical condition and co-occurring mental health or substance use disorders had annual insurance payments 2.4 times larger than those with a chronic medical condition only. Most of the increase in health care claims reflected medical services rather than mental or behavioral health services. This difference translated to a greater estimated annual expenditure of $8.8 billion. Parents of these children also had total insurance payments 59% higher than parents whose children had only a chronic medical condition.

The much higher total health care costs for both children and youth and their parents suggest the potential benefits from preventing or reducing the impact of mental health and substance use disorders among children and youth with chronic medical conditions.

Five child-serving professional organizations (the American Academy of Child and Adolescent Psychiatry, the American Academy of Pediatrics, the Society of Child and Adolescent Psychology, the Society for Developmental and Behavioral Pediatrics, and the Society of Pediatric Psychology) jointly commissioned the Milliman Group (a leading healthcare actuarial company) to analyze a large national database of commercial insurance claims. The goal was to estimate additional payments associated with co-occurring mental health of substance use disorders in children and youth with chronic medical conditions.

This project is notable as the first time these 5 organizations have pooled their resources and expertise on a project of mutual interest. The findings point to potential cost benefits of addressing co-existing mental health and substance use disorders. Integrated or collaborative care, in which mental health problems are diagnosed and treated within the medical setting in collaboration with medical professionals, is widely seen as a way to increase access to mental health services and to intervene earlier before problems become more serious. The degree to which integrated care is adopted across the country depends significantly on financial factors: does it save money (on a per capita basis) compared to our current compartmentalized system? These new data help support the notion of collaborative care as a strategy to improve health care costs. Integrated care approaches may be one of the strategies to prevent or reduce the impact of mental health and substance use disorders in children and youth with chronic medical conditions and their parents.

1. Perrin JM, Asarnow JR, Stancin T, Melek SP, Fritz GK. Mental health conditions and healthcare payments for children with chronic medical conditions. Academic Pediatrics, https://doi.org/10.1016/j.acap.2018.10.001

Perinatal Opioid Overdose – Increased overdose in the year following delivery

Using a novel linked population-based cohort study in Massachusetts that contained administrative and vital statistics, we estimated fatal and nonfatal opioid overdose events in pregnant and postpartum women in Massachusetts, comparing rates in individuals receiving and not receiving pharmacotherapy for opioid use disorder (OUD). We identified that 2.3% of all deliveries in MA between 1/2012-9/2014 were to women with evidence of OUD in the year before delivery and they experienced 242 total opioid-related overdose events (231 nonfatal, 11 fatal) in the year before or after delivery. The overall overdose rate was 8.0 per 100,000 person-days. Overdoses were lowest in the third trimester (3.3/100,000 person-days in the third trimester) and then increased in the postpartum period with the highest overdose rate 7-12 months after delivery (12.3/100,000 person-days). Overall, 64.3% of women with evidence of OUD in the year before delivery received any pharmacotherapy in the year before delivery. Women receiving pharmacotherapy had reduced overdose rates in the early postpartum period. We identified that the year after delivery is a vulnerable period for women with OUD. Additional longitudinal supports and interventions tailored to women in the first year postpartum are needed to prevent and reduce overdose events.

1. Schiff DM, Nielsen T, Terplan M, Hood M, Bernson D, Diop H, Bharel M, Wilens TE, LaRochelle M, Walley AY, Land T. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. Obstet Gynecol. 2018 Aug; 132(2):466-474. PMID: 29995730.

Before School Physical Activity Program

As a modifiable lifestyle habit, physical activity is often cited as a preventive tool against overweight and obesity in children. Beyond this, there is growing evidence that physical activity has a positive impact on child social and emotional wellbeing. Despite this, many children do not receive the recommended amount of physical activity.

This study was a non-randomized trial examining the effects of a 12-week, 1-hour before-school physical activity program ("Build Our Kids Success," or "BOKS") on BMI and social-emotional wellness among students participating in the program. A total of 707 students participated in this study across 24 schools in Massachusetts. Children registered in the program participated in 2 or 3 days/week programming and were compared to non-participating controls. Measurements were collected at baseline and 12-week follow-up and included height and weight (all students) as well as surveys (students ≥ 8 years old).

We found that children in the 3 days/week group had improvements in BMI z-score compared to nonparticipating controls. Improvements in social-emotional wellness were found in both the groups compared to controls. Children in the 3 days/week group had significant improvement

in student engagement as well as non-significant improvement in peer relationships, affect, and life satisfaction, while children in the 2 days/week group had significant improvement in positive affect and vitality/energy when compared to controls. These findings are important because they support a role for before school programs in increasing child physical activity levels. Additionally, the "BOKS" program is a widely available and free physical activity program that may be an effective and efficient way to create more physical activity opportunities for children.

Current work evaluating the impact of the BOKS program is ongoing within Revere Public Schools. Revere is a diverse district, with greater than 50% of enrolled students speaking a first language other than English and over a third from economically disadvantaged families. With support through a community health improvement grant through MGH, we are evaluating the implementation of the BOKS program in this setting. Three schools participated in the initial phase of the implementation evaluation (Spring-Fall 2018), with expansion to three additional schools for 2019 through continued funding through the MGH Executive Committee on Community Health.

1. Whooten RC, Perkins ME, Gerber MW, Taveras EM. Effects of Before-School Physical Activity on Obesity Prevention and Wellness. Am J Prev Med. 2018 Apr;54(4):510-518. doi: 10.1016/j.amepre.2018.01.017. Epub 2018 Feb 12. PubMed PMID: 29449135; PubMed Central PMCID: PMC5901979.

Genetics and Metabolism

The Undiagnosed Diseases Network - Application of cutting-edge protocols to facilitate understanding and research into undiagnosed diseases.

Dr. Sweetser has continued to lead the MGH site of the NIH sponsored Undiagnosed Diseases Network (UDN). Together with Brigham and Women's Hospital and Boston Children's Hospital MGH forms the Harvard Clinical Site of the UDN. Leveraging the unique combination of scientific and medical expertise and resources at the NIH and eleven clinical sites around the country of the Undiagnosed Diseases Network this endeavor is providing answers to patients with mysterious conditions that have long eluded diagnosis, despite extensive analyses, and is advancing medical knowledge about rare and common diseases. We have developed a comprehensive approach to evaluate adults and children with undiagnosed genetic diseases, pooling the clinical and research expertise at our three centers together with a nationwide network of eleven clinical sites in the US. To date we have solved 35% of cases referred to us that had previously defied local diagnostic efforts, in the process have discovered a growing number of new genetic disorders and established research collaborations to better understand the basis of these disorders. We have performed comprehensive phenotypic, genomic, metabolomic, and transcriptomic analyses and have added this data to a nationwide database for curation. Using a model organism cores, we have established the functional significance of many variants and have also teamed up with researchers around the world to further understand the pathogenesis of these disorders. The UDN continues to develop protocols used now as models for clinical investigation by centers around the world. During this second and final planned 4-year phase of NIH support we are working to develop the UDN as a sustainable national resource.

Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease. Splinter K. et al, N Engl J Med 2018; 379:2131-2139

Down Syndrome Clinic to You (DSC2U)

Current estimates suggest that over 95% of individuals with Down syndrome in the United States do not have access to a Down syndrome specialty clinic. A team led by Dr. Brian Skotko, director of the MGHfC Down syndrome clinic, have created "Down Syndrome Clinic to You (DSC2U)" an online form for patients/caregivers, which will generate personalized health recommendations as a way to address this need (dsc2u.org). With DSC2U, caregivers have an opportunity to complete an online intake form, where they can identify current health concerns about their son or daughter with Down syndrome. Some sections ask caregivers to identify current symptoms in the person with Down syndrome, any past medical or behavioral diagnoses, and any recent blood work or diagnostic testing. DSC2U also contains optional sets of questions about nutrition, education, therapies, life skills, and community resources that caregivers are able to complete if more information is desired on these topics. The caregiver's responses will generate two personalized documents: (1) a Caregiver Checklist and (2) a Primary Care Provider Plan. The Caregiver Checklist is intended to provide useful information for the patient based on the answers to the survey and national guidelines. The Primary Care Physician Plan is a document to give to the doctor of the person with Down syndrome. This Plan contains auto-programmed suggestions for the doctor based on answers that provided in the DSC2U form. Dr. Brian Skotko, Principal Investigator, received a grant from PCORI to create DSC2U in collaboration with the MGH Laboratory of Computer Science. Right now, the team is conducting a large randomized control trial hypothesizing that the technology will reduce healthcare disparities and improve quality of life for all people with Down syndrome. After the grant ends on June 1, 2019, the MGH Down Syndrome Program intends to make DSC2U commercially available within MGHfC for patients

and families around the world.

Use of Electronic Health Record Integration for Down Syndrome Guidelines
Published guidance from the American Academy of Pediatrics (AAP) outlines the specific components of medical care for children and young adults with Down syndrome. However, not all patients receive the recommended care. In this study, published in Pediatrics, we added alerts and tracking due dates into the medical record software to remind physicians to place orders. We found that these simple tools led to more patients with Down syndrome receiving the components of care as outlined by the AAP. This approach could be expanded and used at other hospitals, for other genetic syndromes or for other published guidelines.

Santoro SL, Bartman T, Cua CL, Lemle S, Skotko BG. Use of Electronic Health Record Integration for Down Syndrome Guidelines. Pediatrics. 2018;142(3):e20174119. doi:10.1542/peds.2017-4119

Global Health

Advances in cholera research. Jason Harris, an NIH funded investigator, collaborates with investigators in Bangladesh and Haiti to study immunity to cholera and cholera vaccines. During the past year, these research teams made significant contributions including:

- The first evaluation of the long-term effectiveness oral cholera vaccine effectiveness in Haiti which demonstrated that protection lasts over 4 years (Lancet Global Health)
- The discovery that O-antigen specific memory B cell responses are key immunologic correlates of long-term protection following cholera vaccination and infection (papers in Vaccine and PLoS NTD)
- The discovery that in addition to immunity, the specific composition of human gut microbiota strongly predict susceptibility to cholera. This includes identification of a Paracoccus species that increases susceptibility to cholera by promoting virulence (Journal of Infectious Diseases)

Advances in pediatric HIV. Kate Powis, an NIH funded investigator, collaborates with investigators in Botswana to study pediatric HIV infection and exposure to maternal HIV infection. Dr. Powis organized and led the 3rd HIV-Exposed Uninfected Workshop in Paris with sponsorship from the World Health Organization and the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER). Her team made significant advances in 2018 including demonstrating that maternal perinatal acquisition HIV is associated with increased morbidity in HIV-exposed uninfected infants.

Advances in childhood pneumonia. Peter Moschovis completed the data-acquisition phase of a study of a new point of care, smartphone-based diagnostic application to diagnose pneumonia by analyzing the sound of a patient's cough.

Hematology/Oncology

Ewing's sarcoma is caused by a genetic alteration in which the chromosome 22 gene EWS is fused to the chromosome 11 gene FLI1 leading to the fusion protein EWS-FLI1. The current study tested the links between microsatellite activation by EWS-FLI1 and the expression of cancer associated genes and tumor growth. Epigenome editing revealed how a fusion protein found in cancer cells enhances the expression of normally inactive GGAA microsatellites in Ewing sarcoma. Finding regulatory regions such as enhancers in the genome that are specifically utilized in tumors but not in normal cells may lead to new therapeutic targets. Genes and Development 32(15-16): 1008-1019, 2018.

We have identified new target genes of giant cell tumors in the maxillofacial and axial/appendicular skeleton. Five highly expressed genes were found commonly in giant cell lesions and stroma at each location supporting the common origin of these tumors. Only the levels of T-cell immune regulator-1 (TCIRG1) predicted clinical behavior of the maxillofacial tumors and could be a potential target for diagnosis and therapy. Oral Maxillofac Surg 75(2): 298-308, 2017.

Infectious Disease

Dr. Jason Harris has been actively characterizing the B cell response to cholera and cholera vaccines analyzed at the individual cell / antibody level. (see also Global Health). He has identified the basis of partial serotype specificity and long-term memory against the O antigen, and demonstrated that this serologic reactivity is responsible for protection against clinical infection. In addition, he has demonstrated that changes in the human gut microbiome helps to determine susceptibility to cholera infection.

Dr. Warren has continued his work on heme binding agents to block inflammation and is seeking support to test hemopexin in ARDS in clinical trials. He is also continuing his DARPA funded work focused on understanding the underlying mechanisms explaining the natural innate resistance of rodents and certain other species to pro-inflammatory agonists.

Neonatology and Newborn Medicine

Bronchopulmonary dysplasia (BPD) is the most common long-term pulmonary complication associated with extreme preterm birth. BPD is a complex lung injury syndrome caused by a combination of prenatal and postnatal insults associated with prematurity that result in altered lung development. A major challenge to development of adequate prevention and treatment strategies is limited understanding of BPD endotypes—subsets of patients with distinct pathobiological mechanisms. Notably, characterization of the molecular landscape of late stage human lung development and how this phase of lung maturation is affected by premature birth remains incomplete, in part due to limited availability of human tissue samples. To address these limitations, we explored the potential of tracheal aspirate-derived mesenchymal stromal cells (MSCs) to reflect the molecular landscape of the preterm lung. Earlier reports have demonstrated that these cells are lung-resident stromal cells and can be expanded in culture. We applied weighted gene co-expression network analysis (WGCNA) to explore the highly dimensional gene-expression space of premature tracheal-aspirate derived MSC line. The gene regulatory network analysis revealed gene modules that correlated with the gestational age (GA) at MSCs collection and the severity of BPD, suggesting that tracheal-aspirate derived MSC transcriptomes retain transcriptional dynamics of the preterm lung.

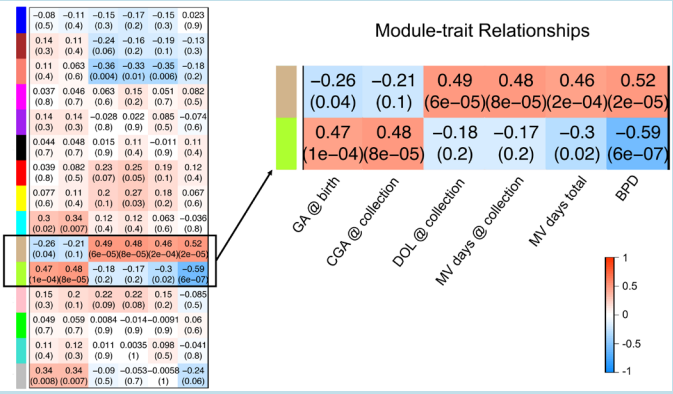
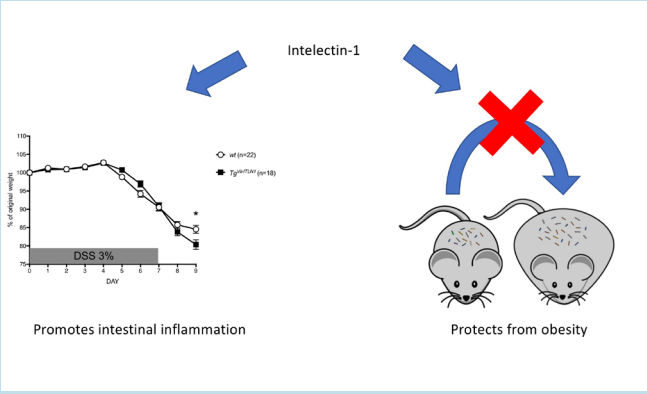


Figure legend: Correlation of nTAD MSC transcriptome WGCNA modules with clinical traits. GA = gestational age; CGA = corrected gestational age; DOL = day of life; MV = mechanical ventilation.



Lung-Resident Mesenchymal Stromal Cells Reveal Transcriptional Dynamics of Lung Development in Preterm Infants.
Spadafora R, Lu J, Khetani RS, Zhang C, Iberg A, Li H, Shi Y, Lerou PH.
Am J Respir Crit Care Med. 2018 Oct 1;198(7):961-964

We have explored the role of Intelectin-1(ITLN1) in the intestinal inflammatory response and have focused on how it modifies the intestinal microbiota.ITNL1 binds glycans expressed in microorganisms, but its physiological role is unclear. We are using murine models to understand how this molecule modifies the susceptibility of the host to intestinal inflammation and obesity at the microbial-intestinal interface. Our results to date suggest that ITLN1 increases the susceptibility of the host to intestinal inflammatory responses, and is protective for the development of obesity in response to a high-fat diet.

Nephrology

In the proximal renal tubules of the kidneys, two sodium-phosphate co-transporters, namely NaPi2a (SLC34A1) and NaPi2c (SLC34A3), are the major facilitators of reabsorption of phosphate from the glomerular filtrate. Inhibition of NaPi2a was therefore expected to enhance urinary phosphate excretion, possibly correcting mineral ion and hormonal derangements associated with hyperphosphatemic disorders. To date, only non-selective NaPi inhibitors have been described. We now discovered the first series of selective NaPi2a inhibitors through high-throughput screening. One of these inhibitors (PF-06869206) is orally active and is now being explored in animal models of tumoral calcinosis, acute kidney injury, and early stages of chronic kidney disease (CKD). Prevention of hyperphosphatemia through the NaPi2a inhibitor thus preventing

elevations in FGF23 levels in CKD patients could help slow progression of renal disease towards end-stage.

Filipski K, Sammons M, Bhattacharya S, Panteleev J, Brown J, Loria P, Boehm M, Smith A, Shavnya A, Conn E, Song K, Weng Y, Facemire C, Jüppner H, Clerin V. The discovery of orally bioavailable selective inhibitors of the sodium-phosphate co-transporter NaPi2a. ACS Med Chem Lett. 2018; 9:440-445. PMID: 29795756. PMCID: PMC5949730

Steroid-resistant nephrotic syndrome (SRNS) is a common cause of ESRD in patients presenting under 25 years of age. We performed mutation analysis in 24 single-gene causes of SRNS in a cohort of 72 families, who presented with SRNS before the age of 25 years. Within an 18-month interval, we obtained DNA samples, pedigree information, and clinical information from 77 consecutive children with SRNS seen at Boston Children's Hospital (BCH). Mutation analysis was completed by combining high-throughput multiplex PCR with next-generation sequencing. We analyzed the sequences of 18 recessive and 6 dominant genes of SRNS in all 72 families for disease-causing variants. We identified the disease-causing mutation in 8 out of 72 (11.1%) families. Mutations were detected in the six genes: NPHS1 (2 out of 72), WT1 (2 out of 72), NPHS2, MYO1E, TRPC6, and INF2. As our cohort was mostly non-consanguineous patients, our identification rate of 11.1% reflects that of other groups where the population studied was non-consanguineous in nature. This study demonstrates that understanding the molecular diagnosis may have important consequences for the management and treatment of those patients with steroid-resistant nephrotic syndrome. This study helped pave the way for future exome studies once WES technology became cheaper and more feasible.

Tan W, Lovric S, Ashraf S, Rao J, Schapiro D, Airik M, Shril S, Gee HY, Baum M, Daouk G, Ferguson MA, Rodig N, Somers M, Stein D, Vivante A, Warejko JK, Widmeier E, Hildebrandt F. Analysis of 24 genes reveals a monogenic cause in 11.1% of cases with steroid resistant nephrotic syndrome at a single center, Pediatric Nephrology, 2018; 33(2):305-314. PMID: 28921387

Jansen metaphyseal chondrodysplasia (JMC) is caused by heterozygous activating PTH/PTHrP receptor mutations that lead to severe mineral ion abnormalities, delayed chondrocyte differentiation, and short stature. We have now collected clinical and laboratory data for a large cohort of JMC patients and showed all PTHR1 mutations, except for the T410R mutation, were associated with indistinguishable mineral ion abnormalities and similarly severe growth impairment. Hypercalciuria persisted into adulthood. An inverse agonist ligand effectively reduced in vitro PTH-independent cAMP formation at all five PTHR1 mutants, suggesting a potential path towards therapy.

Saito H, Noda H, Gatault P, Böckenhauer D, Loke KY, Hiort O, Silve C, Sharwood E, Matsunaga Martin R, Dillon MJ, Gillis D, Harris M, Rao SD, Pauli RM, Gardella TJ, Jüppner H. Progression of Mineral Ion Abnormalities in Patients with Jansen's Metaphyseal Chondrodysplasia. J Clin Endocrinol Metab. 2018;103:2660–2669. PMID: 29788189

Jerrold F. Rosenbaum, MD, Chief

Psychiatric disorders are the leading cause of disability worldwide. The MGH Department of Psychiatry is dedicated to alleviating the suffering and burden of mental illness through its four-fold mission:

- ***Clinical Care:*** The Department of Psychiatry aims to provide the highest standard of care for our patients and their families across the full spectrum of psychiatric, psychological and substance use disorder, both for adults and children/adolescents. The department's more than 600 affiliated psychiatrists, psychologists and social workers serve as clinicians, researchers, supervisors and/or teachers, and include some of the field's most accomplished and recognized specialists in over 60 clinical and clinical/research programs, particularly in psychopharmacology, cognitive-behavioral therapy and behavioral medicine. For its exceptional results in patient care, the MGH Department of Psychiatry has been rated the #1 department of psychiatry in 19 of the past 24 years (during all of which we have been in the top three) in the annual "America's Best Hospitals" survey by US News & World Report.

- ***Research Innovation:*** The Department's vast array of clinical, translational and basic research programs is dedicated to pioneering advances in neuroscience, genetics, therapeutics and the prevention of psychiatric disorders. The department has one of the three largest clinical research programs in the hospital. Using cutting-edge tools such as neuroimaging, genetics and genomics, and experimental animal and cellular models, Department of Psychiatry researchers are beginning to map the pathways through which brain biology interacts with life circumstances and events to produce psychiatric illnesses. This research is making it possible to pinpoint affected areas of the brain; understand inherited risk factors and the role of environmental stress; develop more effective psychotherapies, medications, and neurotherapeutic treatments; and ultimately to prevent these illnesses from occurring by intervening early. In FY18, the Department had almost $70 million in research support, continuing its record of successful funding despite an increasingly challenging funding environment.

MGH Department of Psychiatry
Publications 2018

Journal Articles	850
Books/chapters	5
	855

- ***Professional Education: T***he Department of Psychiatry offers in-depth postgraduate education that trains the next generation of mental health professionals. For our colleagues at MGH and across the globe, our experts share the latest clinical and research advances to help improve access to and quality of psychiatric care. Each year, we train close to 100 adult and child psychiatry residents, psychology interns and clinical fellows to be leaders in their areas of specialization. In addition, our educational efforts reach another 65,000 psychiatrists, non-psychiatric physicians and other health professionals through the Psychiatry Academy and its dozens of webinars, simulations, online courses, live conferences and more. The Department also educates professionals in education, law enforcement, and the military who work with patients and families affected by psychiatric conditions. Through an array of programs, our experts provide them with an enhanced understanding of mental health techniques they can use to assist affected individuals.

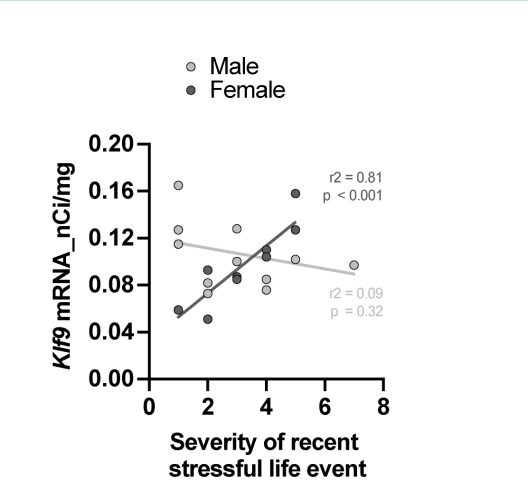
  The Psychiatry Academy continued to grow its new program, Mass General Visiting. Visiting's goal is to reduce the risks and disparities associated with physician shortages, improve patient outcomes, and provide education and quality leadership in health care systems. Partnering with health care organizations of all sizes, the program creates high-level quality improvement programs. We do this by engaging the extensive faculty and resources of Massachusetts General Hospital and Harvard Medical School and apply that expertise to provide customized solutions for provisional clinical services, telehealth, interim leadership personnel, continuing medical education, and clinical and financial consultation. In 2018, the Visiting program grew from 8 to 14 assignments, a 75% increase.

- ***Community Service:*** To address the mental health needs of people who live in MGH neighborhoods and suffer from mental illness, substance use disorders, poverty, immigration challenges, homelessness and multiple trauma, the Department of Psychiatry partners with local organizations through its Division of Public and Community Psychiatry. Last year and continuing, as part of the MGH Strategic Plan, and with the Department of Medicine, we are engaged in a hospital wide Substance Use Disorders (SUDS) initiative, one

feature of which involves the inclusion of people in recovery from addiction ("recovery coaches") as part of the treatment team. New in FY18 is the Hope Clinic, which provides care and treatment for pregnant women with substance use disorders and their families, through the first three years of life of their child. The Department also offers free patient and family education programs in Boston through its Psychiatry Academy. To serve the hospital's global neighbors, the Chester M. Pierce, MD Division of Global Psychiatry, the first hospital global psychiatry program in the United States, addresses the acute shortage of mental health professionals in developing countries through program development and training.

Besnard et al: A genetic regulator of resilience to chronic stress in mice and humans

Stress exposure is associated with the pathogenesis of psychiatric disorders including post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Furthermore, the incidence of stress-related psychopathologies including MDD and PTSD is higher in women than in men. Thus, identifying molecular and circuit level changes that mediate vulnerability or resilience to chronic stress may edify new strategies to treat these debilitating disorders. Here, Dr. Sahay and his team at the Center for Regenerative Medicine and Department of Psychiatry identified a stress-responsive gene, Klf9, that moderates the detrimental effects of chronic stress on neuronal connectivity and fear responses. The authors found that acute stress elevated, whereas chronic stress decreased, levels of Klf9 expression in the hippocampus of male and female mice. To determine if these changes in Klf9 expression mediated the effects of stress or protected against stress, the authors used molecular genetic strategies to silence Klf9 expression before and after the onset of stressor. Dr. Sahay's team found that silencing Klf9 expression prior to, but not after the stressor, prevented chronic stress related alterations in synapses, circuits and fear-related behavior. In collaboration with Dr. Boldrini's group at Columbia University, the authors found that that Klf9 expression was elevated in the hippocampus of women with stressful life experiences and major depressive disorder. These observations suggest that a greater understanding of Klf9 dependent actions on hippocampal circuitry may illuminate strategies to confer resilience to chronic stress.



Women with stressful life experiences and with MDD, unlike men, exhibit elevated levels of Klf9 in the hippocampus.

Antoine Besnard , Tomer Langberg, Sally Levinson, Duong Chu, Cinzia Vicidomini, Kimberly N. Scobie, Andrew Dwork, Victoria Arango, Gorazd Rosoklija, John J. Mann, Rene He, Eduardo D. Leonard, Maura Boldrini and Amar Sahay. Targeting Kruppel-like factor 9 in excitatory forebrain neurons protects against chronic stress-induced impairments in dendritic spines and fear responses. Cell Reports 2018 23 (11): 3183-3196.

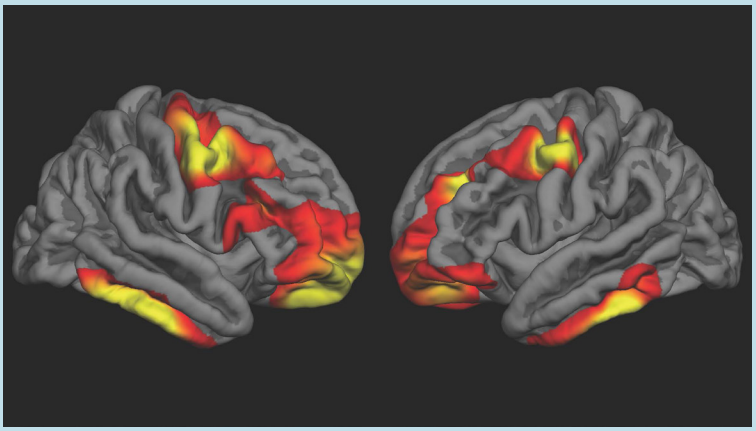
Cao et al 2018: Analgesic Effects Evoked by Real and Imagined Acupuncture.

Acupuncture can provide therapeutic analgesic benefits but is limited by its cost and scheduling difficulties. Guided imagery is a commonly used method for treating many disorders, such as chronic pain. A large body of literature suggests that common brain areas are activated / deactivated during direct and vicarious (observational) experiences. We developed a new treatment method that combines video-guided imagery and acupuncture, entitled "video-guided acupuncture imagery treatment" (VGAIT), and compared the analgesic effects of real acupuncture, sham acupuncture, VGAIT, and VGAIT control using a crossover design in 27 healthy subjects.

We found that VGAIT can produce greater analgesic effects than VGAIT control, and the effect is comparable with real acupuncture. Functional magnetic resonance imaging analysis showed that real acupuncture produced greater activation of the insula compared with VGAIT. VGAIT produced greater deactivation at the rostral anterior cingulate cortex, a key region in default mode network. Now, we are testing VGAIT on a chronic pain population. If successful, it will provide a new, more cost-effective treatment option for patients with chronic pain and may reduce prescription opioid usage.

Jin Cao, Yiheng Tu, Scott P. Orr, Courtney Lang, Joel Park, Mark Vangel, Lucy Chen, Randy Gollub and Jian Kong. Analgesic Effects Evoked by Real and Imagined Acupuncture: A Neuroimaging Study. Cerebral Cortex, 2018, doi: 10.1093/cercor/bhy190. [Epub ahead of print]

Eryilmaz et al. 2018: Association of prenatal exposure to population-wide folic acid fortification with altered cerebral cortex maturation in youths.



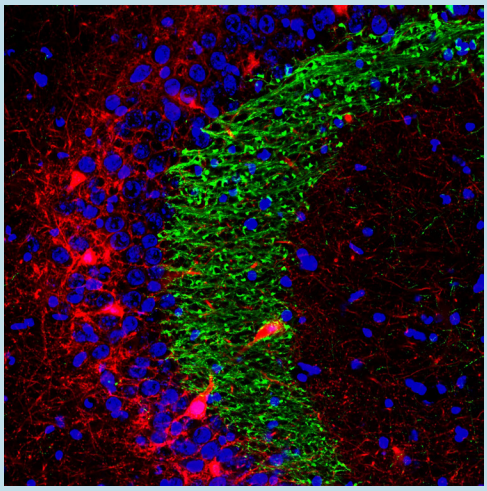
Effects of prenatal folic acid fortification exposure on brain development. Colored areas indicate regions of the cerebral cortex that are significantly thicker in youths who were exposed to folic acid fortification during pregnancy, compared to youths who were not exposed.

Risk for schizophrenia begins in the womb, and fetal development may present a window for primary prevention. However, to date no specific prenatal interventions have been associated with protection against schizophrenia risk later in life. Building on our previous clinical trials of folic acid in chronic schizophrenia patients, we examined effects of increased prenatal folic acid exposure on brain development and psychosis risk during childhood and adolescence. After a review of >3,000 medical records, we identified 3 matched groups of 8- to 18-year-old youths who underwent clinical brain MRI scans at MGH, and who received variable prenatal folic acid exposure by virtue of having been born just before, during, or just after the implementation of government-mandated grain product fortification in the late 1990s. Youths who were exposed to fortification exhibited more favorable patterns of cortical development, a pattern that replicated in a second cohort of 862 youths enrolled in the Philadelphia Neurodevelopmental Cohort (PNC). Among PNC participants, folate-related changes in brain development were also associated with reduced risk of psychosis spectrum symptoms. This work suggests that prenatal folic acid exposure may protect against subsequent risk for schizophrenia through long-lasting changes in postnatal brain development. With >70,000 article views, it is the most widely read paper published in JAMA Psychiatry in 2018 and has received coverage in international (Daily Mail), national (Reuters, US News), and local (Boston Herald) media.

Eryilmaz Y, Dowling KF, Huntington FC; Rodriguez-Thompson A, Soare TW, Beard LM, Lee H, Blossom JC, Gollub RL, Susser E, Gur RC, Calkins ME, Gur RE, Satterthwaite TD, Roffman JL. Association of Prenatal Exposure to Population-Wide Folic Acid Fortification With Altered Cerebral Cortex Maturation in Youths. JAMA Psychiatry. 2018;75(9):918-928.

Guo et al: A synaptic regulator of memory precision and generalization

All memories lose details over time and this results in memory generalization. Excessive loss of memory precision characterizes age-related cognitive decline and over-generalization of traumatic memories is a hallmark of post-traumatic stress disorder (PTSD). By identifying a molecular factor, Ablim3, that governs hippocampal synaptic connectivity underlying GABAergic inhibition, Dr. Sahay and his team at the Center for Regenerative Medicine and Department of Psychiatry found that they could slow down the time-dependent decay of details of fear memories. Dr. Sahay's group used an arsenal of cutting-edge approaches to demonstrate that targeting ABLIM3 resulted in increased GABAergic inhibition in the hippocampus and stabilization of memory traces over time. And this in turn, slowed down the loss of details and generalization of fear memories in both adult and aged mice. Interestingly, Ablim3 expression is dysregulated in blood of aged individuals who exhibit memory impairments. Dr. Sahay's work predicts that the same circuit-based endophenotypes (such as loss of hippocampal GABAergic inhibition) may underlie memory over-generalization in PTSD and age-related cognitive decline. Drugs that target Ablim3 may represent a new class of connectivity-based cognitive enhancers that improve memory precision in aging and decrease fear over-generalization in PTSD.



A cross section of the hippocampus showing green finger like synaptic projections called filopodia contacting red "inhibitory" neurons —a circuit-based substrate for memory precision and generalization in adulthood and aging.

Nannan Guo, Marta E. Soden, Charlotte Herber, Michael TaeWoo Kim, Antoine Besnard, Paoyan Lin, Xiang Ma, Constance L. Cepko, Larry S. Zweifel and Amar Sahay. Dentate granule cell recruitment of feedforward inhibition governs engram maintenance and remote memory generalization. Nature Medicine 2018 24(4):438-449.

Radiation Oncology

Department Report

Jay S. Loeffler, MD, Chief

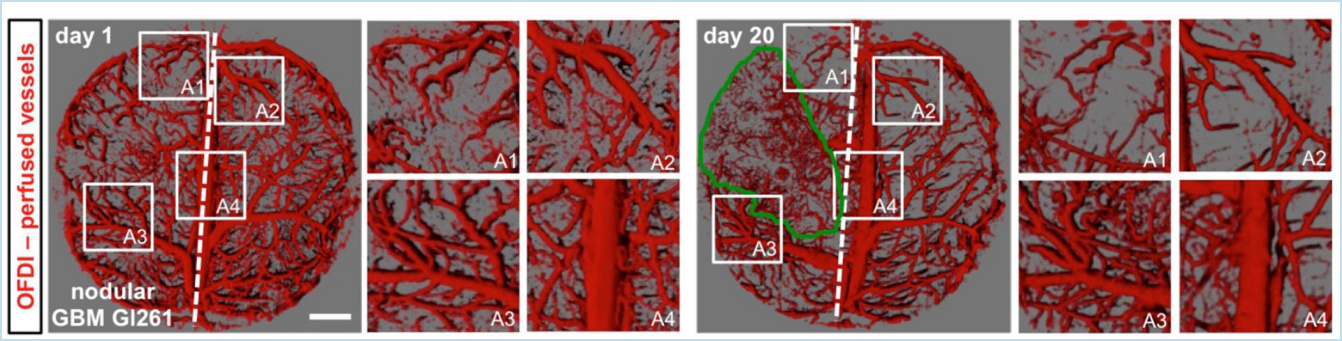
The Mass General Department of Radiation Oncology spent approximately $23M on research work in 2018. Nearly 80% of the department's research funding originates from NIH/NCI support. The department has an impressive record as a highly collaborative research team, reflected in the rich publication record of our faculty with over 256 publications in 2018.

Presently, the main areas of research focus within the department include clinical trials, proton research, pediatric research, physics research, translational research, and laboratory-based basic research. The department boasts an extensive physics research program including efforts in bio-mathematical modeling, outcome modeling, Monte Carlo simulations, and optimization of intensity-modulated photon and proton therapy. Mass General Radiation Oncology also has an active tumor and radiation biology program with major interests in tumor microenvironment, DNA repair, and precision radiation medicine. It is anticipated that research conducted in the Department of Radiation Oncology will lead to improved approaches to radiation therapy in cancer treatment and will help further understanding of mechanisms of radiation-induced toxicities, leading to development of novel targets for cancer therapy as well as new preventative approaches.

Achievements from Calendar year 2018:

1) Department General Achievements:

The Department places emphasis on providing resources to promote research activities by conducting an annual research retreat. In 2018, The Department of Radiation Oncology's Annual Research Retreat took place on September 13, 2018 and focused on "Big Data for Radiation Oncology Researchers," with researchers inside and outside the Department of Radiation Oncology discussing their experiences working with Big Data. Hugo Aerts, PhD, Director of the Computational Imaging and Bioinformatics Laboratory at Harvard-DFCI, spoke on "Artificial Intelligence in Cancer Imaging," and Kevin Hughes, MD, Surgical Director of the Breast Screening Program at MGH Cancer Center provided "A successful example of conducting Big Data Research." Radiation Oncology clinicians Yen-Lin Chen, MD and Torunn Yock, MD, MCH; physicists David Craft, PhD and Susu Yan, PhD; and Steele Labs researcher Lance Munn, PhD provided insights on Big Data activities and directions within the department.

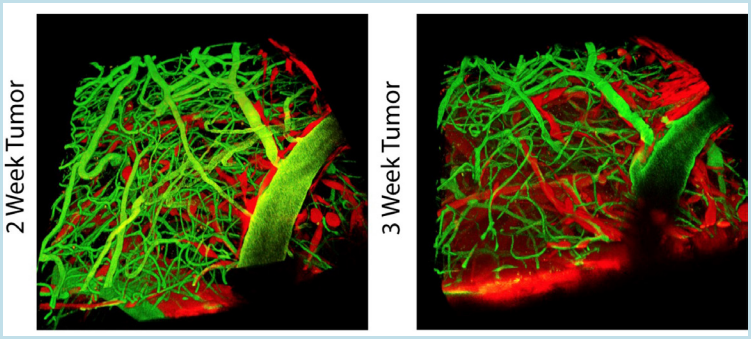


Growth-induced forces affect physiology in glioblastomas. Using clinical imaging and preclinical studies, we discovered that a subgroup of primary and metastatic brain tumors, classified as nodular based on the growth pattern, exert solid stress on the surrounding brain tissue, leading to a decrease in local vascular perfusion, as well as neuronal death and impaired function. The image shows disruption of the vasculature using longitudinal OCT intravital angiography (perfused vessels) of the nodular GI261 mouse model. Scale bar: 1 mm [From Seano et al., "Neurological dysfunction caused by brain tumor-generated solid stress is reversed by lithium", Nature Biomedical Engineering, published online on Jan 7, 2019].

2) Physics Achievements:

- Thomas Bortfeld, PhD, Chief of the MGH Physics Division in Radiation Oncology, was awarded the Glocker Medal, the highest award from the German Medical Physics Society (DGMP). The award is named after Richard Glocker, one of the last PhD students of C.W. Röntgen. Dr. Bortfeld received this award in September 2018 at the annual DGMP meeting in Nuremberg, Germany.
- Jan Schuemann, PhD, Head of the Multi-Scale Monte Carlo Modeling Lab in the Physics Division and Assistant Professor of Radiation Oncology, received the 2018 Michael Fry Research Award from the Radiation Research Society. This award recognizes junior scientists who have made extraordinary contributions to the field of radiation research.
- Jan Schuemann, PhD was also awarded the Damon Runyon-Rachleff Innovation Award from the Damon Runyon Cancer Research Foundation. The Ramon Runyon-Rachleff Innovation Award provides funds to extraordinary researchers with ideas that have the potential to impact our understanding and/or approach to prevention,diagnosis, and treatment of cancer.

- Stefan ten Eikelder, MS, received the Jan Hemelrijk Award for his Master's thesis "Optimal fractionation for combined photon-proton treatments" from The Netherlands Society for Statistics and Operations Research.
- Stefan ten Eikelder, MS, received the Tilburg University Master's Thesis Prize 2017
- Stefan ten Eikelder, MS, received the Philips prize for Data Science in Healthcare, one of the Young Talent Awards of the Royal Holland Society of Sciences and Humanities.
- David Gierga, PhD, was elected as a Fellow of the American Association of Physicists in Medicine (AAPM).
- Jay Flanz, PhD, was re-elected as the Chairman of the Particle Therapy Co-Operative Group (PTCOG) for the second term.
- Susu Yan, PhD, received an early career scholarship award at the Winter Institute of Medical Physics
- Harald Paganetti, PhD, Director of Physics Research, received an R01 grant on "Fast Individualized Delivery Adaptation in Proton Therapy" from the National Cancer Institute



Growth-induced forces affect physiology in glioblastomas. Using clinical imaging and preclinical studies, we discovered that a subgroup of primary and metastatic brain tumors, classified as nodular based on the growth pattern, exert solid stress on the surrounding brain tissue, leading to a decrease in local vascular perfusion, as well as neuronal death and impaired function. The image shows disruption of the vasculature using longitudinal OCT intravital angiography (perfused vessels) of the nodular GI261 mouse model. Scale bar: 1 mm [From Seano et al., "Neurological dysfunction caused by brain tumor-generated solid stress is reversed by lithium", Nature Biomedical Engineering, published online on Jan 7, 2019].

- Harald Paganetti, PhD, is also the site-PI of a multi-million dollar U24 grant awarded by the NCI (PI, Faddegon, UCSF) leveraging the TOPAS TOol for PArticle Simulation software, which was launched on NCI funding in 2009 and further advanced through a R01 at MGH (PI, Jan Schuemann, PhD). This a breakthrough software that allows a better understanding of how subatomic particles travel through apparatus and tissue. It will be used to create a fully integrated platform for improving advanced radiotherapy including multi-modality treatments and a broad range of image guidance.
- The prompt gamma proton range detector developed by Joost Verburg, PhD, and his team was listed as one of the five breakthroughs of the year 2018 in medical physics and biosciences.

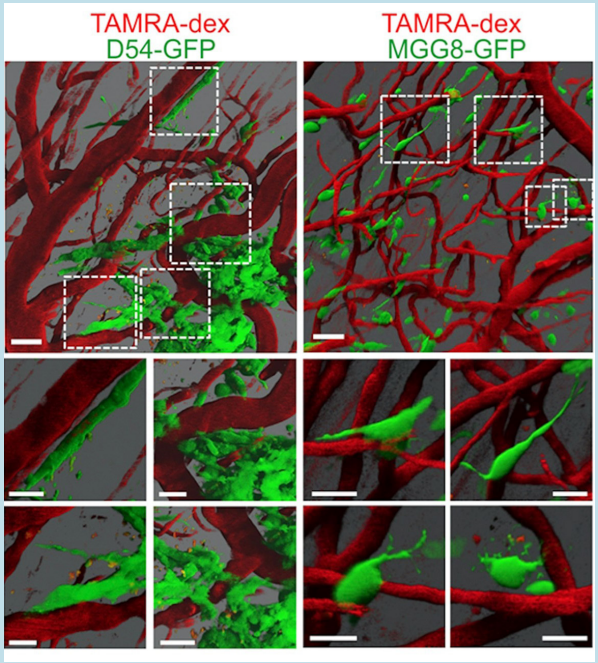
3) Clinical Research Achievements:

- In 2018, the Department of Radiation Oncology maintained 42 active clinical trials, with an additional 6 that were completed, and 369 clinical trial accruals.
- U19 investigators from MGH (Thomas F. Delaney, MD, and Noah C. Choi, MD) and lead authors at the MDACC published in the Journal of Clinical Oncology the results of the first completed randomized clinical trial comparing proton beam therapy to standard photon radiation employing the same radiation doses, which was conducted in patients with locally advanced non-small cell lung cancer.
- The Pediatric Proton Consortium Registry (PPCR), a consented registry established and headed by Torunn Yock, MD, MCH, Associate Professor of Radiation Oncology, to expedite outcomes research on proton radiotherapy and to better define the role of proton radiation in treating pediatric cancers, celebrated in January 2018 the milestone of having enrolled its 2000th patient.
- William U. Shipley, MD, Jason A. Efstathiou, MD DPhil, and colleagues reported on the results of NRG/RTOG 0712, a randomized phase II trial examining different chemo/radiation regimen in muscle-invasive bladder cancer, which was published in the Journal of Clinical Oncology. Both regimens achieved high rates of disease control and organ preservation.
- Helen A. Shih, MD, and colleagues reported important data on the safety of combining immune checkpoint inhibitor therapy with stereotactic radiosurgery in an institutional analysis of 163 lung cancer patients with brain metastases, published in the Journal of Thoracic Oncology.
- In a physics/clinical collaboration, Harald Paganetti, PhD, Director of Physics Research, and Rachel Jimenez, MD, Breast Radiation Oncologist, obtained provocative data suggesting that proton beam radiation can have different biological effectiveness in normal tissues in the thorax than previously assumed – published in the International Journal of Radiation Oncology, Biology, Physics.
- Theodore S. Hong, MD, published a paper on the research study of Borderline resectable Pancreatic Cancer in JAMA Oncology 2018 – 50 patient phase II neoadjuvant FOLFIRINOX followed by radiation demonstrating a 3 yr. Overall survival (OS) > 60%
- At the ASCO 2018 meeting, Theodore S. Hong, MD, presented on his research study on Locally advanced Pancreatic Cancer of 50 patient phase II of neoadjuvant FOLFIRINOX with Losartan followed by Radiation demonstrating resection rate of > 60% (historical 10%). This

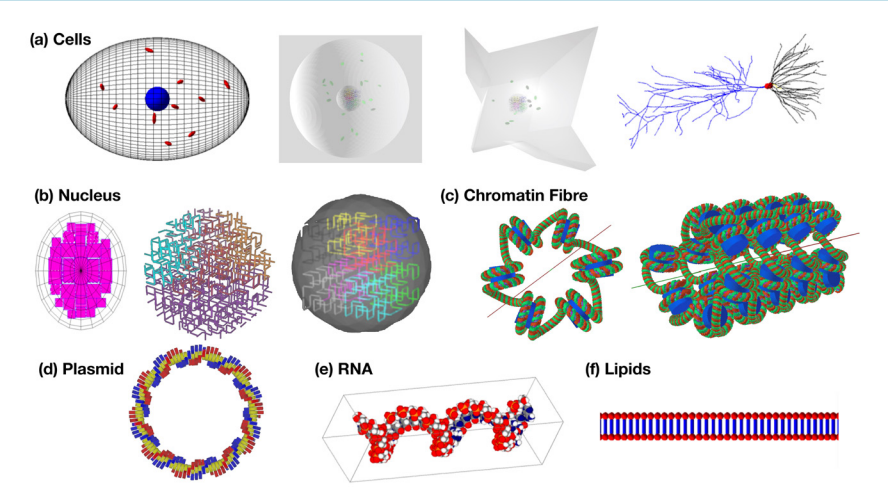
publication provided data for the SU2C grant and multi-institutional randomized trial (Grant PI- David Ryan, study PI- Hong). The scientific rationale was built on ground breaking work from Yves Boucher PhD and Rakesh Jain, PhD.

4) Biology Achievements:

- Kathryn D. Held, PhD, Associate Radiation Biologist in the Department of Radiation Oncology at MGH and Associate Professor of Radiation Oncology (Radiation Biology) at Harvard Medical School, has been selected to serve as the sixth President of the National Council on Radiation Protection and Measurements (NCRP), effective January 1, 2019.
- David Miyamoto, MD, PhD, Assistant Professor of Radiation Oncology, and his research team published a new method to detect and characterize circulating tumor cells in the blood more accurately and efficiently than existing methods, with important implications for treatment decision making in prostate cancer. "An RNA-based digital circulating tumor cell signature is predictive of drug response and early dissemination in prostate cancer" was published in the March 2018 edition of Cancer Discovery.
- David Miyamoto, MD, PhD and Henning Willers, MD, were awarded a $150,000 grant to support their research proposal on investigating mechanisms of DNA repair after proton radiation by the Aid for Cancer Research (ACR) at the 70th annual ACR luncheon on May 21, 2018. Drs. Willers and Miyamoto aim to establish a differential effect of proton radiation on the production and removal of chromosomal DNA breaks, as compared to standard photon radiation.
- Received notice of award for a $2.8M U01 grant proposal on High-Throughput Screening and Validation of Molecular Targeted Chemoradiosensitizers, which is being co-led by Henning Willers, MD, \Director of the Thoracic Radiation Oncology Program, and Cyril Benes, PhD, Director of the MGH Center for Molecular Therapeutics. This grant, one of four U01s awarded by the NCI on this topic, aims to identify biomarker-correlated combinations of chemoradiation with targeted agents in difficult-to-treat cancers.
- Melin J. Khandekar, MD, PhD, clinician-scientist, and colleagues published a paper in the Proceedings of the National Academy of Science USA reporting that a novel type of anti-diabetic drug working on the PPAR-g protein can increase the efficacy of chemotherapy in lung cancer. Modulation of this pathway in patients using already existing anti-diabetic drugs may be a viable strategy to increase the efficacy of conventional anti-cancer therapies.



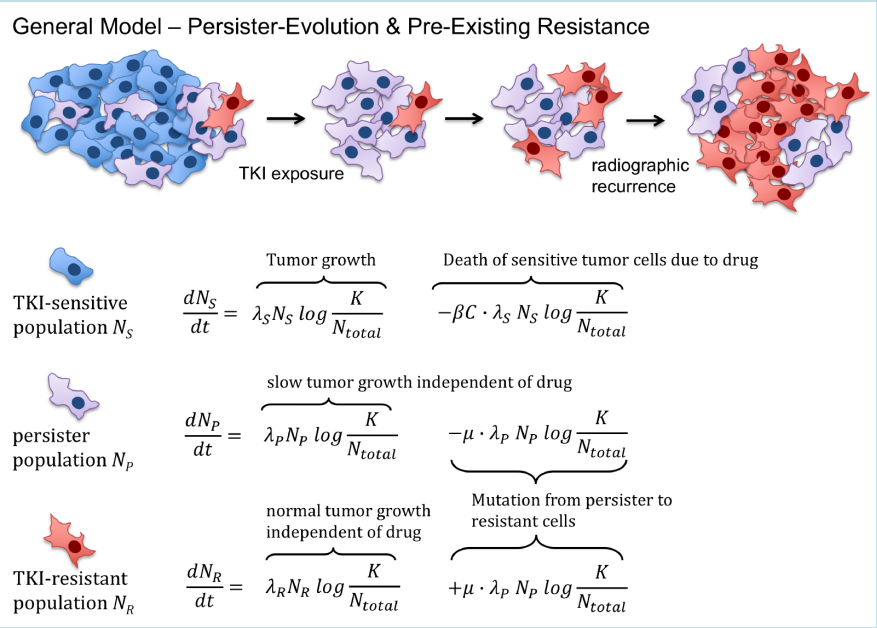
Schematic of intravital imaging procedure and 3-D renderings of 20-μm-deep z-stacks of patient-derived glioblastoma cell lines D54-GFP and MGG8-GFP (green) implanted in nude mice. Blood vessels were visualized using TAMRA (tetramethylrhodamine)-dextran (red). Scale bars, 50 μm and 25 μm (insets). Intriguingly we observed that D54 used collective migration, while MGG8 predominantly employed single-cell migration. [From A Griveau, et al. A glial signature and Wnt7 signaling regulate glioma-vascular interactions and tumor microenvironment. Cancer Cell (2018)].



Computer simulations (using the in-house developed TOPAS-nBio toolkit) of cellular and sub-cellular structures to study energy deposition events caused by ionizing radiation as well as subsequent biological damage and repair. (a) An ellipsoid cell shown with a nucleus (blue) and mitochondria (red), a spherical and a fibroblast cell with nucleus and mitochondria. Also shown is a hippocampal neuron with a soma (red) and dendrites (black and blue). (b) Three full nucleus models, one based on the Geant4-DNA example (left) and two different fractal models (center and right). (c) A chromatin fiber consisting of nucleosomes each composed of histone proteins (blue) wrapped by two turns of a double helix DNA (green and red). (d) A circular plasmid consisting of 100 basepairs. (e) RNA strand recreated using the TOPAS-nBio interface to the protein database. (f) A lipid (membrane) layer. From the Schuemann Lab.

Edwin Steele Laboratories Highlights:

- Rakesh K. Jain, PhD, was elected to the National Academy of Inventors and received the Earl Benditt Award, North American Vascular Biology Organization (NAVBO); and gave the 2018 Maud Menten Lecture at University of Pittsburgh
- Rakesh K. Jain, PhD was also named to the list of "Highly Cited Researchers 2018" by Clarivate Analytics / Web of Science. This list "recognizes world-class researchers selected for their exceptional research performance, demonstrated by production of multiple highly cited papers that rank in the top 1% by citations for field and year in Web of Science." This is the fifth year in a row that Dr Jain has been a Highly Cited Researcher.
- Timothy Padera, PhD, head of the Padera Lab of the Edwin L. Steele Laboratories for Tumor Biology and Associate Professor in Radiation Oncology at Harvard Medical School, was elected to the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows in the Class of 2019. This peer-nominated recognition is designated for the most accomplished and distinguished scientists, academic researchers, and clinical practitioners in the fields of medical and biological engineering.
- Dan G. Duda, DMD, PhD, director of Translational Research in GI Radiation Oncology and head of the Duda Lab of the Steele Laboratories, received the 2018 Pilot Project Grant Award from the Neuroendocrine Tumor Research Foundation – along with colleague Jennifer Chan, MD, MPH, of the Dana Farber Cancer Institute (DFCI)
- Lei Xu, MD, PhD, received the 2018 Drug Discovery Initiatives Award from the Children's Tumor Foundation
- Dennis Jones, PhD, was named a STAT 2018 Wunderkind
- Shuichi Aoki, MD, PhD, received the 2018 Cholangiocarcinoma Foundation Fellowship Award for his project on understanding the role of PlGF in shaping liver cancer microenvironment and treatment resistance
- Kosuke Kawaguchi, MD, PhD, received Japan Society of Promotion of Science Overseas Research Fellowship
- Nilesh Talele, MSc, PhD, received Cancer Research Institute Irvington Postdoctoral Research Fellowship
- Sampurna Chatterjee, PhD, received a Pediatric Cancer Foundation Post-Doctoral Fellowship
- Jun Ren, PhD, received Tosteson-FMD Postdoctoral Fellowship from MGH-ECOR



Determining persistent and resistant cancer cell populations during treatment with targeted therapies based on patient-specific tumor growth trajectories. The figure shows our general model and system of differential equations describing the temporal evolution of all subpopulations, including both persister-evolution and pre-existing resistance. The model can be sued to design treatment regimens when combining TKI inhibitors with radiation. From the Grassberger Lab.

Radiology

Department Report

James Brink, MD, Chief

Under the leadership of Dr. James Brink, the Department of Radiology provides excellence in patient care, teaching and research. The research mission of the Department includes primary radiology research and extensive collaborative research with investigators from Departments and Centers at MGH, Harvard and MIT. Our strategic priority is the continuous development of intellectual and physical resources to enable researchers within and outside of Radiology to translate and apply their research into clinical care.

Primary Radiology Research includes:

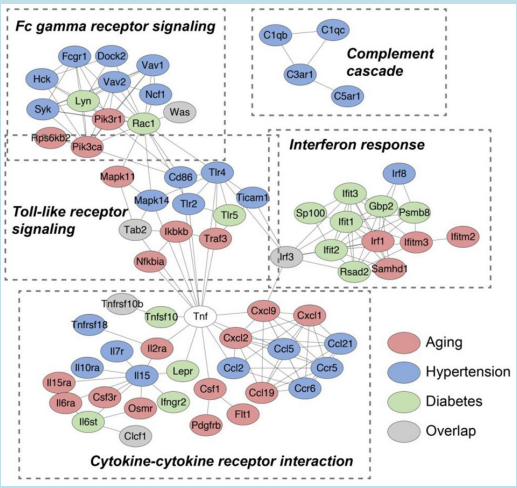
- Instrumentation and algorithm development for data acquisition and analysis to discover and/or measure novel biological processes and structures;
- Design and synthesis of molecular agents (PET, MR, optical) for assessment of receptors, abnormal proteins and other biological targets of disease;
- Assessment of novel instrumentation and molecular imaging agents in preclinical disease models and in clinical research;
- Translation of these discoveries, in concert with industry, into patient care and;
- Development and application of analytic tools including machine learning to support economically-based assessment of medical imaging technologies and outcomes.

Our research enterprise is conducted through Radiology Centers (The Martinos Center, The Gordon Center and The Center for Clinical Data Science); The Institute of Technology Assessment; research Programs including the Cardiac MR PET CT Program (a joint radiology cardiology program) and a Program in Neuroprotection. The Department also operates Core Facilities: the MRI Core, the PET Core and the Tumor Imaging Metrics Core that support many MGH research investigators especially from Cardiology, Neurology and Oncology.

Through its research Centers, major Programs and Core facilities, the Department has significantly enabled the research efforts of many investigators in Cardiology, Neurology, Oncology, Pathology, Psychiatry, Radiation Medicine, Surgery and other MGH Departments. The MGH Radiology Department is recognized as the national leader in Radiology research based on its scientific output and NIH funding. For the past 16 years among all academic Radiology departments, MGH has held the #1 ranking in annual NIH funding (FY18 ~ $70M) received. Approximately 200 Radiology members serve as principal investigators on one or more grants, either from the NIH or other funding sources, with total research funding of ~ $100M for 2018.

Neuroprotection Research Laboratory - Eng H. Lo, PhD

Over the past 5 years, we have been developing the concept of the vasculome, wherein the microvascular network in the brain is not merely inert plumbing. Instead, this network may represent a trophic endocrine organ embedded within the brain itself. The vasculome contributes to brain pathophysiology and may also release measurable biomarkers into systemic circulation. A diseased vasculome may significantly alter brain susceptibility to injury and disease. We mapped the brain and heart vasculomes in young versus old mice, normotensive versus hypertensive mice, and normal versus diabetic mice. Four overall patterns arose from these comparative analyses. First, organ differences between brain and heart were larger than effects of age and co-morbidities per se. Second, across all conditions, more genes were altered in the brain vasculome compared with the heart. Third, age, hypertension and diabetes perturbed the brain and heart vasculomes in mostly distinct ways, with little overlap. Fourth, a few common pathways were detected in the brain, expressed mostly as a suppression of immune response. These initial drafts of the brain and heart vasculomes in the context of aging and vascular comorbidities should provide a framework for designing future investigations into potential targets and mechanisms in CNS disease.



Guo et al, Effects of aging, hypertension and diabetes on the mouse brain and heart vasculomes. Neurobiol Dis 2018.
Subsets of immune network alterations in brain vasculome comprise cytokine-cytokine receptor interactions, Toll-like signaling, complement cascades, and Fc gamma receptor signaling. Note that in spite of the overall suppression of immune function, responses to aging, hypertension and diabetes were mostly unique and showed very little common genes (gray indicates genes affected in all 3 conditions).

Musculoskeletal Division - William Palmer, MD

Sex differences in body composition and association with cardiometabolic risk
Melanie Schorr, MD et. al. Mav Biol Sex Differ. 2018 Jun 27;9(1):28
Body composition differs between men and women, with women having proportionally more fat mass and men more muscle mass. Although men and women are both susceptible to obesity, health consequences differ between the sexes. The purpose of our study was to assess sex differences in body composition using anatomic and functional imaging techniques, and its relationship to cardiometabolic risk (CMR) markers in subjects with overweight/obesity.

We prospectively recruited 208 subjects with overweight/obesity who were otherwise healthy (94 men, 114 women, age:37±10 years, BMI: 35 ±6 kg/m2). Subjects underwent dual-energy X-ray absorptiometry (DXA) and computed tomography (CT) for fat and muscle mass, proton MR spectroscopy (1H-MRS) for intrahepatic (IHL) and intramyocellular lipids (IMCL), an oral glucose tolerance test, serum insulin, lipids and inflammatory markers. Men and women were compared by Wilcoxon Signed Rank test, linear correlation and multivariate analyses between body composition and cardiometabolic risk markers were performed.

Women had higher %fat mass, extremity fat and lower lean mass compared to men ($p \leq 0.0005$). However, men had higher visceral adipose tissue (VAT) and IMCL and higher age-and BMI-adjusted IHL ($p < 0.05$). At similar age and BMI, men had a more detrimental cardiometabolic risk profile compared to women ($p < 0.01$). However, VAT in women, and IMCL in men, were more strongly associated with CMR's, while more lower extremity fat was associated with a more favorable cardiometabolic profile in women compared to men ($p \leq 0.03$). Although the male pattern of fat distribution is associated with a more detrimental CMR's profile compared to women of similar age and BMI, VAT is more strongly associated with CMR markers in women, while IMCL are more detrimental in men. Lower extremity fat is relatively protective, in women more than in men. This suggests that detailed anatomic and functional imaging, rather than BMI, provides a more complete understanding of metabolic risk associated with sex differences in fat distribution.

MGH Institute for Technology Assessment - Pari Pandharipande, MD, MPH

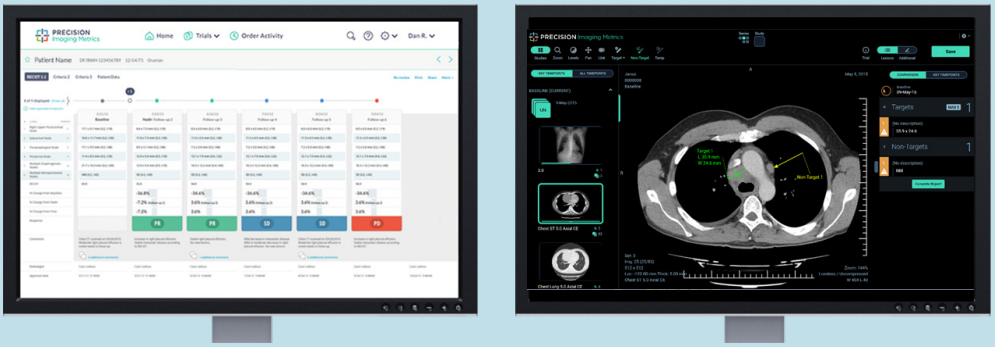
Dr. Chung Yin Kong, together with a team comprised of both ITA researchers and oncologists from the MGH Cancer Center, conducted a study to evaluate the cost-effectiveness of treating patients with unresectable stage III non-small cell lung cancer with durvalumab consolidation therapy (immunotherapy) after definitive chemoradiation. They developed a decision-analytic microsimulation model to estimate the cost per quality-adjusted life-year tradeoff of such a treatment strategy compared to no consolidation therapy. Durvalumab consolidation therapy was estimated to improve quality-adjusted survival by nearly 10% and resulted in an estimated incremental cost-effectiveness ratio of $67,421/quality-adjusted life-year. Using a willingness-to-pay threshold of $100,000/quality-adjusted life-year, durvalumab consolidation therapy was, therefore, found to be cost-effective. Their results suggest that utilizing immunotherapy earlier in the course of treatment represents a viable option from a health economics standpoint, although the overall budgetary implications could be substantial and point to the importance of a reduction in drug price or improved patient selection via biomarkers.

Criss SD, Mooradian MJ, Sheehan DF, Zubiri L, Lumish MA, Gainor JF, *Reynolds KL, *Kong CY (*equal contribution). Cost-effectiveness and Budgetary Consequence Analysis of Durvalumab Consolidation Therapy vs No Consolidation Therapy After Chemoradiotherapy in Stage III Non–Small Cell Lung Cancer in the Context of the US Health Care System. JAMA Oncology. 2018 Dec 13.

Radiology Tumor Imaging Metrics Core - Gordon J. Harris, PhD

The Tumor Imaging Metrics Core (TIMC), co-Directed by Annick D. Van den Abbeele, MD (DFCI) and Gordon J. Harris, PhD (MGH), is a shared resource that was founded in 2004 to provide standardized, longitudinal tumor metrics of radiological scans (CT, MR and PET) for patients enrolled in oncologic clinical trials across the five Harvard teaching hospitals of the Dana-Farber/Harvard Cancer Center (DF/HCC). The independent web-based tumor response measurements provided by the Core facilitates the evaluation of new therapies tested and/or developed at DF/HCC and other Cancer Centers. The ordering, communication, workflow, results reporting, electronic signatures, audit trails, criteria conformance, and chargeback billing are all managed through a web-based informatics platform, Precision Imaging Metrics, developed by TIMC, which is currently in use at eight NCI-designated Cancer Centers around the country, with several other Cancer Centers considering implementing it soon. Clinical trials imaging assessment results are provided with high-quality data compliant with the trial-specific protocol criteria. Results are available on-line in time for review at the point of care in as little as one hour after completion of scanning. TIMC currently manages over 1,000 active clinical trials and performs over 17,000 image assessments per year for DF/HCC investigators. The figure below shows

the PIM web-based informatics and workflow management system on the left and the integrated oncology clinical trials imaging assessment web-viewer on the right.



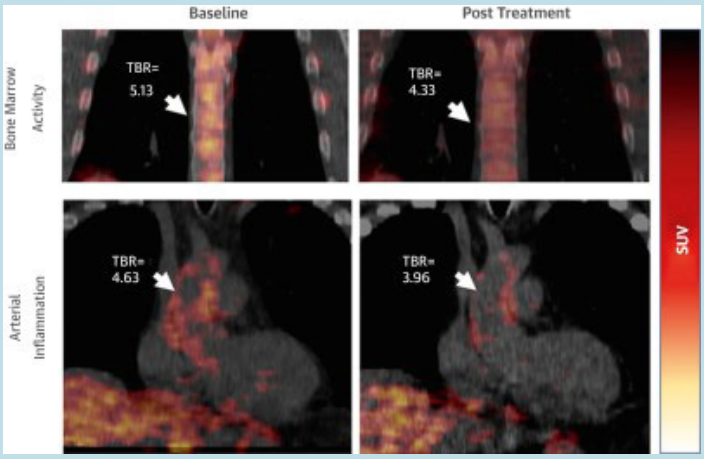
The TIMC/PIM team received an NCI U24 grant to develop a cloud-hosted open-source web-viewer for performing clinical trial imaging assessments, which has been integrated with the PIM workflow management platform and will be rolling out to TIMC and other PIM sites in the coming year. The free, open source web-based imaging viewer technology that is being supported through this grant is being widely adopted by many academic imaging groups, including the MGH/BWH Center for Clinical Data Science (CCDS) and The Cancer Imaging Archive (TCIA) as well as a broad range of industry imaging projects around the world. See www.ohif.org and www.cornerstonejs.org for source code and example implementations.

Cardiac MR PET CT Program - Udo Hoffmann, MD, MPH

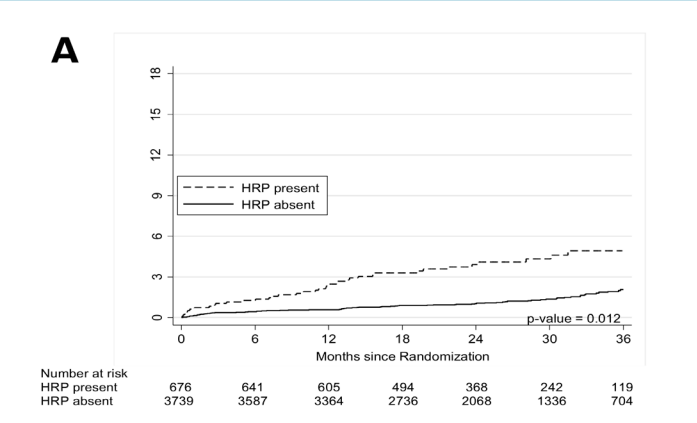
In 2018, the MGH Cardiac MR PET CT program increased total research funding by 22% as compared to 2017. This work is carried out in a highly synergistic fashion by five independently funded principal investigators from Radiology and Cardiology in a highly synergistic fashion who oversee 33 actively funded research projects, including 17 NIH grants and a NHLBI funded T32 program in CV Imaging.

This success is owed to strengthening the boulders of our scientific mission: 1) randomized clinical trials (ROMICAT, PROMISE, REPRIEVE) to determine whether integrating advanced coronary artery disease phenotyping is associated with health and economic benefits for patients, 2) posing key biological questions to a) understand the mechanisms of atherosclerosis and myocardial disease in the context of inflammation and systems biology and b) to discover new phenotypic biomarkers that improve risk stratification.

Among the highlights of more than 75 publications in 2018 were:



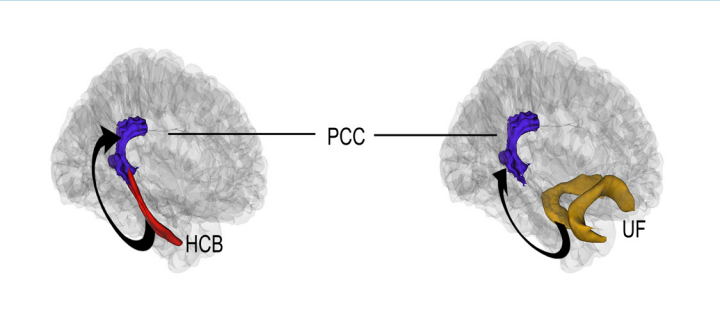
1) Dr. Tawakol and colleagues used FDG-PET/CT to measure bone marrow activity and arterial inflammation in individuals living with HIV and showed that a single dose of monoclonal antibody to IL-1β (canakinumab) significantly reduced inflammatory markers, arterial inflammation, and leukopoietic activity in HIV. Hsue PY, Tawakol. A et al. IL-1β Inhibition Reduces Atherosclerotic Inflammation in HIV Infection. Journal of the American College of Cardiology 2018.
2) Dr. Neilan and colleagues showed that the prevalence of myocarditis may be higher than anticipated (1%) and occurs early after starting treatment (median time of onset: 34 days after starting ICI). Moreover, ICI-associated myocarditis has a malignant course as 46% developed major adverse cardiac events over the next 3 to 6 months, including a 4-fold increased risk of MACE with troponin T. Mahmood SS, Neilan TG et al. Myocarditis in Patients Treated with Immune Checkpoint Inhibitors. Journal of the American College of Cardiology 2018
3) Dr. Hoffmann and colleagues demonstrated that high-risk plaque detected by coronary CTA was associated with a two-fold increased risk for MACE after adjustment for significant stenosis and cardiovascular risk factors ASCVD risk score and SS (adjusted hazard ratio (aHR), 1.72;



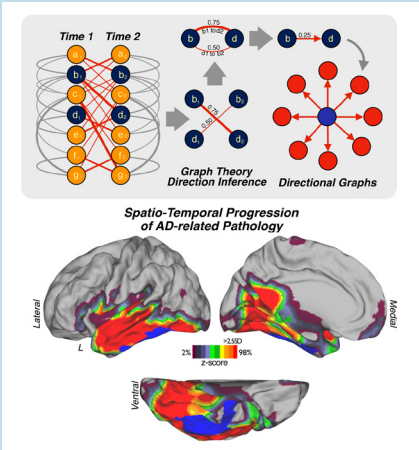
95% CI, 1.13-2.62). High-risk plaque could provide practice-changing optimizations in coronary artery disease care, especially in patients with nonobstructive coronary artery disease (aHR, 4.31; 95% CI, 2.25-8.26), younger patients (aHR, 2.33; 95% CI, 1.20-4.51), and women (aHR, 2.41; 95% CI, 1.25-4.64). Ferencik M., Hoffmann U. et al.: Use of High-Risk Coronary Atherosclerotic Plaque Detection for Risk Stratification of Patients with Stable Chest Pain: A Secondary Analysis of the PROMISE Randomized Clinical Trial. JAMA Cardiology 2018

Gordon Center for Medical Imaging - Georges E Fakhri, PhD

The Gordon Center for Medical Imaging saw another year of significant accomplishments in developing and translating molecular imaging technologies in a wide range of medical specialties. This has resulted in significant increase in funding of ground-breaking research including a BRAIN U01 to build the first ultra-high resolution brain PET scanner for in vivo autoradiography imaging with a resolution approaching 1mm, new funding in the Center for Molecular Imaging Technology and Translation P41 and the endowment of the Nathaniel and Diana Alpert Chair in Radiology. We select below two Nature publications that describe a snapshot of some of the work performed in two of the 18 Labs in the Center.



An exciting new work published in Nature Neuroscience revealed an association between Aβ, Tau, Circuitry and Cognition [Jacobs HI, Hedden T, Schultz AP, Sepulcre J, Perea RD, Amariglio RE, Papp KV, Rentz DM, Sperling RA, Johnson KA; Structural tract alterations predict downstream tau accumulation in amyloid-positive older individuals; Nat Neurosci. 2018, 21(3): 424-431]. Using longitudinal multimodal imaging data collected in healthy older individuals, Dr Jacobs and Johnson provided in vivo evidence in humans that amyloid deposition facilitates tau spread along structurally connected pathways and this combination of events is associated with memory decline. The results of this study showed that hippocampal volume at baseline, a proxy for neurodegenerative processes including tau pathology, predict changes in diffusivity in a tract innervating the hippocampus, the hippocampal cingulum bundle (HCB), and not in a control tract, the uncinate fasciculus (UF). These diffusivity changes in the hippocampal cingulum bundle were in turn associated with accumulation of tau pathology outside the medial temporal lobe, in the connected posterior cingulate cortex (PCC), in individuals with elevated levels of amyloid pathology. These findings suggest that amyloid plays a crucial role in driving neurodegenerative processes and cognitive decline, and that monitoring the spread of tau pathology will be important in clinical trials focused on removing amyloid plaques in the earliest stages of the diseases.



Dr Jorge Sepulcre and his team have published a novel and high impact work in Nature Medicine on Neurogenetic contributions to amyloid beta and tau spreading in the human cortex. Nat Med. 2018 Dec;24(12):1910-1918. Unraveling the genetic background for the regional vulnerability of Alzheimer's disease proteinopathies can help in understanding the mechanisms of pathology progression. To that end, Sepulcre and his colleagues developed a novel graph theory approach and used it to investigate the intersection of longitudinal Aβ and tau positron emission tomography imaging of healthy adult individuals and the genetic transcriptome of the Allen Human Brain Atlas. They identified distinctive pathways for tau and Aβ accumulation, of which the tau pathways correlated with cognitive levels. They found that tau propagation and Aβ propagation patterns were associated with a common genetic profile related to lipid metabolism, in which APOE played a central role, whereas the tau-specific genetic profile was classified as 'axon related' and the Aβ profile as 'dendrite related'.

MGH Center for Ultrasound Research & Translation - Anthony E. Samir MD MPH
The Center for Ultrasound Research & Translation (CURT) is focused on translational innovation in medical ultrasound. In 2018, CURT achieved multiple milestones: A comprehensive strategic plan was developed, creating a series of programs, including a (1) Clinical Translational Research Program, (2) a Machine Learning Program, (3) an Acoustic Signal Processing Program, (4) a Contrast Agent Chemistry Program, (5) an Educational Program, and (6) an Operations Core.

Dr. Samir and colleagues developed a novel approach to the detection and quantitation of liver fat via estimation of true intrahepatic sound speed. This technology can be implemented on existing ultrasound imaging hardware at minimal cost to provide non-invasive disease detection of non-alcoholic fatty liver disease, one of the commonest diseases and a major risk factor for both liver and cardiac morbidity.

Benjamin A, Zubajlo RE, Dhyani M, Samir AE, Thomenius KE, Grajo JR, Anthony BW. Surgery for Obesity and Related Diseases: I. A Novel Approach to the Quantification of the Longitudinal Speed of Sound and Its Potential for Tissue Characterization. Ultrasound Med Biol. 2018 Dec;44(12):2739-2748.

Zubajlo RE, Benjamin A, Grajo JR, Kaliannan K, Kang JX, Bhan AK, Thomenius KE, Anthony BW, Dhyani M, Samir AE. Experimental Validation of Longitudinal Speed of Sound Estimates in the Diagnosis of Hepatic Steatosis (Part II). Ultrasound Med Biol. 2018 Dec;44(12):2749-2758. doi: 10.1016/j.ultrasmedbio.2018.07.020. Epub 2018 Sep 26. PubMed PMID: 30266215.

Athinoula A. Martinos Center for Biomedical Imaging
Bruce Rosen, MD, PhD, Director

The Martinos Center held its inaugural "Women in Science" seminar series in spring 2018, bringing together investigators, staff and others from throughout the community for a host of important and thought-provoking discussions. Topics included "Implicit and Explicit Race and Gender Bias in STEM" and "How to Respond to Sexism in the Moment." The series proved so successful the organizers—including Allison Stevens (left) and seminar series chair Emma Boyd (right)—hosted another in the fall.

The Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital is one of the world's premier research centers devoted to the development and application of biomedical imaging technologies. Located on the MGH Research Campus in Charlestown, it is home to approximately 120 faculty researchers and more than 200 affiliated and visiting faculty, postdoctoral fellows and graduate students. In addition to driving the development of cutting-edge imaging technologies, the investigators use those technologies, separately and in concert, to explore a broad range of biologically and medically important questions.

Center investigators have worked at the vanguard of biomedical imaging for nearly four decades. Among their many groundbreaking contributions to the field: the introduction of functional magnetic resonance imaging (fMRI) (1991); the installation of the first clinical 7T MRI scanner (2000); the first images of the human connectome (2008); and the first combined PET/MRI scans in humans (2009).

The researchers continued their track record of success in 2018. For example, they devised a host of new ways to improve the quality and efficacy of medical imaging—including by harnessing the power of artificial intelligence. Recent advances in imaging technology have increased radiologists' ability to make accurate diagnoses. However, acquiring sufficient data to generate the best quality images comes at a cost—higher radiation dose for computed tomography (CT) and positron emission tomography (PET) or uncomfortably long scan times for magnetic resonance imaging (MRI). In March, the Center's Bo Zhu, Matt Rosen and colleagues published a paper in the journal Nature describing an artificial intelligence-based technique—dubbed AUTOMAP (automated transform by manifold approximation)—that allows clinicians to acquire higher quality images without having to collect additional data. The technique takes advantage of a new paradigm in which the best image reconstruction algorithm is automatically determined by "deep learning" artificial intelligence.

Recent findings in the Center could also contribute to the development of new and better therapies. In a study reported in September in the journal Brain, Behavior and Immunity, researchers Daniel Albrecht, Marco Loggia and colleagues found widespread inflammation in the brains of patients with fibromyalgia: a disorder characterized by symptoms including chronic widespread pain, sleep problems, fatigue, and problems with thinking and memory. Currently there are no good treatment options for fibromyalgia, so identifying a potential treatment target could lead to the development of innovative, more effective therapies. Also, finding objective neurochemical changes in the brains of fibromyalgia patients could help reduce the stigma that many patients face, as they are often told their symptoms are imaginary and there is nothing really wrong with them.

In December, the Center held the first-ever "ART in mARTinos" gallery event, with nearly 30 prints, paintings, sculptures, and other works of art by members of the Martinos community. The event celebrated the beauty of biology both in the images produced by Center investigators and in the art that it inspires. Seen here on the left is a seminal image by Marco Loggia showing evidence of glial activation in the brains of chronic pain patients. This 2015 study paved the way for Loggia's more recent investigation of widespread inflammation in the brains of patients with fibromyalgia.

Martinos investigators have long been at the forefront of achieving better understandings of neurodegenerative disorders and, in this regard, 2018 was no different. One example: The Center's Sheraz Khan and David Cohen used magnetoencephalography (MEG)—a technology that measures brain activity by detecting the weak magnetic fields produced by the brain's normal electrical currents—to measure levels of the iron-based mineral called magnetite in the human brain. While magnetite is known to be present in the normal brain and to accumulate with age, evidence has also suggested it may play a role in Alzheimer's disease and other, similar disorders. The newly described ability to measure and localize magnetite in the living human

In November, the Martinos Center celebrated two landmark events for its MEG program: MEG Core director Matti Hämäläinen's promotion to full professor of radiology at Harvard Medical School and the renaming of the Center's MEG facility in honor of David Cohen, the Martinos faculty member and "father of MEG." Shown here are Cohen and Martinos faculty member Sheraz Kahn, authors of the Human Brain Mapping study measuring levels of magnetite in the human brain.

brain will enable new studies of its role in both the normal brain and in neurodegenerative disease. For instance, studies could investigate whether the amount of magnetite in the hippocampal region of the brain could predict the development of Alzheimer's disease and whether treatments that influence magnetite could alter disease progression. Sheraz and Khan reported their findings in the journal Human Brain Mapping.

In another example, the Center's Tonya Gilbert, Jacob Hooker and colleagues used a PET scan radiotracer developed by Hooker's team to identify, for the first time, epigenetic differences between the brains of individuals with schizophrenia and those of unaffected study participants. In a paper published in December in the Journal of Clinical Investigation, the researchers describe measuring differences in the expression of histone deacetylase (HDAC) enzymes, important regulators of gene transcription that could change cognition. Researchers had previously observed lower HDAC levels in postmortem tissue samples from schizophrenia patients. Now, using the new radiotracer—called Martinostat—the Martinos-based team showed they could measure HDAC expression and distribution across the entire living brain in a single PET scan. In addition to the comparisons of diseased and healthy brains, the findings could enable long-term studies exploring the relationship between HDAC levels and disease onset, progression and symptom severity.

In June, the Center's MR Physics & Instrumentation Group traveled to Paris, France, for the 2018 meeting of the International Society for Magnetic Resonance in Medicine (ISMRM). The group was a major presence at the meeting, with 90 presentations including 30 oral presentations and nine "power pitch" presentations, eight Summa Cum Laude awards for highly rated abstracts and ten Magna Cum Laude awards.

Bruce D. Walker, MD, Director

The Ragon Institute of MGH, MIT and Harvard was officially established in February 2009 with a dual mission: to contribute to the accelerated discovery of an HIV/AIDS vaccine and to establish itself as a world leader in the collaborative study of human immunology. The vision of the Institute is to harness the immune response to prevent and cure human disease, and the initial goal has been to develop an effective HIV vaccine and cure for HIV infection. The Institute, now in its tenth year, is sponsoring an efficacy trial in Africa of a candidate HIV vaccine developed by one of its founding members, Dr. Dan Barouch. The Institute is expanding its scope, and is now transitioning to funding through an endowment that is being established by Terry and Susan Ragon. Recent faculty recruits have broadened the initial focus, having brought expertise in autoimmunity (Shiv Pillai), membrane biochemistry and influenza (Daniel Lingwood), basic B cell immunology (Facundo Batista) and most recently structural biology (Aaron Schmidt). Now with 11 faculty and plans to add at least 10 additional faculty, as well as engagement of Associate Members, the Institute is well positioned to continue to make significant contributions to the field of human immunology. What makes the Institute so unique is our ability to combine approaches and fields that have often remained separate, including:

- Catalyzing non-traditional partnerships among outstanding scientists and engineers with different but complementary backgrounds;
- Providing infrastructure and novel technologies to open new avenues of research;
- Providing a means for rapidly funding promising studies and emerging concepts in the field;
- Integrating key facets of current vaccine development efforts that have tended to follow separate tracks;
- Providing a substantial pool of accessible, flexible funding that will help lower the threshold for scientists to pursue risky, unconventional, yet potentially high benefit avenues of study that are unlikely to attract funding from traditional sources. Such funding encourages innovation, compresses the time it takes to conduct bench-to-bedside research and attracts new minds to the field.

Ragon Institute Employees at the 2018 Ragon Retreat in Lincoln, NH

Development of a platform for high throughput immunoprofiling

Alter G, Dowell KG, Brown EP, Suscovich TJ, Mikhailova A, Mahan AE, Walker BD, Nimmerjahn F, Bailey-Kellogg C, Ackerman ME. High-resolution definition of humoral immune response correlates of effective immunity against HIV. Mol SystmBiol. 2018 Mar 26;14(3):e7881. doi: 10.15252/msb.20177881. PubMed PMID: 29581149;PubMed Central PMCID: PMC5868198.

Defining correlates of immunity by comprehensively interrogating the extensive biological diversity in naturally or experimentally protected subjects may provide insights critical for guiding the development of effective vaccines and antibody-based therapies. Dr. Galit Alter at the Ragon Institute has developed a novel approach to comprehensive, high throughput humoral immunoprofiling and has applied it to elucidate hallmarks of effective immune control of HIV and pathogens as well as vaccine-elicited immune responses. In a paper published in 2018, systematic serological analysis was performed for a cohort of HIV-infected subjects with varying viral control conducted using this high-resolution,

high-throughput biophysical antibody profiling approach, which provided unbiased dissection of the humoral response, along with functional antibody assays, and identified antibody-directed effector functions such as complement fixation and phagocytosis as central to protective immunity. Profiles of subjects with varying viral control were computationally analyzed and modeled in order to deconvolute relationships among IgG Fab properties, Fc characteristics, and effector functions and to identify humoral correlates of potent antiviral antibody-directed effector activity and effective viral suppression. The resulting models reveal multifaceted and coordinated contributions of polyclonal antibodies to diverse antiviral responses and suggest key biophysical features predictive of viral control. This platform, funded by the Bill and Melissa Gates Foundation, is now being used to evaluate immune responses elicited by other pathogens and by candidate vaccines.

Development of a platform for the rapid generation of transgenic mice
Lin YC, Pecetta S, Steichen JM, Kratochvil S, Melzi E, Arnold J, Dougan SK, Wu L, Kirsch KH, Nair U, Schief WR, Batista FD. One-step CRISPR/Cas9 method for the rapid generation of human antibody heavy chain knock-in mice. EMBO J. 2018 Sep 14;37(18). pii: e99243. doi: 10.15252/embj.201899243. Epub 2018 Aug 7. PubMed PMID: 30087111; PubMed Central PMCID: PMC6138433.

The ability to create transgenic mice is critical for gaining mechanistic insights into the functioning of the immune system and unfortunately this has always been a long and laborious task. A team at the Ragon Institute, under the leadership of Dr. Facundo Batista, has now dramatically shortened this process using a one-step, in vivo CRISPR/Cas9 nuclease-mediated strategy to generate knock-in mice. This strategy allows the generation of KI mouse models in about 3 weeks with a high frequency of homologous recombination (30-50%). In the initial description of this method reported in EMBO, Dr. Batista recombined a 1.9-kb DNA fragment bearing a pre-arranged human B-cell receptor heavy chain into the native murine immunoglobulin locus. The methodology relies on Cas9 nuclease-induced double-stranded breaks directed by two sgRNAs to occur within the specific target locus of fertilized oocytes. These double-stranded breaks are subsequently repaired via homology-directed repair by a plasmid-borne template containing the pre-arranged human immunoglobulin heavy chain. To validate the knock-in mouse model, they examined the expression of the KI immunoglobulin heavy chains by following B-cell development and performing single B-cell receptor sequencing. They optimized this strategy to generate immunoglobulin KI mice in a short amount of time with a high frequency of homologous recombination as high as 50%. In the future, we envision that such knock-in mice will provide much needed vaccination models to evaluate immune responses against immunogens specific for various infectious diseases.

Publication of presentations from a symposium on Physician-Scientists in the Evolving Landscape of Biomedical Research
Lu LL, Kwon DS, Barczak AK. Introduction: Physician-Scientists in the Evolving Landscape of Biomedical Research. J Infect Dis. 2018 Aug 14;218(suppl_1):S1-S2. doi: 10.1093/infdis/jiy105. PubMed PMID: 30124978.

One aspect of the vision for the Ragon Institute is to not only focus on the study of human immunology, but to translate this knowledge as rapidly as possible to benefit patients. To this end, the engagement of physician scientist investigators is seen as a key part of the mission. To further support and highlight the efforts of this community of investigators, the Ragon Institute sponsored a symposium of leading physician scientists from around the country to explore the variety of ways in which clinical training influences research, and to develop ideas of how to more completely support the careers of physician scientists. A product of this effort was a collection of articles written by speakers at the symposium that appeared as a supplemental issue of the Journal of Infectious Diseases entitled, "Physician-Scientists in the Evolving Landscape of Biomedical Research." The issue featured articles highlighting notable achievements, as well as the varied career paths and professional challenges of leading physician scientists. It also included a joint statement by the Infectious Disease Society of America (IDSA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS) with policy recommendations for optimizing the physician scientist workforce. This supplement helped to place the Ragon Institute and MGH at the center of the national discussion of how to best maintain the pipeline of physician scientists to help drive new translational developments as we move into the future.

Identification of spatially dependent innate immune factors for induction of effective B cell immune responses
Gaya M, Barral P, Burbage M, Aggarwal S, Montaner B, Warren Navia A, Aid M, Tsui C, Maldonado P, Nair U, Ghneim K, Fallon PG, Sekaly RP, Barouch DH, Shalek AK, Bruckbauer A, Strid J, Batista FD. Initiation of Antiviral B Cell Immunity Relies on Innate Signals from Spatially Positioned NKT Cells. Cell. 2018 Jan 25;172(3):517-533.e20. doi: 10.1016/j.cell.2017.11.036. Epub 2017 Dec 14. PubMed PMID: 29249358; PubMed Central PMCID: PMC5786505.

The recruitment of Dr. Facundo Batista as the Associate Director of the Ragon Institute has led to a deeper focus on the basic immune mechanisms driving B cell and antibody induction. B cells constitute an essential line of defense from pathogenic infections through the

generation of class-switched antibody-secreting cells (ASCs) in germinal centers. Although this process is known to be regulated by follicular helper T (TfH) cells, the mechanism by which B cells initially seed germinal center reactions remains elusive. Dr. Batista's group found that NKT cells, a population of innate-like T lymphocytes, are critical for the induction of B cell immunity upon viral infection. The positioning of NKT cells at the interfollicular areas of lymph nodes facilitates both their direct priming by resident macrophages and the localized delivery of innate signals to antigen-experienced B cells. Indeed, NKT cells secrete an early wave of IL-4 and constitute up to 70% of the total IL-4-producing cells during the initial stages of infection. Importantly, the requirement of this innate immunity arm appears to be evolutionarily conserved because early NKT and IL-4 gene signatures also positively correlate with the levels of neutralizing antibodies in Zika-virus-infected macaques. These data support a model wherein a pre-TfH wave of IL-4 secreted by interfollicular NKT cells triggers the seeding of germinal center cells and serves as an innate link between viral infection and B cell immunity.

Surgery

Department Report

Keith D. Lillemoe, MD, Surgeon-in-Chief

The research mission of the Department of Surgery is to guide and foster basic, translational, and outcomes research activities in a broad range of surgical subspecialties with a goal of advancing knowledge and improving patient care. To accomplish this goal, scientists and clinicians engage in multiple scientific disciplines to solve everyday challenges in clinical medicine. We serve a diverse group of patients, and our research enterprise is similarly diverse, being distributed among multiple Centers and clinical Divisions.

Surgical Research Council

The Surgical Research Council (SRC), chaired by Richard Hodin, MD, was established to help the Department achieve its research mission. The SRC has a broad membership that includes the Department Chair, the Division Chiefs and Center Directors, and other members representative of each division and the large community of PhD and MD researchers. The SRC meets quarterly and holds research town hall meetings twice a year that bring the entire department research community together in a forum designed to exchange information and promote collaboration.

Centers of Excellence

The Department of Surgery has four specialized centers of excellence in research that are designed to enhance the research environment, foster collaboration, and leverage expertise and resources to expand the productivity and output in areas of interest.

Center for Transplantation Sciences (CTS)

The CTS at Massachusetts General Hospital is a multidisciplinary research center working at the interface between basic science and clinical applications in transplantation immunology and related fields. It was established in 2015 by merging the Transplantation Unit Surgery Research Laboratory and the Transplantation Biology Research Center, with Joren C. Madsen, MD, DPhil and James F. Markmann MD, PhD serving as co-directors, with newly recruited, Richard N. Pierson III, MD serving as scientific director. The position of scientific advisor is held by David H. Sachs, MD.

The mission of the Center for Transplantation Sciences (CTS) at Massachusetts General Hospital is to improve the number and the lives of recipients with organ, tissue and cell transplants by:

- Better understanding the mechanisms underlying the immune response
- Developing novel means of inducing immune tolerance
- Finding creative ways of increasing the supply of donor organs

Center for Surgery, Innovation and Bioengineering

The Center for Surgery, Innovation & Bioengineering engages in the basic sciences, clinical medicine and engineering to solve every day biomedical challenges for patients. Our team of clinically-inspired engineers, physicians and biologists, among others, use creative scientific approaches to improve health care delivery and further the use of personalized medicine, minimally invasive therapies and new technologies for today's and tomorrow's diagnostics and treatments.

The Center's position within the MGH clinical and research environments enables not only the traditional academic triad of sciences, technology, and clinical medicine, but its position also enables a fourth dimension – innovation. Serving as co-directors; Ronald Tompkins, MD, ScD, Mehmet Toner, PhD, and Martin Yarmush, MD, PhD.

Vital Organ Engineering and Tissue Regeneration

Joseph P Vacanti, MD, and his team continue to focus on the development of implantable tissue engineered living devices to replace structures damaged by disease, trauma, or congenital deformities. Currently, they are focusing on neural innervation of skeletal muscle, CNS implants, and hepatic tissue for implantation. In addition, they are applying their engineered blood vessel expertise to produce an in vitro model of a physiologic vasculature to be commercialized for drug testing applications. Harald Ott, MD, is focusing on furthering the development of perfusion decellularized scaffolds as a platform for organ engineering by developing conditions suitable for human organs, deriving adult cell populations from patients, designing human size bioreactor systems, and developing human organ culture conditions

Codman Center for Clinical Effectiveness in Surgery

The Codman Center's mission is to deliver the safest, highest value patient care through innovative research and education. Local, regional and national initiatives analyze and promote the clinical effectiveness of surgical care. The Codman Center collaborates with Partners HealthCare hospitals and other hospitals throughout the state to promote quality improvement in Massachusetts. Nationally, the center's leaders are the architects of quality and safety metrics used in hospitals across the country with Matthew Hutter, MD, serving as the medical director, David Shahian, MD, serving as the associate director, and David Chang, PhD, as the director of healthcare research and policy development.

Research Achievements

Image guided breast cancer surgery using the LUM Imaging System

Obtaining tumor-free margins is critical for local control in breast cancer surgery. Unfortunately, with current technologies 20-40% of lumpectomy patients have positive margins that require a second surgical excision. We are evaluating the LUM Imaging System (Lumicell, Wellesley, MA) for real-time, intraoperative detection and excision of residual tumor in breast cancer patients. This system uses LUM015, a cathepsin-activatable fluorescent agent, given IV 4±2 hrs prior to surgery. Areas of fluorescence generated at sites of residual tumor in lumpectomy cavities were evaluated with a sterile hand-held device, displayed on a monitor, excised and correlated with histopathology. This approach has the distinct advantage of assessing in vivo lumpectomy cavity walls rather than excised specimens, to enable more accurate excision of residual tumor.

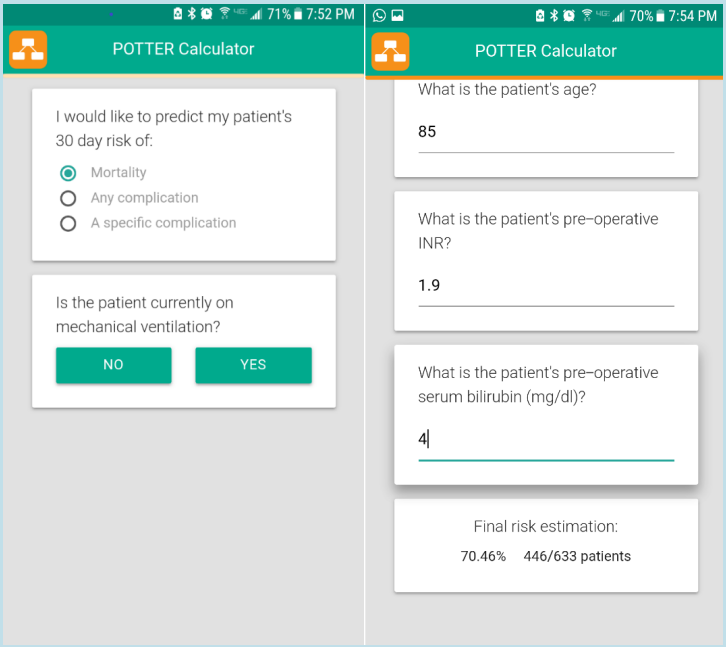
In vivo lumpectomy cavities were imaged with the LUM Imaging System in 60 breast cancer patients. The test set included 569 cavity margin surfaces assessed intraoperatively and excised. Image acquisition for each 2.6 cm diameter margin took approximately 1 second. The LUM Imaging System showed 100% sensitivity and 73% specificity for detection of tumor <2mm from the margin. Invasive ductal cancer (IDC), invasive lobular cancer (ILC) and areas of DCIS 1mm in size could be identified. 8 patients had positive margins on standard histopathology analysis. The LUM System correctly identified all positive final lumpectomy margins identified by standard histopathology and correctly predicted negative re-excisions in 2 of 8 patients.

Barbara L. Smith, MD, PhD, Division of Surgical Oncology, is now leading an open R44-funded multicenter Pivotal trial of the LUM Imaging System in breast cancer surgery and have R01 funding for another multicenter trial to extend the use of this system. Other MGH investigators are exploring the use of the LUM Imaging in GI cancers and other sites are exploring use in GYN and CNS cancers and sarcomas, with use in other tumors under investigation.

Surgical Risk is Not Linear: Derivation and Validation of a Novel, User-Friendly, and Machine-Learning-based Predictive, OpTimal-Trees-in-Emergency-Surgery, Risk (POTTER) Calculator

Most existent risk assessment tools assume that the impact of risk factors is linear and cumulative. Using novel Artificial Intelligence (AI) and Machine-Learning techniques on Big Data (the ACS-NSQIP 2007-2013 database), comprehensive decision-making algorithms were derived, and the Predictive, OpTimal-Trees-in-Emergency-Surgery, Risk (POTTER) instrument was created where the provider's answer to a question interactively dictates the subsequent question. For any specific patient, the number of questions needed to predict mortality or any of 18 complications ranged from 4 to 11. The mortality c-statistic was 0.92 and reached as high as 0.94 for some complications, all significantly higher than those of any other existent risk predictive models such as ASA, ESS, or the ACS-NSQIP Risk Calculator. Unlike classic heuristics (e.g. logistic regression), OCT is not only highly accurate and user friendly, but also adaptive and reboots itself with each variable, thus accounting for non-linear interactions among variables.

The pioneering work, led by George Velmahos, MD, and Haytham M. Kaafarani, MD, Trauma, Emergency Surgery, Surgical Critical Care, was

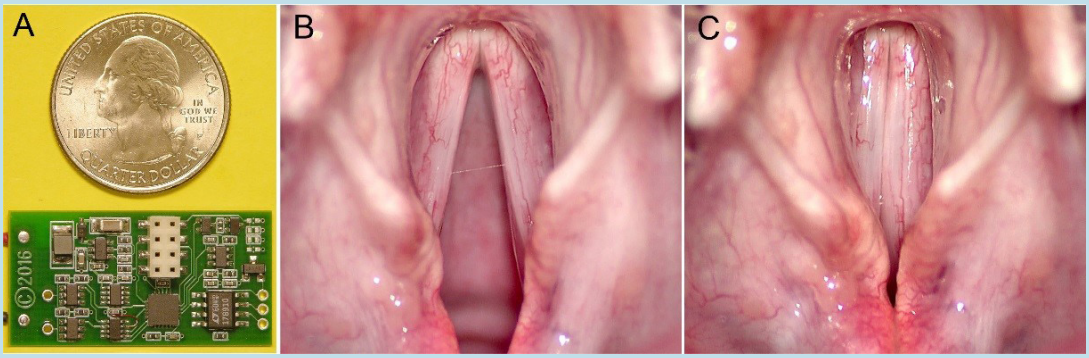


presented at the American Surgical Association, published in the Annals of Surgery, discussed on the Behind the Surgical Knife Podcast, and reported in Surgery News. POTTER is now available on android and iphone platforms and has been downloaded by hundreds to thousands of surgeons across the world, as a useful point-of-care tool for bedside preoperative counseling of the Emergency Surgery patients and families. As exciting, the MGH-MIT team continues to work on developing similar tools for high risk elective surgery such as pancreatic, liver, cardiac and thoracic procedures.

Closed-Loop Stimulation Implant Developed to Reanimate Paralyzed Vocal Folds

When neural control of the larynx is lost it can cause voice, swallowing and airway compromise that diminishes quality of life or can threaten life itself. Pioneering experiments exploring electrical stimulation to re-animate paralyzed vocal folds were first performed at the Physiological Laboratory of Harvard Medical School and the Massachusetts General Hospital in the 1880s. A resurgence in laryngeal functional electrical stimulation (FES) research at MGH began in 2013 when Steven Zeitels M.D., Director of Laryngeal Surgery at MGH, received funding from the National Philanthropic Trust to develop a laryngeal FES implant to treat laryngeal paralysis. This research effort has focused on modification of currently available "off the shelf" implantable stimulators, as well as the creation of a custom implant system in collaboration with MIT engineers. For example, the MGH team worked with Inspire Medical Inc. (Maple Grove, MN) to double the stimulation capabilities of their obstructive sleep apnea implant so that it could stimulate paralyzed laryngeal muscles instead of the hypoglossal nerve. The MGH team implanted the Inspire device in multiple dogs and documented its ability to stimulate vocal fold closure after paralysis (caused by motor nerve transection) across survival periods extending up to 4 years.

Although commercial implants have proven capable of stimulating vocal fold movements using preset patterns, no system available today does so in a "closed-loop" manner, whereby stimulation is delivered in response to the intentions or moment-by-moment needs of the implant recipient. To create a closed-loop stimulator, the MGH team worked with David Otten M.S., an electrical engineer at the MIT Laboratory for Electromagnetic and Electronic Systems, to create a stimulator that is triggered by an electromyographic input. In cases of unilateral laryngeal paralysis, the implant can monitor muscle actions on the healthy side of the larynx to detect when symmetrical movements should be stimulated on the paralyzed side. The same approach can be used for treating chronic cases of Bell's palsy notes James Heaton Ph.D., and James Kobler Ph.D., the scientific team leaders of this work at MGH. To treat bilateral paralysis, the team has used extra-laryngeal muscles in the neck to determine when the vocal folds should be stimulated. The implant circuit is about the size of a quarter (see photo) and has proven effective for both unilateral and bilateral vocal fold stimulation in the dog model of laryngeal paralysis. Two manuscripts describing the new closed-loop implant and several years of animal testing will appear in early 2019 in the Annals of Otology, Rhinology, and Laryngology – a leading peer-reviewed ENT journal.



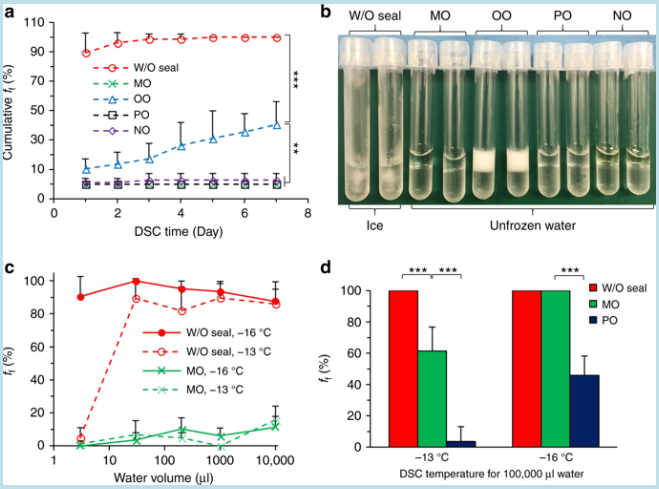
The closed-loop laryngeal stimulator circuit is shown adjacent to a quarter. When stimulating electrodes are inserted in the dog vocal fold muscles controlling glottic closure, paralyzed folds (B) can be stimulated to close (C) for phonation (i.e. voice) or airway protection.

Deep-Supercooling of Water and Red Blood Cells for Long-Term Preservation

Investigators from the MGH Department of Surgery Center for Engineering in Medicine (CEM) have developed a simple method to maintain water and water-based solutions in a liquid state at temperatures far below the usual "freezing point" for greatly extended periods of time. While they currently have accomplished this for volumes of only a few ounces may someday enable safe, extended preservation of blood cells, tissues and organs, along with improved food preservation.

In most real-world environments, water and water-based solutions begin to freeze when the temperature reaches below 0° C/32° F, with ice crystals randomly forming where the liquids contact air or various impurities in the solution. Supercooling – reducing a liquid below its usual

freezing point without crystallization – has been achieved for very small volumes and brief periods of time or by using high pressure equipment that is both costly and possibly damaging to tissues or other biological materials. Reducing the temperature of any biological material – such as cold storage of perishable foods and organs for transplantation – slows down metabolic and other reactions. Supercooling extends this metabolic deceleration further without the damage caused by ice crystallization. The team first found that sealing the surface of a small (1 ml) water sample with a hydrocarbon-based oil – such as mineral oil, olive oil or paraffin oil – could suppress ice formation at temperatures as low as -13° C (around 9° F) for up to a week. Through a series of experiments both with more complex oils and with pure simple hydrocarbons, such as alcohols and alkanes, they succeeded in keeping 1 ml samples of water and cell suspensions supercooled at -20° C (-4° F) for 100 days and 100 ml (3.2 oz) samples for a week.

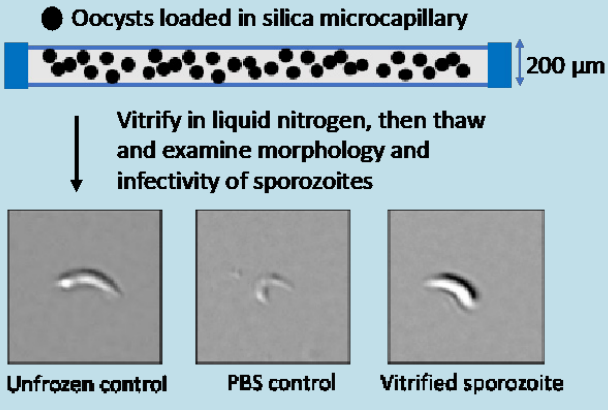


The team also demonstrated application of their deep supercooling method to the extended preservation of red blood cells. While red blood cells are usually stored at 4° C (39° F) for as long as 42 days, recent reports have suggested that cell quality at that temperature begins to decline after around 14 days, and irreversible cellular injury sets in after 28 days, challenging current blood banking practice. The CEM team's preliminary experiments indicated that their deep supercooling approach could safely preserve red-blood-cell suspensions of up to 100 ml at -13° C for as long as 100 days, more than doubling the current storage time. This work is part of a larger research initiative at the CEM where multiple investigators collaborate to preserve exotic cell types, human tissue and organs among other living things.

Huang H, Yarmush ML, Usta OB. Long-term deep-supercooling of large-volume water and red cell suspensions via surface sealing with immiscible liquids. Nature Communications 2018; 9: 3201.

Cryopreservation of Cryptosporidium parvum oocysts

Cryptosporidiosis is a leading cause of enteric illness in developing and available anti-parasitic drugs are insufficient, necessitating the development of novel therapeutics. Limiting progress in this area is the inability to cryopreserve Cryptosporidium oocysts, thus requiring continuous propagation in susceptible animals. To overcome this challenge, Mehmet Toner, PhD and Rebecca Sandlin, PhD at the BioMEMS Resource Center teamed with Saul Tzipori, DVM PhD, at the Cummings School of Veterinary Medicine at Tufts University to develop a cryopreservation method. As a result, the investigators recently developed the first ever method to cryopreserve Cryptosporidium oocysts (Jaskiewicz, et al. Nat. Comm. 2018; 9: 2883).



As Cryptosporidium oocysts are extremely impermeable, the team first developed a protocol to enable penetration of cryoprotectant additives (CPAs), molecules that protect the parasites from the damaging effects of cryopreservation. After careful selection of optimal CPA conditions, a vitrification or "ice-free" method of cryopreservation was used to cool the cells to cryogenic temperatures. Vitrification was achieved by loading oocysts into small diameter microcapillaries which facilitate rapid cooling rates, such that an amorphous solid is formed rather than crystalline ice, an approach that may be gentler to delicate cells (see Figure). Following vitrification, thawed oocysts contained sporozoites that exhibited high viability and normal morphology and were infectious to the mouse model. Sporozoites from PBS controls were damaged and failed to infect mice. This protocol will enable biobanking of a wide range of Cryptosporidium strains and enable the storage of well-characterized and standardized batches of oocysts for human-challenge studies.

Trial of Treg induced immune tolerance in liver transplant recipients

The need for chronic immunosuppression is responsible for untold morbidity and mortality in solid organ transplant recipients. Approaches to gain rejection free graft survival without immunosuppression have long been sought. Combined bone marrow kidney transplantation pioneered at MGH has shown success in renal transplant recipients but made be limited in applicability due the need for intensive conditioning that may preclude use in sick recipients of heart, liver or lung transplants. Under the direction of James Markmann, MD, Division of Transplant Surgery, his team has been exploring a novel approach that relies on delivery of regulatory T cells that can selectively down regulate the recipients response to the donor, thereby avoiding prolonged global immunosuppression. They recently conducted a pilot trial as a part of the International EU sponsored OneStudy in which a institutions each with their own regulatory population of interest, tested their cells in a common phase I safety trial. At MGH, they partnered with investigators from the DFCI to test a population of Tregs that they were testing the in bone marrow setting and adapted this for renal transplant recipients. Pilot results were encouraging, with each of three recipients on live donor kidney transplants and donor antigen specific Tregs showed evidence of Treg accumulation in the transplant and were able to wean to monotherapy immunosuppression without evidence of rejection.

They are now about extend the studies to a liver trial named LITTMUS (Liver Treg Tolerance at MGH and UCSF) that is funded by the NIAID sponsored Immune Tolerance Network. Like the OneStudy, UCSF and MGH-DFCI will utilize their own Treg manufacturing method to treat liver transplant recipients using a common protocol in which Tregs will be administered about 3 months post-transplant; treatment is delayed until this point to allow the patient to recover from their liver disease and the transplant procedure. Unlike the pilot kidney trial, we will attempt complete immunosuppression withdrawal in these patients. This will be the first use of purified donor antigen specific Tregs for this purpose in the transplant setting. The trial is scheduled to begin enrollment in early 2019.

Advances Toward Personalized Lung Engineering for Transplantation

Dr. Harald Ott's team has continued to investigate and develop the methods for whole organ regeneration. This had included a series of advances towards the goal of patient-specific lung tissue engineering. These build on previous methods developed by Dr. Ott, in which a native organ can be stripped of its own cells, creating a protein scaffold suitable for cellular repopulation and ex vivo tissue regeneration.

The design and optimization a fully automated high-throughput bioreactor system had helped to define a multiphase lung culture protocol, which achieves consistent tissue regeneration across lungs culture and ex vivo regeneration, further promoting overall tissue repair and maturation

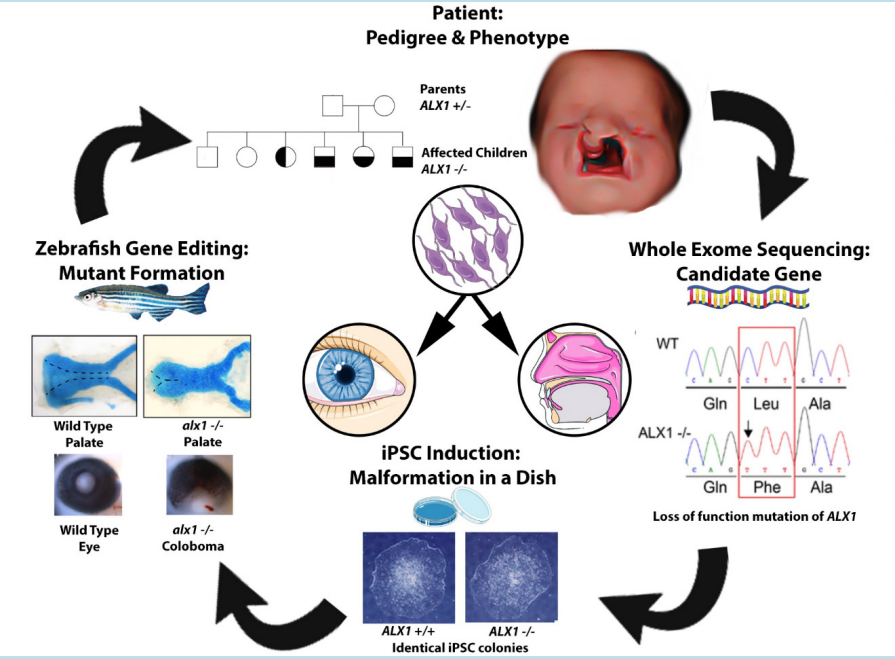
Additionally, Dr. Ott's group has successfully utilized a novel platform technology for manufacturing click-reactive organ scaffolds, thereby enabling efficient and chemoselective functionalization of these matrices to enhance their regenerative properties and post-implantation performance.

These advances have been successfully translated to clinical scale grafts, with porcine recipients receiving recellularized lung grafts now able to withstand physiological blood flow from the recipient's pulmonary circulation, and to exchange gases upon ventilation, in a non-survival model.

Elucidating how a face forms using human stem cells and zebrafish models

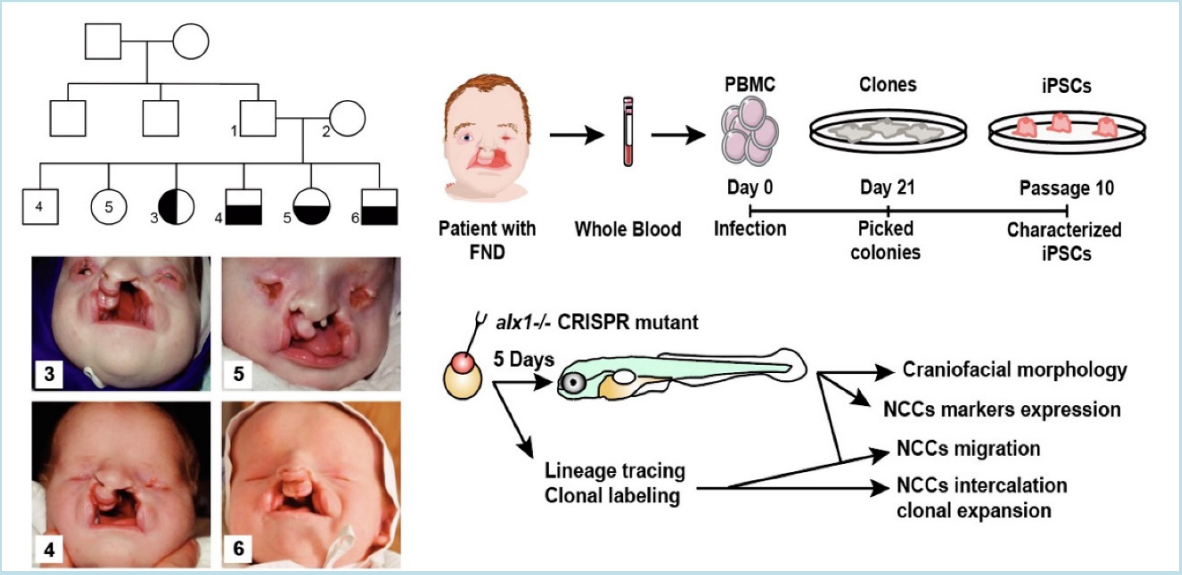
The 30 square centimeters in the central part of the human face contains key anatomic features and sensory organs that allow us to interact with the world and define us as individuals. In this midface region reside the eyes, the nose, upper lip and maxilla. The embryologic processes that are coordinated to form structures of the midface are tightly regulated. Derangement of this developmental process results in craniofacial anomalies, which are among the most common human birth defects.

At the Mass General for Children, Dr. Eric Liao, Tenaglia MGH Research Scholar and Director of the Cleft and Craniofacial Program, is caring for patients with congenital craniofacial disorders and uncovering the genetic basis of craniofacial anomalies. Dr. Liao is working at the MGH Center for Regenerative Medicine with collaborators Mike Talkowski (MGH), Jim Gusella (MGH), Cynthia Morton (BWH) and Dick Maas (BWH), where



his team carries out detailed functional analysis of genes associated with craniofacial anomalies. While traditional mouse models continue to be employed, novel human derived induced pluripotent stem cells (iPSC) and zebrafish models provide additional advantages. Dr. Liao's group is able to transform blood or discard specimen from patients to iPSC and direct differentiate the cells into neural crest cells, the unique embryonic cells that give rise to facial structures.

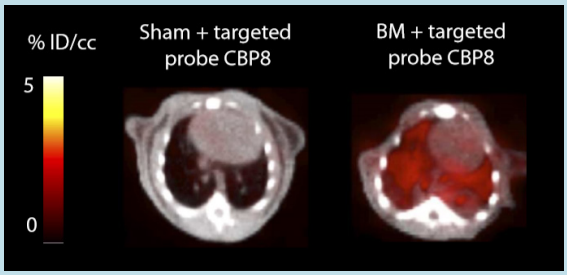
By carrying out molecular and cellular analysis on the iPSC neural crest cells, Dr. Liao is able to form hypothesis about how dysregulation of neural crest lead to craniofacial disorders. With CRISPR gene editing, hypotheses on the molecular pathogenesis of craniofacial malformation can be tested in the zebrafish models. Utilizing these complementary approaches, Dr. Liao is uncovering the molecular pathogenesis of frontonasal dysplasia, a rare and complex craniofacial condition where children are born with severe clefts on either side of the upper face, extending into the orbit. Dr. Liao has performed surgical repair for three children in this family, defined the genetic culprit in a key homeodomain transcription factor ALX1, and elucidated the mechanistic basis of how frontonasal dysplasia occurs during embryonic development. His lab is now identifying ALX1 target genes to understand the transcriptional pathway that regulate how faces form.



New PET probe detects pulmonary fibrosis and radiation induced lung injury

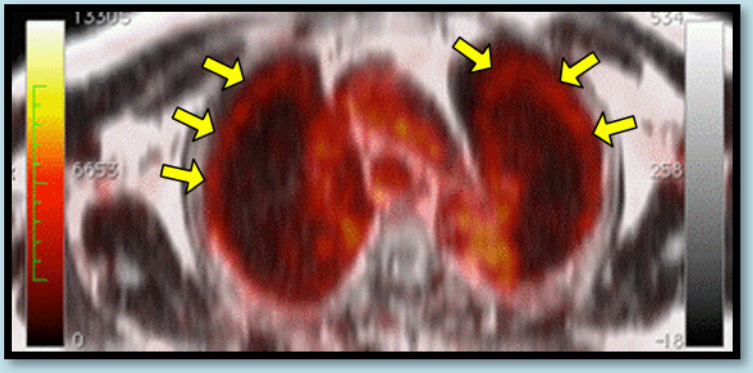
Molecular imaging of pulmonary fibrosis may be more sensitive than high resolution CT chest in detecting early fibrosis, and may also be able to distinguish new, active fibrosis from stable disease. Through a collaboration with Peter Carvan, PhD at the Martino Center for Biomedical Imaging, Dr. Michael Lanuti and his research team have developed and tested a new type I collagen-specific positron emission tomography (PET) probe for human imaging to better characterize disease pathogenesis and activity in patients with idiopathic pulmonary fibrosis and radiation-induced lung injury. This particular PET probe, named © Collibright (68Ga-CBP8), binds with high specificity to type 1 collagen and has been

validated in a pre-clinical murine model of bleomycin induced pulmonary fibrosis.



68Ga-CBP8 is specifically taken up by fibrotic but not healthy lungs. Representative fused PETCT images show specific accumulation of 68Ga-CBP8 in fibrotic (Bleomycin + targeted probe) but not in control lungs (Sham + targeted probe).

After obtaining Investigational New Drug approval by the FDA, the research team was awarded NIH funding to bring the PET probe into a human clinical trial. The Collibright PET probe is currently being tested in healthy volunteers, patients with idiopathic pulmonary fibrosis [Figure 2], and in patients treated with radiation as part of multimodality therapy for locally advanced non-small cell lung cancer. Radiated lung tissue along with treated lung cancer will be resected as part of standard of care and correlated histologically to preoperative PET probe uptake.



Fused PET-MRI axial T2-weighted chest image of a patient with a known diagnosis of pulmonary fibrosis. Arrows mark bands of probe uptake along areas of fibrosis at the lung periphery

Michael L. Blute, Sr., MD, Chief

The Department of Urology is expanding clinically and in its research endeavors. The department is committed to advancing urologic research through impactful clinical and translational research in urologic oncology, nephrolithiasis, pediatric urology and benign lower urinary tract dysfunction. The department supports research efforts that focus on health sciences and patient outcomes, advances in surgical technique and translational medicine. Supported by a talented faculty, the department is prominently featured nationally in leadership roles in professional and sub-specialty societies and is supported by extramural funding from the NIH, Department of Defense and industry sponsored research grants. The department has had $6.9 million in grant funding since 2007 and continues to grow. We are adding faculty with a focus and commitment to research and continuing to build our research infrastructure with clinical databases and administrative support so that faculty can be more productive in their scholarly activity. Our collaborative relationship with Pathology, Radiology, Medical Oncology and Radiation Oncology helps to facilitate our team approach to urologic research. Our residents and Urologic Oncology fellows are actively involved in our research endeavors with dedicated research time during their training.

Notable Research Achievements in 2018

A Multigene Signature Based on Cell Cycle Proliferation Improves Prediction of Mortality Within 5 Yr of Radical Nephrectomy for Renal Cell Carcinoma. Morgan TM, Mehra R, Tiemeny P, Wolf JS, Wu S, Sangale Z, Brawer M, Stone S, Wu CL, Feldman AS. Eur Urol. 2018 May;73(5):763-769

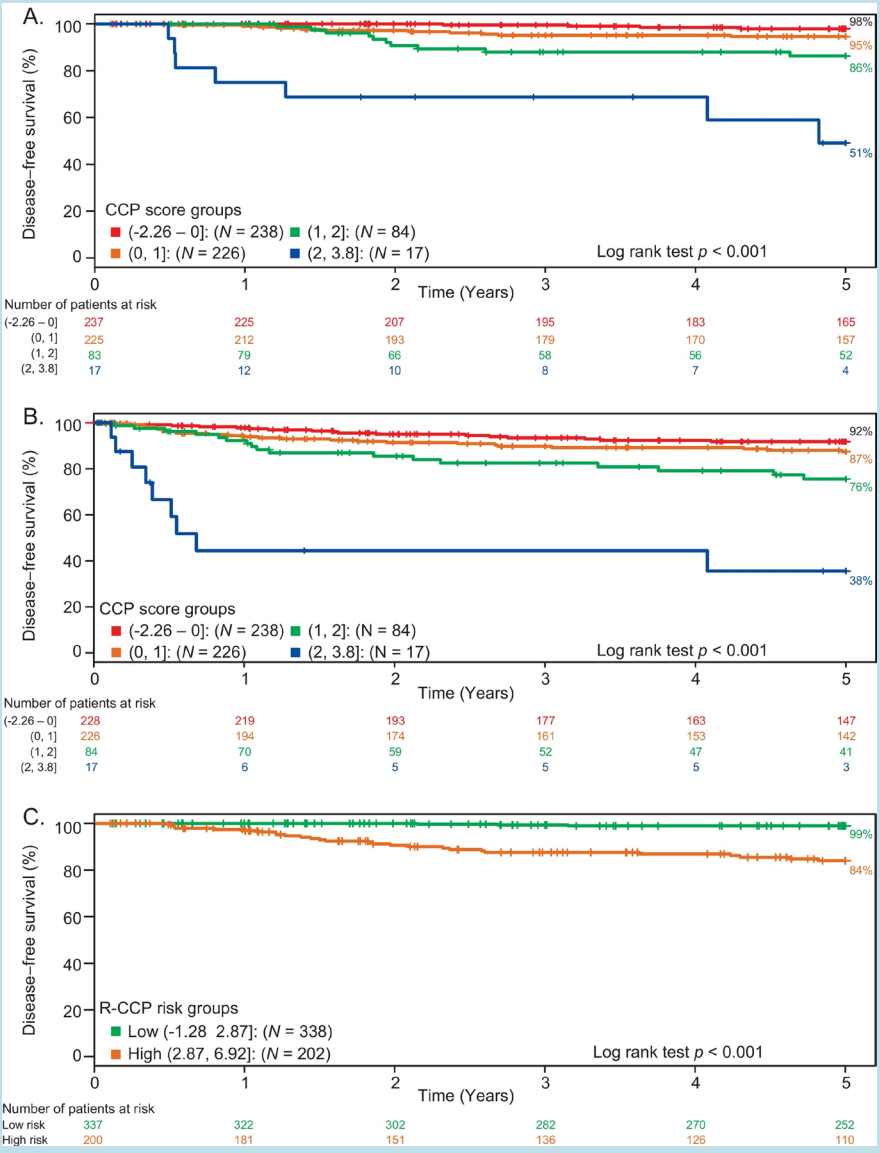
Abstract:

BACKGROUND: There is a critical need for improved prognostic discrimination in patients with renal cell carcinoma (RCC) given the increasing awareness that some patients may be managed with active surveillance, while others with higher-risk disease might benefit from adjuvant therapy following surgery.

OBJECTIVE: To determine whether a multigene proliferation signature predicts long-term oncologic outcomes in surgically resected RCC.

DESIGN, SETTING, AND PARTICIPANTS: The cell cycle proliferation (CCP) score was determined after radical nephrectomy for localized clear cell, papillary, or chromophobe RCC in 565 patients. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: The primary end point was disease-specific mortality (DSM), and disease recurrence was a secondary end point. Association with outcomes was evaluated by Cox proportional hazards survival analysis. The CCP score was compared with the Karakiewicz nomogram, and a composite (R-CCP) score was developed.

RESULTS AND LIMITATIONS: A total of 68 patients (12%) recurred and 32 (6%) died of disease within 5 yr of nephrectomy. The CCP score was an independent predictor of recurrence (hazard ratio [HR] 1.50, 95% confidence interval [CI] 1.07-2.09) and DSM (HR 2.49, 95% CI 1.53-4.04) after adjusting for clinical variables using the baseline nomogram. The composite R-CCP

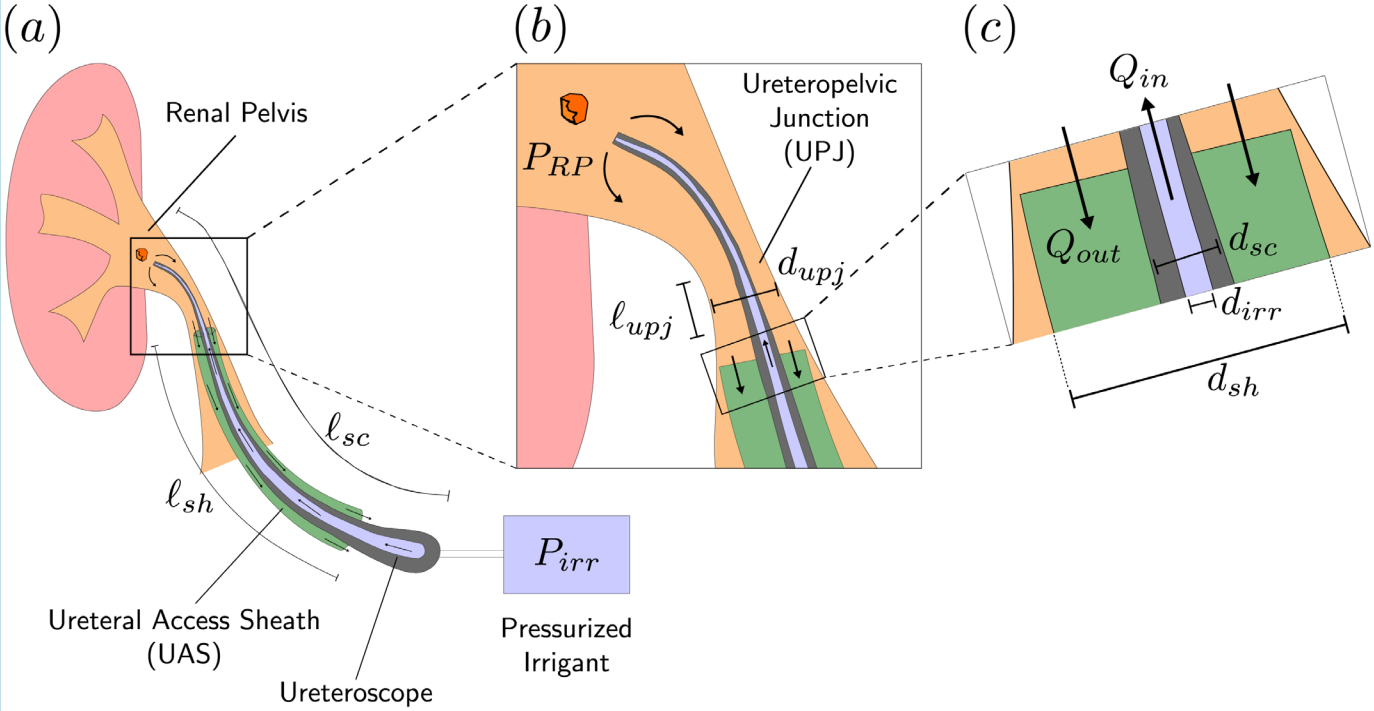


Kaplan-Meier plots showing (A) cancer-specific mortality and (B) cancer recurrence over time stratified by CCP score category for the entire patient cohort (p < 0.001 for both outcomes). (C) Patients are stratified by the prespecified combined R-CCP score risk groups, with high-risk patients demonstrating a greater likelihood of cancer-specific mortality (p < 0.001). CCP = cell cycle progression.

score gave a Harrell's concordance index of 0.87 and stratified patients into low- (n=338) and high-risk (n=202) categories with 99% and 84% cancer-specific survival probabilities, respectively (p<0.001). CONCLUSIONS: The CCP score is a significant, independent predictor of long-term oncologic outcomes in patients who have undergone nephrectomy for RCC. Combining the molecular classifier with baseline clinical variables allows for accurate, patient-specific risk assessment for use in guiding clinical management.

A simple fluid dynamic model of renal pelvis pressures during ureteroscopic kidney stone treatment. Oratis AT, Subasic JJ, Hernandez N, Bird JC, Eisner BH. PLoS One. 2018 Nov 29;13(11)

Abstract:
Ureteroscopy is an endoscopic kidney stone removal procedure which increases the internal pressure in the renal pelvis, the kidney's urinary collecting system. Elevated renal pelvic pressure may result in systemic absorption of irrigation fluid and urine, which can increase the risk of postoperative fever and sepsis. Urologists have investigated the effects of various surgical parameters on the renal pelvic pressure. However, it still remains unknown which surgical parameter has the most dominant effect on the renal pelvic pressure over time. Here we develop a physical model that computes the renal pelvic pressure as a function of time based on parameters that can be varied during ureteroscopy. The model is developed by applying pipe network analysis to the regions of the urinary tract that are involved in a representative ureteroscopic procedure. Our model unifies the findings of the previously published studies on this topic; an ex-vivo porcine study and an in-vivo human study. Furthermore it allows simulation of surgical procedures based on various techniques. Our simulation demonstrates that the two strong regulators of renal pelvis pressure during ureteroscopy are the size of the gap between ureteroscope and ureteral access sheath and the frequency and duration of ureteroscope withdrawal.



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A, Feldman AS, Hakimi AA. J Clin Oncol. 2018 Oct 29

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