70th Annual Meeting of the MGH Scientific Advisory Committee

SAC 2018

March 28 & 29, 2018 | Simches Research Building

Celebration of Science

The Mass General Research Institute: Growing Stronger Together

Executive Committee on RESEARCH

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

RESEARCH INSTITUTE

Welcome

Welcome to the 70th Meeting of the MGH Scientific Advisory Committee (SAC) on March 28th and 29th, 2018. Dr. Daniel K. Podolsky has graciously agreed to chair our SAC meeting again this year.

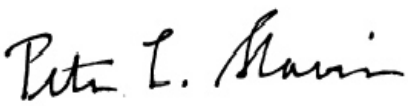
As in past years, we will begin our two-day SAC meeting with a Celebration of Science at MGH. Our poster sessions begin at 10:00 am on Wednesday, March 28, followed by an afternoon Research Symposium from 2:00 pm to 5:00 pm. David N. Louis, MD, will begin the symposium with a report on the past year 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 2018 Howard Goodman Award recipient, Mo Motamedi, PhD, and the 2018 Martin Research Prize recipients, Florian S. Eichler, MD, and Miguel N. Rivera, MD.

The theme of SAC this year will be *The Mass General Research Institute: Growing Stronger Together*. We are honored to have as our keynote speaker, Donald E. Ingber, MD, PhD, Founding Director of the Wyss Institute for Biologically Inspired Engineering at Harvard University, who will begin our morning on Thursday, March 29. After this address, we will turn our attention to the Mass General Research Institute and specifically focus on our marketing and fundraising initiatives, our interactions with industry and our Division of Clinical Research, as we look at where we are now and how we can succeed at accomplishing all that lies ahead of us.

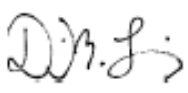
Also on Thursday, SAC members will have the opportunity to meet and hear from MGH investigators in small, unstructured, informal conversations during lunch.

To maximize the time for discussion during the day, the annual MGH Research Institute Executive Report and financials for FY18 have been provided in these printed materials (starting on page 10) for your review in advance of the meeting. Dr. Louis 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 N. Louis, MD
Chair, Executive Committee on Research (ECOR)

Harry W. Orf, PhD
Senior Vice President for Research

Agenda

Wednesday, March 28, 2018
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
Peter L. Slavin, MD, President, Massachusetts General Hospital

Opening Remarks
David N. Louis, MD, Chair, Executive Committee on Research (ECOR)

2:15 - 2:55 pm — **ECOR Report**
David N. Louis, MD, Chair, ECOR

2:55 - 3:30 pm — **2018 Goodman Fellowship**
Role of heterochromatin in cellular dormancy
Mo Motamedi, PhD

3:30 - 3:50 pm — **BREAK**

3:50 - 4:25 pm — **2018 Martin Prize for Clinical Research**
Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy
Florian S. Eichler, MD

4:25 - 5:00 pm — **2018 Martin Prize for Fundamental Research**
Cancer-Specific Retargeting of BAF Complexes by a Prion-like Domain
Miguel N. Rivera, MD

Agenda

Thursday, March 29, 2018
Simches 3.110

9:00 - 9:05 am — **Welcome and Introduction**
David N. Louis, MD, Chair, Executive Committee on Research (ECOR)

9:05 - 9:55 am — **Wyss Institute: A New Model for Crossing the Academic-Industrial Interface**
Donald E. Ingber, MD, PhD, Founding Director, Wyss Institute for Biologically Inspired Engineering at Harvard University

9:55 - 10:25 am — **Overview of the Research Institute**
Harry W. Orf, PhD, Senior Vice President for Research
Susan A. Slaugenhaupt, PhD, Scientific Director, MGH Research Institute (RI)

10:25 - 11:05 am — **Externally Promoting the Research Institute**
Moderator: Susan A. Slaugenhaupt, PhD, Scientific Director, MGH RI
Panelists: Misty Hathaway, Chief Marketing Officer
Peggy Slasman, Senior Vice President, Public Affairs

11:05 - 11:15 am — **BREAK**

11:15 - 11:55 am — **Fundraising for the Research Institute: Advancement Session**
Moderator: Robert E. Kingston, PhD, Chief, Molecular Biology
Panelists: Susan Buchanan, Senior Director of Development
Britain W. Nicholson, MD, Senior Vice President for Development
Susan A. Slaugenhaupt, PhD, Scientific Director, MGH Research Institute (RI)

12:00 - 1:00 pm — **SAC MEMBERS & FACULTY LUNCH**

1:15 - 1:55 pm — **Partnering with Industry: Strategic Alliances Session**
Moderator: Bob Tepper, MD, Third Rock Ventures, Research Institute Advisory Council Member
Panelists: Gabriela Apiou, PhD, Director, Translational Research Training & Development, MGH RI
Jean-Francois Formela, MD, Atlas Venture, Research Institute Advisory Council Member
Patrick Fortune, PhD, Vice President for Market Sectors, Partners HealthCare
Rajiv Kaul, Fidelity Investments, Research Institute Advisory Council Member

1:55 - 3:00 pm — **Promoting and Sustaining the Clinical Research Mission**
Maurizio Fava, MD, Director, Division of Clinical Research
Mason W. Freeman, MD, Director and Founder, Translational Research Center
David M. Nathan, MD, Program Director, Clinical Research Center

3:00 - 3:15 pm — **Open Discussion**

3:15 - 3:30 pm — **BREAK**

3:30 - 4:00 pm — **SAC Member Session** *(closed)*

4:00 - 4:30 pm — **Executive Debrief** *(Leadership & SAC Members)*

Howard M. Goodman Fellowship

2018 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.

Mo Motamedi, PhD
Assistant Professor
Department of Medicine
Cancer Center

Role of heterochromatin in cellular dormancy

Over time, many cancers recur or become resistance to radiation and chemotherapy. These are unsolved clinical challenges resulting in a large number of deaths every year. Recent work has revealed that a major contributor is a subpopulation of tumor cells, which exists in non-dividing, dormant state called quiescence (or G0). These cells are long-lived, treatment resistant and, most problematically, retain their ability to exit dormancy and cause cancer recurrence years after seemingly successful therapy. Currently, we know little about how to target dormant cancer cells. To address this knowledge gap, my lab recently developed the fission yeast as a model for cellular dormancy. Using this system, we identified a group of proteins that together act as a switch, turning on a pathway critical for G0 cell survival. Because many of these proteins are conserved from yeast to human cells, we asked whether the same proteins are also essential for survival of resistant cancer cells. Remarkably, our results support this hypothesis, revealing an exciting and targetable node of vulnerability for killing G0 cancer cells. We are now pursuing these targets in collaboration with several labs at the MGH Cancer Center.

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
Florian S. Eichler, MD
Associate Professor
Department of Neurology
Center for Genomic Medicine

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

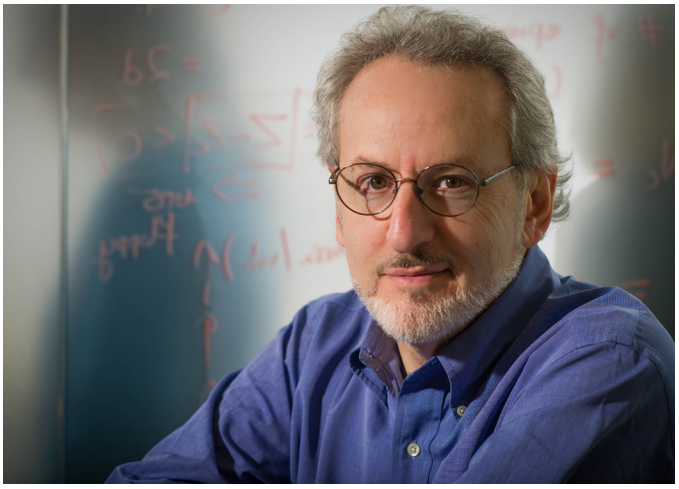
Cerebral adrenoleukodystrophy (ALD) affects 30 to 40 percent of boys between 4 and 8 years old who are born with a mutation in the X-linked ATP-binding cassette, subfamily D, member 1 (ABCD1) gene. The boys with ALD quickly begin to lose their ability to walk and talk. In the New England Journal of Medicine, researchers now reported using a lentivirus to infuse a normal copy of the ABCD1 gene into the bone marrow of boys with ALD. The corrected protein stopped disease progression. This is the first successful gene therapy treatment to halt a fatal brain disease.

Fundamental Research
Miguel N. Rivera, MD
Assistant Professor
Department of Pathology
Cancer Center

Cancer-Specific Retargeting of BAF Complexes by a Prion-like Domain

This study published in Cell describes a new mechanism involving disordered prion-like proteins that explains how transcription factors can be altered in cancer to activate new gene expression programs. Ewing sarcoma is the second most common bone cancer in children and is often driven by a single genetic abnormality that creates a fusion between two genes, EWS and the transcription factor FLI1. EWS belongs to a family of proteins with prion-like domains that undergo phase transitions such as forming liquid-like compartments or abnormally aggregating in neurodegenerative diseases. The researchers found that the phase-transition properties of these prion-like domains confer transcription factors with the ability to bind and activate otherwise inaccessible parts of the genome in order to induce abnormal gene expression. These findings explain why prion-like proteins are frequently altered in cancer and points to new potential treatment strategies.

Keynote Speaker



Donald E. Ingber, MD, PhD, is the Founding Director of the Wyss Institute for Biologically Inspired Engineering at Harvard University, Judah Folkman Professor of Vascular Biology at Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital, and Professor of Bioengineering at the Harvard John A. Paulson School of Engineering and Applied Sciences. He received his BA, MA, MPhil, MD and PhD from Yale University.

Ingber is a pioneer in the field of biologically inspired engineering, and at the Wyss Institute, he currently leads a multifaceted effort to develop breakthrough bioinspired technologies to advance healthcare and to improve sustainability. His work has led to major advances in mechanobiology, tumor angiogenesis, tissue engineering, systems biology, nanobiotechnology and translational medicine. Through his work, Ingber also has helped to break down boundaries between science, art and design.

Ingber has authored more than 425 publications and 173 patents, founded 5 companies, and been a guest speaker at more than 475 events internationally. He is a member of the National Academy of Medicine, National Academy of Inventors, American Institute for Medical and Biological Engineering, and the American Academy of Arts and Sciences. He was named one of the Top 20 Translational Researchers world-wide in 2012 (Nature Biotechnology), a Leading Global Thinker of 2015 (Foreign Policy magazine), and has received numerous other honors in a broad range of disciplines, including the Robert A. Pritzker Award and the Shu Chien Award (Biomedical Engineering Society), the Rous Whipple Award (American Society for Investigative Pathology), the Lifetime Achievement Award (Society of In Vitro Biology), the Leading Edge Award (Society of Toxicology), Founders Award (Biophysical Society) and the Department of Defense Breast Cancer Innovator Award.

Some of Ingber's most recently developed technologies include an anticoagulant surface coating for medical devices that replaces the need for dangerous blood-thinning drugs; a dialysis-like sepsis therapeutic device that clears blood of pathogens and inflammatory toxins; a shear stress-activated nanotherapeutic that targets clot-busting drugs to sites of vascular occlusion; and Human Organs-on-Chips created with microchip manufacturing methods and lined by living human cells, which are being used to replace animal testing as a more accurate and affordable in vitro platform for drug development and personalized medicine. In 2015, Ingber's Organs-on-Chips technology was named Design of the Year by the London Design Museum and was also acquired by the Museum of Modern Art (MoMA) in New York City for its permanent design collection. His Organs-on-Chips were also named one of the Top 10 Emerging Technologies of 2016 by the World Economic Forum.

Scientific Advisory Committee 2018

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

Richard P. Lifton, MD, PhD
President and Head of Laboratory of Human Genetics and Genomics
The Rockefeller University
SAC 2014 through SAC 2018 (2nd 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)

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)

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

Daniel K. Podolsky, MD
President
University of Texas Southwestern Medical Center
SAC 2014 through SAC 2018 (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)

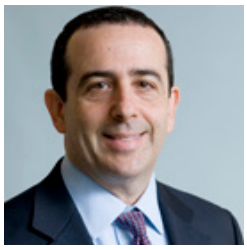
E. Albert Reece, MD, PhD, MBA
Executive Vice President for Medical Affairs
University of Maryland, Baltimore
Dean and Akiko K. Bowers Distinguished Professor
University of Maryland School of Medicine
SAC 2014 through SAC 2018 (2nd term)

Vivian S. Lee, MD, PhD, MBA
Professor of Radiology, University of Utah
Senior Fellow, Institute for Healthcare Improvement
SAC 2015 through SAC 2019 (1st term)

Ex Officio
George Q. Daley, MD, PhD
Dean, Faculty of Medicine
Caroline Shields Walker Professor of Medicine
Investigator, Howard Hughes Medical Institute
Harvard Medical School
Ex Officio

Executive Committee on Research
Officers and Members 2018

ECOR CHAIR
April 2015 - March 2018
David N. Louis, MD
Chief, Pathology



ECOR VICE CHAIR
April 2015 - March 2018
David E. Fisher, MD, PhD
Chief, Dermatology

ECOR IMMEDIATE PAST CHAIR
April 2015 - March 2018
Robert E. Kingston, PhD
Chief, Molecular Biology

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 Bannister, RN, PhD*
Executive Director, Institute for Patient Care
May 2017 – April 2021

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

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

Merit E. Cudkowicz, MD, MSc*
Chief, Neurology
April 2012 - March 2018

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 2012 - March 2018

Steven K. Grinspoon, MD
Program in Nutritional Metabolism/ Neuroendocrine
Elected Representative
January 2016 - December 2018

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

Kurt J. Isselbacher, MD
Honorary Member

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

*Chair Appointment, ‡ Chiefs Council

Executive Committee on Research
Officers and Members 2018

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 2012 - March 2018

David J. Milan, MD
Cardiology/Cardiovascular Research Center
Elected Representative
January 2016 - December 2018

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

Christopher Newton-Cheh, MD, MPH
Cardiology
Committee on Clinical Research (CCR) Representative
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 2012 - March 2018

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

Brian Seed, PhD
Director, Center for Computational & Integrative Biology
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

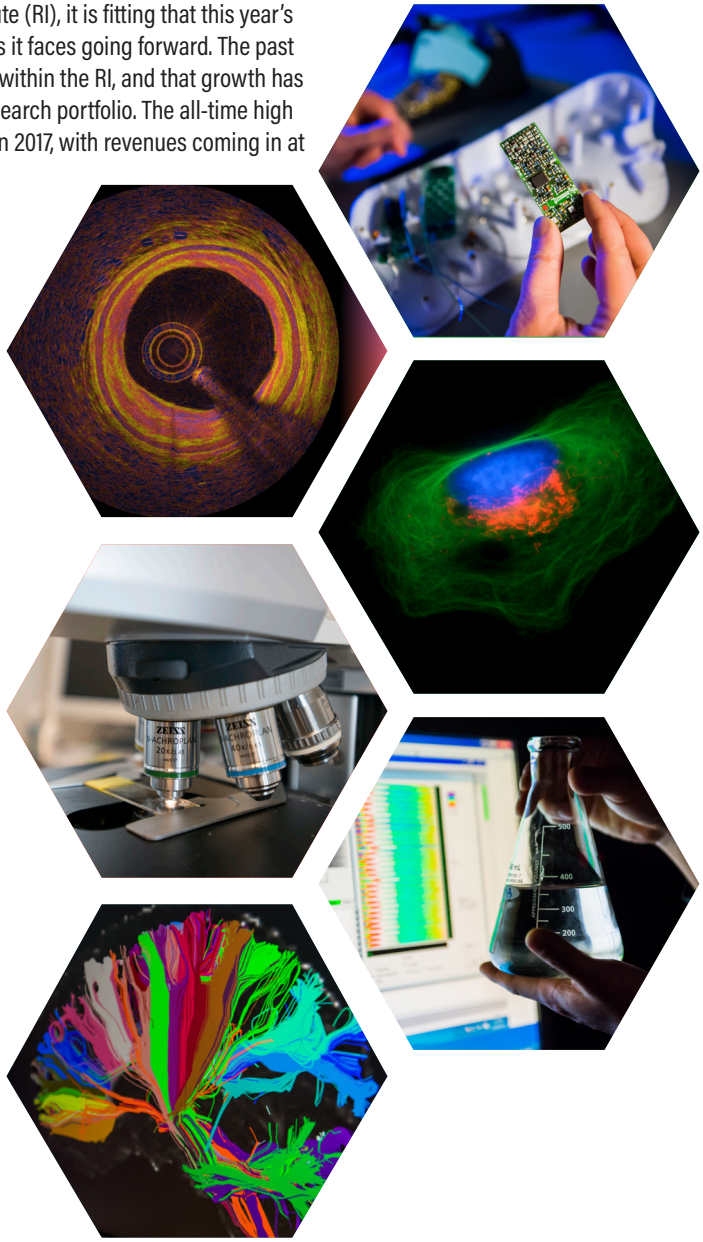
Kristin White, PhD
Dermatology, CBRC
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

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

*Chair Appointment, ‡ Chiefs Council

The Research Institute Shifts into High Gear

With 2017 marking the third full year of operation of the MGH Research Institute (RI), it is fitting that this year's SAC meeting focus on the RI, its accomplishments to date and the challenges it faces going forward. The past year has seen continued progress in all of the strategic initiatives underway within the RI, and that growth has been accompanied by another year of exceptionally strong growth in our research portfolio. The all-time high in research revenues reported in 2016 of $850M was exceeded significantly in 2017, with revenues coming in at $912M.



Highlights of RI accomplishments/milestones in 2017 include:

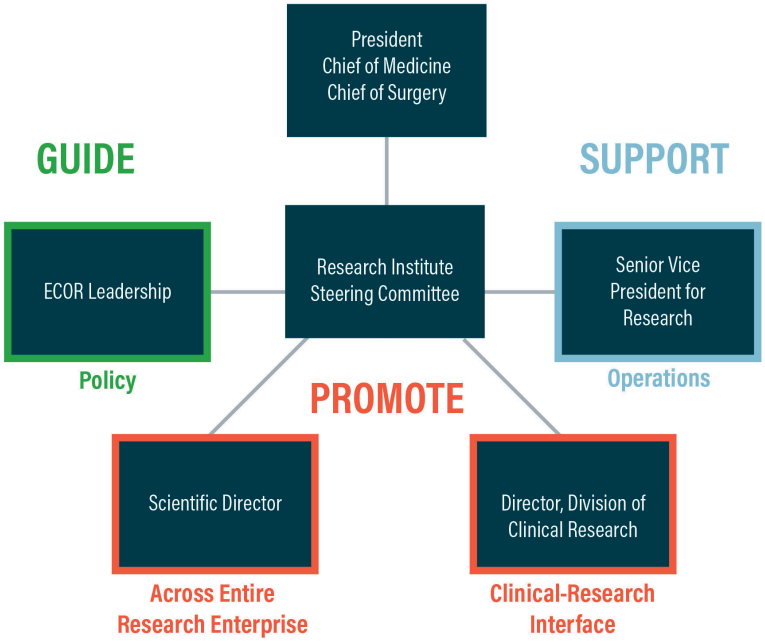
- Growth in every income category of research revenues (NIH, industry, foundation), with an impressive 18% growth in industry income.
- The appointment of the 50th MGH Research Scholar and the second RI Endowed Chair.
- An increase in the number of inpatient research studies in the one-year old Translational and Clinical Research Center from 8 to 31.
- The addition of a fifth Strategic Alliance thematic program in cardiometabolics, which brought together 24 MGH investigators from eight departments and centers.
- The creation of the Committee on Fundamental Research from the independent PhD Steering Committee to more formally acknowledge and represent the specific interests of fundamental researchers.
- New communication and marketing efforts, including the launch of an MGH RI blog and the creation of Snapshot of Science, a monthly newsletter that includes lay-person summaries of publications by MGH researchers from high impact journals.
- Continued growth of services within the Division of Clinical Research (DCR), with the formation of its new Trial Innovation Unit bringing the DCR support service totals to 9 centers, 10 units, and 4 think tanks.
- Strong growth in the Partners Biobank at MGH, with consented patient recruitment now over 75,000 and genotyped samples exceeding 20,000.
- Continued growth in use of the Isuggest program, with the number of suggestions to improve research services at the end of 2017 exceeding 1,000 and the number implemented exceeding 500.
- Development of the first-ever program component of New Employee Orientation that specifically targets research employees and provides them a uniform introduction to and overview of the MGH RI.
- Completion of major process and organizational changes to the animal care and IACUC programs, which resulted in a recommendation from the 2017 AAALAC triennial site visit team for full continued accreditation with, for the first time, no mandatory findings.

These and other important developments from the past year are reported below, in the new sectional format first used last year, which aligns with the organizational components (Guide, Promote, Support) of the RI governance structure. The report concludes with a new section, Looking at the Year Ahead, in which the most notable challenges and opportunities for the research enterprise in 2018 are discussed.

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. 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 $13M 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 Louis, MD (Chief, Pathology); the Vice Chair is David Fisher, MD, PhD (Chief, Dermatology); and the Immediate Past Chair is Robert Kingston, PhD (Chief, Molecular Biology). 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. Following our SAC 2018 meeting, Merit E. Cudkowicz, MD, MSc (Chief, Neurology) will assume the role of Vice Chair of ECOR and Dr. Kingston will step down from his role as Past Chair of ECOR but will remain a member of the Research Institute Steering Committee.

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.

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.

Following an effort to reconstitute the Research Council in the Spring of 2016, ECOR asked Chiefs and Center Directors to appoint two faculty members to serve as representatives for their department or center to Research Council to increase the flow of communication between ECOR and the Research Community. Appointed representatives are asked to make every effort to attend the meetings, be willing to ask questions or speak to one of the elected representatives regarding issues in their department, and report back to their department on issues of interest.

2018 Research Council Designated Department Representatives

(Listed and displayed alphabetically, left to right)

Meredith August, MD, DMD, Oral & Maxillofacial Surgery; Ravikumar Balasubramanian, MBBS, PhD, Medicine; Alejandro Balazs, PhD, Ragon Institute; Charles Bragdon, PhD, Orthopaedics; Priscilla Brastianos, MD, Cancer Center

Bobby Cherayil, MD, MBBS, Pediatrics; Joseph Elkhoury, MD, Medicine; A. Eden Evins, MD, Psychiatry; William Faquin, MD, PhD, Pathology; Adam Feldman, MD, MPH, Urology

Michael Filbin, MD, Emergency Medicine; Jane Flanagan, PhD, ANP-BC, Nursing; Esther Freeman, MD, PhD, Dermatology; Randy Gollub, MD, PhD, Psychiatry; Stephen Haggarty, PhD, Center for Genomic Medicine;

Allyson Hindle, PhD, Anesthesia; Jayashree Kalpathy-Cramer, PhD, Radiology; William T. Kimberly, MD, PhD, Neurology; Robert Kingston, PhD, Molecular Biology; Clotilde Lagier- Tourenne, MD, PhD, Neurology

Elizabeth Lawson, MD, Medicine; Andrew Liss, PhD, Surgery; Mauro Longoni, MD, Pediatric Surgery; Michael Mansour, MD, PhD, Medicine; Alexander Marneros, MD, PhD, Dermatology

Marcos Vidal Melo, MD, Anesthesia; Madhusmita Misra, MBBS, Pediatrics; David Miyamoto, MD, PhD, Radiation Oncology; Raul Mostoslavsky, MD, PhD, Cancer Center; Patricia Musolino, MD, PhD, Center for Genomic Medicine

Seemantini Nadkarni, PhD, Wellman Center for Photomedicine; Andrew Nierenberg, MD, Psychiatry; Ebru Oral, PhD, Orthopaedics; Sareh Parangi, MD, Surgery; Zachary Peacock, MD, DMD, Oral & Maxillofacial Surgery

David Pepin, PhD, Pediatric Surgery; Mikael Pittet, PhD, Center for Systems Biology; Yakeel Quiroz, PhD, Psychiatry; Samuel Rabkin, PhD, Neurosurgery; Megan Rice, ScD, Medicine

Miguel Rivera, MD, Pathology; Joshua Roffman, MD, Psychiatry; Bo Rueda, PhD, Obstetrics & Gynecology; Mary Sabatini, MD, PhD, Obstetrics & Gynecology; Amar Sahay, PhD, Center for Regenerative Medicine

Anthony Samir, MD, Radiology; Brian Seed, PhD, Center for Computational and Integrative Biology; Radhika Subramanian, PhD, Molecular Biology; Mario Suva, MD, PhD, Pathology; Filip Swirski, PhD, Center for Systems Biology

Benjamin Vakoc, PhD, Wellman Center for Photomedicine; Zongwei Wang, MD, Urology; Erica Warner, ScD, Medicine; Ziv Williams, MD, Neurosurgery; Xu Yu, MD, Ragon Institute

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 page 7.

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.

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 2014, the Warren Prize has been awarded on 42 occasions to 72 recipients. Twenty-three 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.

A medallion of Dr. Warren, presented to recipients

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. Topics of discussion during 2017 meetings included:

- NHP housing improvements
- Off-site housing requirements
- Simches Research Center animal facility construction updates
- Charlestown Navy Yard animal facility construction updates
- New rodent documentation program
- Regulatory and accreditation requirements

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 141 members - 44 Professors, 58 Associate Professors, and 39 Assistant Professors. Approximately 49 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 our SAC in 2015, ECOR began the process of creating a Division to serve the post doctoral community. The newly formed 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 post doctoral 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 post doctoral fellows affiliated with MGH.

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 5 years and 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.

Charlestown Navy Yard (CNY) Quality of Life Survey

One of ECOR's 2018 initiatives will include surveying the members of our research community located in the Navy Yard in Charlestown. The goal of the survey is to get a better understanding of the challenges of working in the Navy Yard for students, post-doctoral fellows, staff and faculty. Respondents will have the opportunity to give suggestions for improving the quality of life and work environment in the Navy Yard.

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.

In FY17, $13.2M went to 122 Investigators.

Grant	$	PIs
Interim Support (Formulaic/Deliberative)	$5.8M	76
MGH Research Scholars	$4.0M	8
Claflin Distinguished Scholars	$690K	6
FMD & Tosteson Fellowships (Postdoctoral Awards)	$1.6M	22
Other Awards*	$1.1M	10

**Other Awards includes Goodman, Martin and PSDA*

Awards and Grants

ECOR manages a multi-million-dollar grant program, virtually a mini-foundation, which annually reviews nearly 800 applications from MGH investigators and fellows, and awards approximately 130 internal grants. Over the past several years, there has been a significant increase in the number of grant mechanisms offered 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.

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: over 90% of investigators who received funding from the Interim Support Program from 2006-2017 are still working within the institution. Since the program's inception in 2006, ECOR has awarded $52M of interim support funding. Our investigators have gone on to leverage these funds nine-fold, bringing in over $531M 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.

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 $47,500.

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, 76% have been promoted and received ~$420 million in total external grant funding. In FY17, six women received the Claflin Award.

MGH Physician-Scientist Development Award

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 FY17, two investigators received this award.

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 have given $750,000 to eight teams of investigators through two cycles of grants. An additional call for applications was announced in the fall of 2017. Five grants of $100,000 (total costs) will be awarded to be spent over 1-2 years.
- 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 have given $750,000 to six teams of investigators.

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 2017, 50 Scholars have been appointed, each receiving research funding of $100,000 a year for five years.

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.

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.

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 for providing 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 2017, the committee championed the nominations of more than 50 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 2017 include the following:

American Academy of Microbiology (AAM)
Laurence Rahme, PhD (Surgery & Molecular Biology)

American Academy of Neuromuscular and Electrodiagnostic Medicine Honorary Membership Award
Merit Cudkowicz, MD, MSc (Neurology)

American Association for the Advancement of Science (AAAS)
David C. Hooper, MD (Infectious Disease)

American Clinical and Climatological Association (ACCA)
Steven Grinspoon, MD (Medicine/Neuroendocrine)

American Heart Association (AHA) Distinguished Scientist Award
Sekar Kathiresan, MD (Center for Genomic Medicine)

American Lung Association Lung Cancer Discovery Award
Johnathan Whetstine, PhD (Cancer Center)

American Physiological Society (APS) President
Dennis Brown, PhD (Medicine/Nephrology & Center for Systems Biology)

American Society for Bone and Mineral Research (ASBMR) Rising Star Award
Marc Wein, MD, PhD (Medicine/Endocrine)

American Society for Clinical Investigation (ASCI)
Ryan Corcoran, MD, PhD (Cancer Center)

American Society for Radiation Oncology (ASTRO)
Alphonse G. Taghian, MD, PhD (Radiation Oncology)

American Statistical Association Mosteller Statistician of the Year
David A. Schoenfeld, PhD (Medicine/Cardiology)

BrightFocus Foundation Outstanding Emerging Researcher Award
Jennifer Gatchel, MD, PhD (Psychiatry)

Cardiology Today's Next Gen Innovators
Hanna K. Gaggin, MD, MPH, FACC (Medicine/Cardiology)

Damon Runyon-Rachleff Innovation Award
Marcela V. Maus, MD, PhD (Cancer Center)

Doris Duke Charitable Foundation Clinical Research Mentorship
Steven Lubitz, MD, MPH (Medicine/Cardiology)

Doris Duke Charitable Foundation Clinical Scientist Development Award
Aaron Hata, MD, PhD (Cancer Center)

Endocrine Society Outstanding Mentor Award
Joel F. Habener, MD (Medicine/Endocrinology)

Foundation for Anesthesia Education and Research (FAER) Academy of Research Mentors in Anesthesiology Mentoring Excellence in Research Award
Jeevendra Martyn, MD (Anesthesia)

Get Konnected's (GK's) Top 50 Most Influential People of Color in the Healthcare and Life Sciences Industry
Emery N. Brown, MD, PhD (Anesthesia)
Joseph R. Betancourt, MD, MPH (Medicine/Internal Medicine)
Jocelyn A. Carter, MD, MPH (Medicine/General Internal Medicine)
Marcela Del Carmen, MD (Obstetrics and Gynecology)
Jonathan D. Jackson, PhD (Neurology)
Laura E. Riley, MD (Obstetrics and Gynecology)
Elsie M. Taveras, MD (Pediatrics)
Michael T. Watkins, MD (Surgery)
Winfred W. Williams, Jr., MD (Medicine/Nephrology)

Glenn Foundation Award for Research in Biological Mechanisms of Aging
Alexander Soukas, MD, PhD (Medicine/Diabetes & Center for Genomic Medicine)

Harrington Prize for Innovation
Joel F. Habener, MD (Medicine/Endocrine)

HMS William Silen Lifetime Achievement in Mentoring Award
R. Rox Anderson, MD (Dermatology & Wellman Center for Photomedicine)

Irish America Healthcare and Life Sciences Honors List
Tomas G. Neilan, MD, MPH, MRCPI (Medicine/Cardiology)

Kuwait Foundation for the Advancement of Science 2017 International Kuwait Prize in Applied Medical Sciences
M. Amin Arnaout, MD (Medicine/Nephrology & Center for Regenerative Medicine)

National Academy of Engineering (NAE)
Mehmet Toner, PhD (Surgery)
Martin Yarmush, MD, PhD (Surgery)

National Academy of Inventors
R. Rox Anderson, MD (Dermatology & Wellman Center for Photomedicine)
Rajesh Jain, PhD (Radiation Oncology)
Bruce Rosen, MD, PhD (Radiology & Martinos Center)

National Academy of Medicine (NAM)
Mark Daly, PhD (Medicine/Analytic and Translational Genetics & Center for Genomic Medicine)

National Institute of Mental Health (NIMH) Biobehavioral Research Award for Innovative New Scientists (BRAINS)
Erin Dunn, ScD (Psychiatry & Center for Genomic Medicine)
Rakesh Karmacharya, MD, PhD (Psychiatry & Center for Genomic Medicine)

National Institutes of Health (NIH) Director's Early Independence Award
Zirui Song, MD, PhD (Medicine/Internal Medicine)

National Institutes of Health (NIH) Director's New Innovator Award
Evan Macosko, MD, PhD (Psychiatry)
Radhika Subramanian, PhD (Molecular Biology)
Brian J. Wainger, MD, PhD (Anesthesia)

Order of Canada Member
Isaac Schiff, MD (Obstetrics and Gynecology)

Patient-Centered Outcomes Research Institute (PCORI) Award
Jennifer Temel, MD (Cancer Center)
Joseph Greer, PhD (Psychiatry)

Pew Scholars Program in the Biomedical Sciences Award
Alan C. Mullen, MD, PhD (Medicine/Gastroenterology & Center for Regenerative Medicine)

Pioneer Award of the International Pediatric Transplant Association
A. Benedict Cosimi, MD (Surgery)

Memorial Sloan Kettering Cancer Center Paul Marks Prize for Cancer Research
Gad Getz, PhD (Pathology)

One Mind/Janssen Rising Star Translational Research Award
Alik Widge, MD, PhD (Psychiatry)

Stand Up To Cancer (SU2C) Phillip A. Sharp Award
David T. Ting, MD (Cancer Center)

Smith Family Award for Excellence in Biomedical Research
Aaron N. Hata, MD, PhD (Cancer Center)

Society for Bone and Mineral Research (ASBMR), John Haddad Young Investigator Award
Vibha Singhal, MD (Pediatrics)

Society for Neuroscience (SfN) Peter and Patricia Gruber International Research Award
Laura Lewis, PhD (Martinos Center)

US Department of Health and Human Services Advisory Council on Alzheimer's Research, Care and Services
Katie D. Brandt, MM (Neurology)
Bradley T. Hyman, MD, PhD (Neurology)

For more information about ECOR, visit our website at http://ecor.mgh.harvard.edu

PROMOTE

The Mass General Research Institute — Susan A. Slaugenhaupt, PhD, Scientific Director

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 Innovation Office.

Below, we expand on each of these initiatives and give a few highlights from the past year.

Marketing and Communications

Newsletters
In 2017, we launched a variety of new communications to help promote the remarkable work of our research community. 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. Launched in September 2017, 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 have received positive feedback from the research community about this new initiative.

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
In February of 2017, we launched our Research Institute Blog as a 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.

Since launching the blog, we've had:

- 300 published blog posts
- 350 new followers
- 11,922 page views
- 8,555 visitors
- 217 post likes

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 2017, we have used promoted posts to reach 23,166 people on Facebook, and those posts generated approximately 7,000 engagements (likes, shares, comments, reactions, link clicks, etc.). In addition, we have:

- doubled our number of Facebook followers from 350 to 700
- added 600+ followers to our Twitter, for a total of 950 followers

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

This year we hosted two communicating science competitions. In April, we teamed up with the Brigham Research Institute to host the Research Rumble as part of the Cambridge Science Festival, and in October we held our second annual "Art of Talking Science Competition" as part of the city-wide HUBweek festival. These events gave researchers an opportunity to give a four-minute science presentation to a panel of celebrity judges, who provided feedback and advice for improvement.

In May, we invited the Alan Alda Center for Communicating Science to campus for "Distilling Your Message," an interactive plenary session and workshop designed to help researchers succinctly and vividly speak about their work in lay person terms. Improvisation exercises helped the participants hone their ability to naturally connect with different audiences.

Internship Program
We also continued our communications internship program 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.

Collaborative Efforts
In March, we collaborated with the Physicians for Policy Action (a Partners-wide initiative) and the MGH Healthcare Advocacy Committee to co-host a rally on the Bulfinch lawn to show support for the Boston March for Science, a sister event to science rallies taking place in Washington, DC. The Boston March for Science celebrated the discovery, understanding and sharing of scientific knowledge and provided the Mass General research community with an opportunity to reaffirm the essential role science – specifically biomedical research– plays in improving life and health.

As advocacy becomes more and more important to our community, the Office of the Scientific Director continues to meet with groups on campus to create and support events and actions that allow the Mass General community to champion scientific discovery, including the use of our communication channels to highlight the effects of shrinking government funding.

We also 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 has 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 2017, we selected eight new MGH Research Scholars, bringing the total number of Scholars awarded unrestricted funding over the past six years to 50. This remarkable donor-supported program has had a substantial impact on the careers of the awardees and the advancement of research at Mass General. We continue to work towards our goal of supporting more members of our research community with MGH Research Scholar Awards and 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 - and through a workshop led by the Alan Alda Center for Communicating Science.

Our Research Institute Development team – including Drs. Slaugenhaupt, Orf, Kingston and others in research leadership - held 42 meetings, lunches, and lab tours with individual donors and prospects in 2017. In addition, we were able to hold donor events in London and Florida. Drs. Slaugenhaupt and Apiou met with members of the Wellcome Trust to further our Strategic Alliance initiatives. In March of 2018, the MGH Research Scholars will participate in a forum held in their honor in Beijing, China.

At the annual Research Institute Advisory Council (RIAC) meeting, the Advancement Committee agreed on new strategies to identify potential donors and the Committee will meet in 2018 in a special session to advance those strategies. 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

The Strategic Alliance Initiative was developed 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 have been able to push many of our programs forward in 2017. The Strategic Alliance Initiative has been 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 a 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 2017, we continued working on a database system to gather scientific outlines from across campus. Our Strategic Alliance program managers then extracted the essence of these outlines into a one-paragraph pitch format. These pitches can be used for press inquiries, donor proposals, and our work creating cross-departmental programs, and can be leveraged for interactions with industry. We also used the 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, 28 investigators have presented at nine 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) programs come from research "themes" that were collected from departments, centers and institutes across campus. In 2016, we built four SA programs around Epigenetics, Cancer Immunotherapy, Neuroinflammation in Neurodegeneration and the Microbiome, which brought together 61 investigators from many departments and thematic centers. In 2017,

we organized eight 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.

We also expanded the initiative to include our Cardiometabolics program, which brought together another 24 investigators from eight departments/centers. This group presented their problem-driven program to our internal industry and venture partners in December, and we are currently working towards introducing this program to hand-selected companies in the next few months. In 2018, we plan to launch two new programs potentially in the areas of rare and infectious diseases.

Translational Research Training Program
The development of an innovative translational training program remains a high priority, and we have been very successful over the past year in building support for this program. We have identified a course co-director from the venture community who shares our vision of improving the transfer of research discoveries through training young scientists to think translationally.

This program aims to teach our scientists:

- 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 20-week didactic course and, for one team per year, a problem-driven research project opportunity. We are currently working on funding the program through foundation and industry support and plan to launch in 2018. As part of the development of the training program, we visited with the National Center for Advancing Translational Sciences (NCATS). During our meeting with the Director, Dr. Christopher Austin, and his team, we identified many common areas in which to explore further collaboration. We also submitted a proposal to the Wellcome Trust to help fund the training program and to potentially expand its reach in the future.

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 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 2017 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 22nd year. The MGH DCR has launched some new initiatives in 2017:

- DCR is leading clinical research integration at Wentworth-Douglass Hospital (WDH) by leveraging the PREP infrastructure
- DCR is beginning discussions with the University of Massachusetts at Amherst Institute for Applied Life Sciences to develop collaborations between their basic scientists and our clinical and translational scientists

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 Harvard Catalyst.

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

DCR Centers

Bioinformatics Consortium, Ruslan Sadreyev
Computational data management, analysis, and interpretation have become 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 & Hang Lee
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 Miller & Andrew Nierenberg
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 (life and online) for clinical investigators and study staff. The Center provides educational programs for 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
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 treatment; 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; monitoring treatment outcomes.

Clinical Research Center (CRC), David Nathan
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
The new CARE Research Center will use 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 will help develop community-wide resources that empower patients and their families to access cutting-edge medical treatment, which also reduces 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
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 partnership 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
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 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 enjoyment and recruitment strategies and tools.

Yvonne L. Munn Center for Nursing Research, Gaurdia Banister
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

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. 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 has been 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 & 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 will brainstorm about drug discovery opportunities in their field of interest with key advisors in pharma and biotech. Topics may include how to approach companies, what companies are looking for and conceptual advice about working with pharma and biotech.

Global Health Research Unit (GHRU), Jessica Haberer

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 & G. Scott Gazelle

The Imaging Biomarkers Unit provides 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 & Carl Blesius

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 have been: 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

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 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

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 & Roman DeSanctis
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 will brainstorm about how to raise philanthropic support for their research with key advisors in the field.

Qualitative Research Unit, Elyse Park, Christina Psaros, Lara Traeger
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, Eric Campbell
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 meetings with representatives from academia, pharma/biotech etc. to discuss programmatic collaboration. Current Think Tanks include:

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

Below is the expanded report on two cornerstone initiatives: The Partners Biobank at MGH, Jordan Smoller and Susan Slaugenhaupt and the Translational Research Center (TRC), Mason Freeman.

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

The Partners Biobank at MGH was devised to be a collaborative effort among patients, clinicians, and scientists to better understand disease, identify targets for therapy, and enable personalized medicine, by collecting and storing fully consented blood, serum, and plasma samples, linked to electronic medical records, from patients across the institution. Through the MGH Research Institute, resources were committed to add personnel, space, and equipment to jumpstart the consent and collection program at MGH. 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 three years, we have seen a dramatic increase in patient recruitment to over 75,000. Through the dedicated efforts of the MGH team, including Biobank manager Nicole Allen, the MGH program has enjoyed great success since the implementation of the strategic plan. From a recruitment standpoint, the MGH program reached record consent and collection metrics in 2017 thanks to the growth of our team and successful partnerships with high volume clinical departments and research teams including the Center for Perioperative Care, Radiology, Dermatology, the Cancer Center, Pathology, Neurology, Chelsea Community Health Center, the Emergency Department research team, the Cardiovascular Biorepository, the Biorepository for Neurological Injury research team, and the Acute Psychiatric Service research team. Notably, the MGH co-directors and team expanded recruitment operations to Spaulding Rehabilitation Hospital's inpatient facility, and supported Dr. Kerry Ressler in setting up Biobank recruitment at McLean Hospital. Most recently, the Biobank partnered with the MGH Department of Medicine on an innovative recruitment protocol that will integrate Biobank enrollment into the largest clinical and educational service at the MGH.

The addition of two dedicated Biobank consent/collection rooms on Wang 2 and Yawkey 3 have made the link between research and clinical care seamless, as patients who come to the Biobank labs can contribute both research and clinical samples at the same time. Increasing awareness of the Biobank to both patients and our investigators is a priority of the Research Institute. Over the past year, we have also greatly expanded visibility for the Biobank by installing interactive electronic Biobank "kiosks" in the Wang and Yawkey lobbies. The Institute hired a marketing and education specialist to help in promoting the Biobank to patients and the MGH community, and efforts to increase active on-line recruitment via Patient Gateway are ongoing. The Community Advisory Panel that launched in 2015 has expanded its membership and continues to be a tremendous success with members contributing much-needed advice for patient engagement techniques. Biobank sample collection has been accelerated by integration of Sunquest sample collection orders into the Epic EHR. 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 provided funding to genotype the first 50,000 Biobank samples. To date, 20,000 have been genotyped and these data have been made freely available to investigators via the Biobank Portal. Because of the success of the Biobank, our co-directors have successfully competed for national grants that brought tremendous resources to the Institution. Biobank investigators are part of 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. Most recently, Partners HealthCare, in collaboration with Boston Medical Center has been named one of the Precision Medicine Initiative's (PMI) health provider organizations to help enroll a diverse cohort of over 1 million people into the NIH-run All of Us Research Program. These new resources, together with the extraordinary efforts of the Biobank staff, have resulted in a major increase in participants recruited. In addition, the Biobank has begun to return medically actionable genetic results to participants. Participants are eligible to receive results for pathogenic variants within 59 genes designated by the American College of Genetics and Genomics. The Biobank is providing genetic counseling services to return these results and assist with clinical confirmation. Finally, a growing number of MGH investigators have been using samples and data from the Biobank to fuel their research efforts, several of which have led to high profile publications. Goals for this coming year include ongoing expansion of Biobank recruitment, launching large-scale recruitment for the All of Us Research Program, 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 moving basic scientific discoveries and new technologies, discovered both at the MGH and in the biopharma community, toward the clinic 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. With the opening of the new TCRC facility in November of 2016, we have spent much of the past year working to build the business relationships with external companies who might select the MGH as the site for future clinical trial work. We have also tapped the TRC staff to assist both less experienced as well as very experienced investigators in more expeditiously completing their IRB submissions and concluding contract negotiations with the CTO.

Accomplishments

1. The TCRC had its official ribbon-cutting ceremony opening the new facility on White 12 on November 30th, 2016, though it began conducting studies in the new space in late October 2016. In the ~ 13-month span since opening, the TCRC has conducted 31 industry-sponsored studies. By contrast, in the first 10 months of 2016, prior to opening, only 8 industry studies were conducted in the old CRC space. Thus, in the first year of operation, the TCRC conducted roughly three times more industry sponsored studies than in the immediate period prior to opening. Simply enlarging the facility from the previous smaller CRC space of 5-8 beds certainly contributed to this increased volume, but the extensive outreach effort conducted by the TRC staff has contributed to the growing awareness of the superb facilities and research staff the MGH can call upon to execute complex clinical trials. Some highlights of the trials that have been conducted in the TCRC in that 13-month span include:

- There has been a broad representation of disease areas and treatments investigated, but neurological diseases are clearly playing an important role in the increased TCRC activity. Studies of patients with X-linked adrenal leukodystrophy, early Alzheimer's, progressive supranuclear palsy, ALS, Parkinson's, and multiple sclerosis represent just part of the spectrum of neuromuscular disorders for which new treatments have been tested in the first year. These studies typically enroll small numbers of patients (5-10) and may follow them with repeat visits in the TCRC over many weeks or months. In addition, they frequently require an IV infusion, a timed, repetitive set of blood tests, or they involve intensive monitoring of the patient's condition, all of which necessitate the use of the in-patient TCRC facility. Other diseases for which novel therapeutic protocols have been approved for study on the TCRC include atypical hemolytic uremic syndrome, non-alcoholic steatohepatitis, severe peanut allergies, calciphylaxis, and hypoparathyroidism, A wide range of companies are sponsoring these trials, including large pharma organizations such as Sanofi, Novartis, and BMS; mid-sized biotechs, Biogen and Shire; and a host of smaller startups such as Selecta Biosciences, Jazz Pharmaceuticals, and Stealth Biotherapeutics. The feedback the TCRC has received from these sponsors clearly indicates that the new, enlarged trial facility has greatly enhanced the eagerness of these industry partners to work with the MGH and its investigative community.

- The administrative challenges of providing outstanding clinical trial services in a timely and efficient manner have continued to evolve in a favorable direction. The outsourcing of all phase 2 trials or later to external, independent IRBs has significantly improved IRB approval times for such studies. We continue to work closely with Dr. Hohmann, head of the IRB, to look for ways to improve the turnaround time of IRB-investigator communications. The TRC staff is now assuming much of the administrative handling of these submissions for time-sensitive TCRC studies. TRC staff, Lynelle Cortellini and Lisa Bernardo, are working closely with the TCRC staff, investigators, and the Partners CTO office to facilitate all administrative aspects of study approval ranging from contract negotiations to IRB responses. Working closely with Suzanne Morin and Maureen Lawton in the CTO, the TRC was able to hire Kristin Collins, JD, Senior Clinical Research Agreement Associate, to expedite trial agreements, CDA's, and other contractual documents for TRC investigators. Kristin's experience and responsiveness is clearly leading to improvements in contract times. We are now finding that delays in contract completion are more likely due to slow industry response times rather than impediments within our own organization. The budgeting process is still complex and time consuming, but as the TRC staff gets more accustomed to the processes we have put in place, we expect to see further gains in productivity and efficiency.

- In March of 2017, we hired Rajesh Ranganathan, PhD, to work as our business development officer. Rajesh came after several years working on therapeutics efforts at NIH under Francis Collins and at the NINDS in establishing the Blueprint funding mechanism. Prior to that, he had a leadership role at Novartis at NIBR. Rajesh's time is shared between the TRC and the Department of Medicine, where he leads the Pathways program. These two jobs are potentially synergistic as the Pathways work often calls for him to interact with local biopharma companies in exploring tools they may have that can be leveraged to tackle unexplained human biology in the Pathways patients. In the first eight months of his time at MGH, Rajesh has been incredibly productive. He has met with more than 60 companies and had > 20 discussions under CDA about their programs. He has conducted multiple tours of the new TCRC facility that have led to a dozen negotiations of future clinical trials at MGH. One trial is now fully underway and is actively recruiting new patients to test a novel drug for fatty liver disease, another has submitted protocols to the IRB for approval of a new therapeutic for celiac disease, and two separate companies with agents aimed at the treatment of spinal muscle atrophy have submitted materials to begin contract negotiations. This business outreach function is central to the success of the TRC and Rajesh is having a major impact in bringing companies to the MGH. In addition to these interactions, Rajesh identified and connected MGH investigators with four companies whose clinical trial protocols did not require the resources of the TCRC but could instead be conducted in Departmental outpatient units.

2. The TRC team, spearheaded by its Program Manager, Dr. Yuan-Di Halvorsen, has continued to provide consultative services to a wide variety of MGH investigators whose research programs have needed input on clinical development, regulatory, or CMC issues of a wide variety. Examples of that support include:

- Several of the programs mentioned in last year's summary generated critical data that have enabled development decisions to be made: 1) Dr. Ed Ryan's shigella-cholera combined vaccine achieved impressive yield improvements in the proteins required for the vaccine that were based on manufacturing protocols recommended by Dr. Halvorsen; a new Gates Foundation/Korean government joint grant has been submitted based on these process improvements and is currently under review 2) Dr. Marc Wein of the Endocrine division had a novel small molecule kinase inhibitor with promising in vivo osteoporosis benefits profiled in a rodent toxicology study arranged via the TRC; the results suggested significant on-target biochemical toxicity that was predicted as a potential liability; this will have to be engineered out of the molecule, if possible, before it could be considered an attractive therapy for human bone disease 3) John Stone completed the phase 2 study of Xencor's XmAb®5871 monoclonal Ab for IgG4-Related Disease, which was conducted in the new TCRD facility, and presented the results at the American College of Rheumatology Annual meeting in Nov 2017; 12 of 15 study subjects completed the study and all 12 met the primary efficacy endpoint.

- Mitobridge, a Cambridge-based biotech company developing novel therapeutics for mitochrondrial and muscle disorders, engaged several faculty consultants working in the fields of ALS and Huntington's. These consultations were enabled using the newly engineered TRC faculty consult pathway that simplifies industry/faculty interactions. Mitobridge's first clinical compound, which the TRC helped shepherd through IND enabling studies, was approved by the FDA for a phase 1, healthy volunteer clinical trial in mid-2017. The molecule, a PPAR-delta agonist, has been administered to multiple cohorts to date with no apparent ill effects. In late November 2017, Astellas announced that it would acquire Mitobridge, partly based on these human data. Astellas is expected to continue the Mitobridge programs. The acquisition of Mitobridge is the first biotech exit to which the TRC made a significant contribution.

- The Theracos SGLT2 inhibitor (bexagliflozin) diabetes program, which represents the first major therapeutic program started in the Translational Medicine Group (predecessor to the TRC) has enrolled its phase 3 cardiovascular safety trial. This trial is testing bexagliflozin in more than 1650 patients around the world. Several other Phase 3 trials of bexagliflozin are concurrently running.

The entire Theracos, international, type II diabetes development program is being managed by Dr. Halvorsen and the TMG staff. Successful completion of this program should lead to an NDA submission to the FDA for marketing authorization of bexagliflozin.

Lessons Learned
The administrative interface between the TRC/TCRC and Partners is critical to the success of the Center. Significant progress was made in 2017 in getting key hires in place and rationalizing the business procedures. This work will need constant surveillance as the TRC grows over time.

The rapid uptick in industry studies in 2017 was gratifying to see but we are still at an early stage in soliciting this work. Business outreach needs to continue at a high level. Finding ways to engage MGH investigators to work with companies on projects that are intellectually stimulating, academically meaningful, and feasible are constant challenges. A key missing element in the services the TRC provides to investigators is recruitment support. The DCR is exploring solutions to this problem now.

Adaptation Planned
With the hiring of Rajesh Ranganathan as the new business development officer, we now need to make sure he has the time and knowledge base to partner qualified investigators with appropriate companies and to help those investigators meet enrollment goals for the trials they perform.

With studies now being directly recruited by the TRC, the challenge of finding available, qualified, and interested investigators requires considerable hospital dialog around how we incentivize participation in this work while enhancing academic careers devoted to the creation, exploration, and development of new therapeutic and diagnostic tools.

SUPPORT

By the Number$ - Another All-Time High — 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 FY17 reached another all-time high of $912M ($710M direct costs and $202M indirect), a $62M increase from FY16. Our awarded dollars from the National Institutes of Health (NIH) in FY16 increased from $365M to $394M, with the percentage of funding awarded to MGH from the entire NIH extramural grant pool (market share) growing slightly to 1.6%, up from 1.5% the previous fiscal year. This is a testament to the quality, perseverance, and resilience of the MGH research community.

Overall, MGH submitted 4,582 research proposals to all sponsors in FY17, down slightly (1.1%) from the prior fiscal year. We did, however, see increases compared to the previous fiscal year in the volume of proposals submitted to DHHS (5%), Federal Subcontracts (2%) and Non-Profit (13%). DHHS success rates for MGH proposals are approximately 23%, four points higher than the NIH national average of 19%.

Research expenditures from direct DHHS funding (which consists mostly of NIH funding), now accounts for 41% of MGH research, down 1% from last year's 42%. Although the percentage of our DHHS research funding base went down, our DHHS-sponsored research expenditures increased from $353M in FY16 to $371M in FY17. Again in 2017, MGH remains the largest recipient of NIH funding among independent hospitals and 15th nationally for all institutions.

Research expenditures for all of our other sponsor types continue to remain strong in FY17, and there was growth in every sponsor category. The overall growth rate was 7.4%, with the largest increases coming from Industry/Corporate expenditures at 18%, Foundations at 14%, and DHHS (NIH) at 5%. The cumulative annual growth rate for FY13-FY17 across all sponsor types was 16%.

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) works 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.
As of Fiscal Year 2017, MGH currently owns or leases approximately 1.27M net assignable square feet (nasf) of space, essentially the same amount as last year, but nearly double the amount of research space in 2000. Research sites now exist in twenty-six buildings across seven campuses in five cities. The percent allocations amongst the campuses are also similar to last year with 43% in CNY, 24% on the Main Campus, 21% in the 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 rose from an average $178 per square foot in Fiscal Year 2016 to $186 per square foot. As was the case last year, new research funding with full overhead, an improved sponsor mix, and more optimal space utilization combined to improve IDC recoveries and densities. Of the major campuses listed above, the Boston Campus has the highest IDC density, $218. Major research groups contributing to the high IDC density have research sites at 125 Nashua St., Shriners, Bowdoin Sq., 101 Merrimac St., 25 New Chardon, and 2 and 5 Longfellow.

Fulfilling outstanding space requests remains one of RSMG's most difficult challenges, particularly when there are limited new space opportunities. RSMG works with RSAC and the research community to better understand the true space requirements, and promote space contingencies amongst collaborative groups. Outstanding space requests have averaged 85,661 nasf over the past five years. In September of this year space requests decreased to 21,400 nasf for wet space and 15,010 nasf for dry space. Never static, the current space request total in December of 2017 is now approximately 72,000 nasf, reflecting new Institution and Department initiatives.

Constantly updating and analyzing data in the Research Space Management System (RSMS), RSMG utilizes this 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 space into active revenue-generating research space.

In Fiscal Year 2017, twenty-one renovation projects, whose costs totaled approximately $19M, were completed. These projects included Anesthesia lab and office renovations on 149-04, Cardiology office expansion and Mother's Room addition on Simches 3, PNGU lab renovation on Simches 6, Cancer Center office expansion on 149-07, Surgery fellows space on Simches 4, and creation of the Market Place on Simches-3. Another major project completed this year was the Translational and Clinical Research Centers on White 12 and 13. Fourteen projects, totaling over $25M in project costs, are ongoing. Major ongoing projects include completion of EDR 1 and EDR 3 renovations for Cardiology, the Gordon Center's renovation on EDR 0, and I3/IBC projects on the second and fourth floors of B149. Depending on the outcome of Capital Requests for Fiscal 2018, there could be as many as nineteen additional projects or feasibility studies over the next few months.

RSMG continues to work with the Partners' Development and Program Team to improve the overall functionality of the Research Space Management System and the Microstrategy Reporting module. Hopefully, in the new year work will begin on implementing new people metrics which will better capture both seat and overall research space utilization at any designated research site with the ability to drill down to the PI site level. This detail is invaluable for senior management to assess space requests and plan for new program initiatives and Institutional expansion needs.

Ongoing RSMG major responsibilities include Core Management for 75 research laboratories and coordination of the annual "Laboratory Cleanup Event". All research equipment continues to be tracked and last year asset unit costs totaled $11.5M. In addition, RSMG is responsible for updating all research floorplans and designing and approving all research furniture purchases. Finally, 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. RSMG looks forward to having this a more automated process soon.

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 both hospital campuses. In addition, the

hospital operates two off-site facilities in Cambridge, MA including a BL-2/BL-3 rodent facility that supports the Ragon Institute in Cambridge, MA, and a rodent facility at 65 Landsdowne. In anticipation of increasing non-human primate housing needs in 2018, a contractual agreement with Biomere, Worcester, MA has been established that expands census capacity by an additional 40-50 more.

The Center for Comparative Medicine (CCM) is the central laboratory animal care service for MGH investigators and is led by Donna Matthews Jarrell, DVM, DACLAM, who also serves as the MGH Attending Veterinarian. CCM facilities are located on the Cambridge Street 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. Over 130 employees, including seven staff veterinarians (six of whom are board-certified in laboratory animal medicine) and a leadership team of 22 mid- and director-level managers, provide these services throughout MGH.

Specific efforts were taken in 2017 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 Cambridge Street 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 FY17.
- CCM's focus on operational excellence was highlighted when the department was chosen as a tour site for the annual meeting of the Association in Manufacturing Excellence (AME) held this past summer in Boston. The department's Continuous Improvement Steering Committee (CISC) also conducted a "lean learning" workshop that utilized some of the innovation and interaction educational sessions utilized as a part of the department's on-boarding of new staff.
- Expand research support services (beyond husbandry) by more than 25% compared to previous years utilizing current front-line technical personnel.

Lastly, CCM continued to host more than 35 site visits in 2017 from manufacturing, healthcare, research and laboratory animal leaders who have 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, Director, Plastic Surgery Research Laboratory, and Assistant Vice Chair-IACUC. The IACUC 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.

An emphasis for the program, under the joint leadership of Drs. Clancy and Jarrell, and with the full participation of their respective departmental leadership teams, was to update and implement standards for animal care and use throughout the MGH enterprise, in accordance with regulatory expectations and with a focus on satellite housing locations and animal procedure spaces.

Significant events in the animal care and use program in the past year:

- AAALAC International conducted a site visit of the animal care and use program. We hosted 4 site visit team members for 3 days and

were recommended for continued Full Accreditation. This successful outcome reflects the high level of engagement of the research staff and administration in the program, and the excellent standards at MGH.
- USDA conducted an annual inspection of the MGH animal research facility; we received a critical citation related to animal welfare in response to two events that had been identified, managed, and reported by the MGH IACUC. A six-month re-inspection identified no concerns and we look to forward to receiving citation-free site visits in the future.
- The City of Cambridge conducted its annual inspection of the MGH animal research facilities; no deficiencies were identified in the program.
- A new program, focused on the post-surgical care of rodents was successfully implemented, improving compliance with regulatory expectations for rodent use.
- The IACUC, in collaboration with the Committee on Fundamental Research, ECOR representatives and others, continued to redesign the IACUC Form set. The new Form set was finalized through a collaboration between the three Partners IACUC offices. This Form set will be rolled out with Insight 4.0 in 2018.
- In response to suggestions from the research community the IACUC collaborated with Partners Research Applications and Analytics and Occupation Health Services to improve data sharing between the departments, to facilitate protocol amendment approval and facility access requests.

A primary role of the IACUC is the review and approval of IACUC applications. Approximately 3,400 transactions were processed by the MGH IACUC in the past year, including almost 130 new IACUC protocols. Complete metrics data for the MGH IACUC are available on the Partners Research Navigator website Research-Analytics-Reporting.

Research Support IS Committee (RSIS) — Carl Blesius, MD & 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.) but 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 2017

- Internal Cloud for Container-Based Research Application Development: two production grade clusters of RedHat Openshift have been put into place in collaboration with Partners Technical Services. 2016 proof of concept projects are in the process of being migrated over to these new clusters. When a support model for this new platform has been put into place this internal cloud platform has the potential to cut the provisioning time for research and clinical systems from weeks to minutes.
- First Phase of Wifi Improvements for Research Space: Working with MGH Network Engineering we identified Wifi more deficiencies in research spaces across MGH. We have determined hardware requirements to bring these spaces up to PHS standards. Site priorities and corresponding budgets for funding requests have be submitted.
- Information Security Policy Creation: Actively participated in Partners Information Security policy working groups to ensure Research needs are addressed and viable under policy constraints.
- "Who we are" Research Community Identification Tool Refinements: Continued to work on improving data feeds which will help us automatically identify who belongs to the research community and what roles they hold.
- Research Training System Phase II: along with significant refinements the Research Training System was enhanced so that it supports course ratings and it can record and track training assignments across systems, show these on a training dashboard, and allow researchers and their supporting teams to have a single training dashboard.
- Radiation Safety System: Finished setup of new Radiation Safety User Management system with cleanup and migration of legacy data to new system.

Strategic Priorities in 2018

We will continue to leverage local expertise to solve problems and identify areas where consolidation and streamlining of resources, services, and procedures can help leverage limited research resources to better meet the technical needs of the research community. Specifically we will be working on:

- Formulate and Champion a Multi-Year Research IS Strategic Plan: Work with in-house departmental technical support groups to outline strategic needs for the coming years. The focus will be to document these needs to provide advice and guidance to MGH & PHS ensuring the needs of the Research Community are represented in enterprise long term planning. Emerging technologies which would allow us to leapfrog lagging elements of institutional infrastructure will be closely examined.
- New Technologies: Strengthen emerging technology implementation efforts through closer coordination with the MGH CIO's office

and Partners IS through RSIS membership and cross institution participation. Help design new workflows and documentation to streamline implementation processes.

- Radiation Safety System: Complete work to implement automatic data capture from Landauer's monthly user reports. Work with Business owner and vendor to tie new system into Core Billing and Training applications.
- Replace "Find a Researcher" on Mass General Site: The current researcher profile search feature on the public facing Mass General website is both outdated and stale. The Profiles working group will be teaming up with the Research Institute to define a fresh page view and integrate the search with the "Who We Are" data feeds to provide real time access to Researcher information at MGH.
- Develop Realtime Streaming and Teleconferencing Recommendations: Implementation of an end-user initiated streaming solution with integrated content capture and editing capabilities for later playback. Identification of products which will support smaller virtual meetings through integration of new A/V technologies
- Research Training System Phase III: The focus of phase III is completing the full circle of research training tracking and reporting (both for individuals, research teams, and administration) with feed based automation where possible so that we truly have a research training dashboard that automatically tracks what folks need to complete.

We will encourage innovation and foster scientific opportunities enabled by technology, pushing the organization towards being more flexible when it comes to technology which will reduce administrative and workflow burdens.

Research Institute Training and Education Committee (RITE) — 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, has continued to develop the LEARN platform (https://learn.partners.org/org/mgh-research-institute/date/) to streamline and organize required compliance trainings as well as elective courses for research professional development. New research hires are now required to complete a survey which then links to their required training dashboard.

The LEARN platform now provides:

- A Learner Dashboard to allow participants and managers to quickly see what courses have been completed (with date and certificate upload available), what courses are overdue, currently enrolled in and what courses to be taken in the future
- A functional course catalogue to allow learners to search for courses by course name, date, program or category and see how other researchers has rated the course
- Course management for administrators who organize courses (participants can sign up, go on waiting lists, be contacted by email, receive acknowledgments about attendance, receive certificates for course completion and view documents/presentations)
- Easy sign up using Partners login or eCommons login
- Tailored compliance trainings based on a survey to determine the specific courses to meet an individual's regulatory and compliance requirements (depending on their responsibilities)
- Outlook Invites to integrate course schedules into a participant's outlook calendar

The RITE committee continues to work to eliminate redundant trainings and increase coordination across MGH and Partners.

MGH Research Policy Updates and Initiatives – Harry W. Orf, PhD, Senior Vice President for Research

Update – Minimum Indirect Cost Rate Requirement Having Desired Impact

Last year, MGH (and all of Partners) implemented an indirect cost (IDC) recovery policy that requires all grants accepted to carry a minimum 15% IDC reimbursement, which is the IDC amount assessed on gifts and hospital sundry funds when they are spent in support of research. Awards from sponsors paying less than the IDC minimum may be accepted only if the PI or their department provides the difference between the sponsor-provided IDC and the 15% minimum. This was put in place as a small, initial attempt to stem some of the losses of tens of millions of dollars of indirect cost (IDC) recovery from sponsors who pay less than our government-negotiated indirect rates. In the last fiscal year alone, this loss was over $90M.

A review of the impact of the policy in its inaugural year shows a positive return of $800K with a projected steady state impact of $3-4M. While the number of foundation awards from sponsors paying less than the 15% IDC minimum declined slightly, revenue from these awards grew substantially. Concurrent with the implementation of the new IDC minimum policy, a more comprehensive plan was put into place to have all IDC reduction requests reviewed through the Partners Chief Academic Officer and the MGH and BWH SVP's for Research. Previously, IDC waivers could be granted solely by the hospital SVP. This new review process has resulted in both a lowering in the number and types of waivers granted and much more consistency across Partners institutions in waiver request reviews.

Update – Isuggest Surpasses 1,000 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 2017, Isuggest reached two important milestones, the 1,000th suggestion received and the 500th suggestion implemented. Specifically, as of year-end, there were 1054 suggestions received, 517 implemented, and 336 being actively engaged by the more than 50 standing working groups in the Isuggest system. Of the 336 suggestions being actively pursued, 105 of them have already been recommended for approval and are in the "pending implementation" status.

Through 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.), members of the research community receive constant reminders about the existence of the program and its effectiveness in reducing administrative burdens across the research enterprise. This has resulted in the now steady stream of 3-4 suggestions per week coming into the program. Additionally, several departments (Medicine, Radiology, and Surgery at MGH as well as the Partners Personalized Medicine group) have taken notice of the program and adapted it for use to vet suggestions specific to their own departments. McLean Hospital is also currently considering using the program at their institution.

The following Suggestion of the Month examples are representative of the breadth and scope of the suggestions implemented this past year.

- Adopting the iThenticate plagiarism software program as a standard across Partners and making it available to all researchers at no charge.
- Restoration of MacMail support after it was announced by Partners IS that it would only support Outlook as a Mac mail client going forward.
- Creation of an electronic platform for vendors to communicate directly with Partners Supply Chain to resolve delivery, invoicing, and contracting issues.
- Suggestion to expand and improve food service in the Simches building led to creation of the Simches Marketplace, a self-serve food dispensary with fresh food offerings changed daily and open 24/7.
- Creation of a "Text for Service" number that people can use from their smartphone whenever there is an urgent environmental service need (e.g., restroom flood, elevator or corridor spill, etc.).
- Creation of a template for common procedures found in IACUC protocols to facilitate protocol writing and approval during committee reviews.

Update – Research Safety Committee Celebrates Five Years of Progress
Meeting #20 of the Research Safety Committee (RSC) took place in December, marking the end of five 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.

In its first four years, the RSC developed a substantial number of new programs and processes that raised the visibility of safety across the research enterprise and bolstered compliance with safety policies and procedures. Notable among these accomplishments are:

- Creation of a quarterly Safety Newsletter.
- Development of a web-based electronic lab safety survey program.
- Establishment of a Research Safety website.
- A complete review, update, and reorganization of all research safety documentation.
- Development of a safety training database to track individual safety training/compliance.
- Establishment of an annual "Lab Spring Cleaning Week".
- Creation of a system to track the purchases of hazardous materials and notify the Safety Office so appropriate specialty training can be provided.

Additional accomplishments completed in 2017 include:

- Creation of a new MGH Emergency Card to accompany the MGH ID Badge.
- Development of an abbreviated safety orientation for short-term lab visitors/workers.

- Creation of a single-sheet template guide for orientation of new lab personnel.

And special presentations given in 2017 included:

- Information Security for the Research Community
- Safety Programs within Animal Care and Use
- Violence in the Workplace
- MGH Controlled Substance Policy as it Pertains to Research

Update – MGH Onsite Indirect Cost Rate Goes Down

Starting this past year, 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 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.

New Initiative – Research Orientation

The restructuring and addition of new support components that led to the formation of the Research Institute three years ago 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, 35 road shows have been given at various departments and centers to audiences ranging from 20 to over 200.

While the road shows have successfully reached 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, Research Management developed a thirty-minute, condensed version of the Research Road Show that can be presented to new research employees during the weekly employee day-and-a-half orientation and the professional staff benefits orientation. The research orientation will start in Spring 2018 and will be given by a rotating group of young research administrative and scientific leaders. A thirty-minute video is also being produced that will be shown to new faculty, postdocs, graduate students, and others who do will not otherwise get the new research orientation presentation.

New Initiative – Partners 2.0 for Research

(From the Partners website) "More than ever before, major changes in technology, transparency and the economics of health care are calling upon Partners HealthCare and all its member institutions to function more as an integrated system and less like separate entities. Partners 2.0 is a new, multi-year, system-wide initiative that will optimize efficiency across Partners and improve our entire system to achieve better health for our patients."

MGH Research Management plays an active role in the research component of Partners 2.0. Focus is on both improving the quality and efficiency of research services and enhancing revenue opportunities to lower the research investment resulting from the large gap in under-recovered indirect costs ($90M at MGH alone in 2017). Among the numerous process improvement initiatives underway, three promise to show significant return in the near term. First, the implementation of the 15% IDC minimum policy described earlier in this section was a Partners 2.0 initiative and is already yielding results.

Second, 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. At the time this report was submitted, several proposals for altering the Partners royalty distribution policy are

being considered. Each proposal effectively raises the institutional share to between 30-35% and some of the proposals provide the option of a small raise for the inventor share. Partners and hospital leadership agree that a new distribution policy will be put into effect starting in FY19 (October 2018) and will decide soon among the options.

Third, there has long been a desire to improve the grant pre- and post-award processes between Partners Research Management (the central department that officially reviews, submits and closes out grants) and the departments where the research takes place and where most of the post-award management of grants occur. As part of the Partners 2.0 initiative, a pilot program is underway using a "national guard" model, where departmental grant managers become an official part of the central Partners RM team but still reside in their departments. They receive formal training in all federal grant-related policies, have their competency regularly reviewed, attend Partners RM staff meetings, and (eventually) will be given the authority to submit grants directly from their department. This new approach is intended to strengthen the grants management relationship between Partners RM and institutional departments and improve the timeliness and efficiency of the grants submission and management processes.

New Initiative – Digital Health at MGH and Partners

Our current ECOR chair, David Louis, MD, offers the following brief definition of digital health. "The creation (often via novel devices) and use (often via novel analytics) of digital data to optimize healthcare." The growth of artificial intelligence (AI) and machine learning in healthcare, the exploding number of healthcare apps available on smartphones and smart watches, the increasing ability of personal wearable devices to stream physiological data directly into one's healthcare record, and the enhanced ability to intelligently store, triage, and mine data from electronic health records are converging rapidly to provide opportunities to dramatically improve the way healthcare will be provided and managed in the near future. Major digital technology companies (Apple, Microsoft, Google, Nvidia, GE, Qualcomm, etc.) are already working on ways to integrate the digital and AI revolutions into healthcare.

MGH and BWH have long been leaders among academic medical centers in the development of tools to mine electronic medical records and create innovative ways to improve healthcare, both from the patient's and physician's perspectives. At MGH, initiatives in digital health have be developed by many different PIs independently and by unit- or department-sponsored programs. The Healthcare Transformation Lab, Ambulatory Practice of the Future, Kittyhawk Project, Plug n Play Lab, Computational Pathology Initiative, and Telehealth Program are just a few examples of sponsored programs within MGH that have existed for several years and are already improving aspects of healthcare using digital technology. Also, at the institutional level, MGH leadership has recently engaged in discussions with several major companies about collaborative opportunities in digital health.

In spite of these productive initiatives, to date (end of 2017) there has been no formal organization at the hospital level to resource and manage digital health. Similarly, at Partners, it has been recognized that a strategy for coordinating, supporting, and providing infrastructure for digital health is needed across the entire Partners Healthcare System. Accordingly, both at MGH and at Partners, task forces have been formed to develop programs to formally organize, drive, and manage digital health. As of the writing of this report, a recommendation for standing up a Center for Digital Health at MGH is about to be presented to hospital leadership, and Partners is in the process of interviewing researchers, physicians, and IS and senior leaders at its institutions in order to formulate its strategy going forward.

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 Harry W. Orf, PhD, Senior Vice President of Research at MGH, and Paul Anderson, MD, Chief Academic Officer and Senior Vice President of Research at BWH, and research leadership at other PHS hospitals to create a collaborative and compliant research culture that supports the research community and provides key infrastructures to enable advances in basic and clinical research.

The office of the Partners CAO directly oversees several departments that supports a $1.6 Billion research enterprise ($900M 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, productive, and cutting-edge research enterprise. Research infrastructure at Partners also includes Research Management, Research Compliance, Biosafety Office and the Office of Industry Interactions to ensure all aspects of MGH's research and 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).

IRB Activity (PHS) FY17 (10/1/16 - 9/30/17)	Full	Expedited
Initial protocol review	404	2,133
Continuing review	832	5,702
Staff amendments		14,706
Other amendments	281	6,466
Other (e.g., adverse events)	66	1,317
Totals	**1,583**	**30,324**

The IRBs and QI Program in combination are responsible for the ethical and regulatory oversight of research involving humans at MGH, BWH, Faulkner, McLean, North Shore, Spaulding and Newton Wellesley Hospitals. 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. Details of each of these reviews are mandated and informed by federal and state laws as well as myriad conditions of grant award. IRB review is not conducted in a vacuum, it 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.

QI Program Activity (PHS) 12/1/16 - 11/30/17	Number
On-site reviews	81
IND assistance/training	15
Regulatory Binder consultation	14
Presentations	35

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.

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.

The PHS HRA has grown as IRB oversight of most of the PHS hospitals has been consolidated under PHS: McLean in 2014; Spaulding Rehab in 2016 and Newton Wellesley in 2017. In addition to review of protocols, HRA provides access to the QI Program as well as all HRA educational and support resources to each of these sites.

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. IRBs must now deal with risk/benefit analysis of genetics, Big Data, data sharing, mobile apps, gene therapy and perhaps soon CRISPR. The HRA must be able to flex up to deal with these changes as they come.

In addition, myriad changes in federal regulations and in conditions of grant award is a constant concern. At the present time, we are experiencing a virtual tsunami of change that will have a large impact on the workings of the IRBs, the QI Program and the HRA Office in general. Examples include:

- As of January 25, 2018, NIH funded domestic multi-site research must be reviewed by a single IRB. HRA is responding to this in several ways: agreeing to serve as the single IRB, facilitating reliance on IRBs at other academic institutions, expanding the use of commercial IRBs and developing a QI assessment for investigators who cede review to an external IRB.
- Regulations and policies regarding ClinicalTrials.gov have changed by expanding the scope of research that will require registration and results reporting, and requiring posting of protocols and analysis plans. The QI Program has responded with tools and resources to support investigators' compliance with CT.gov.
- 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 18, 2018 (note, there is a possibility of a delay).
  This new Rule includes significant changes in; among others, the categories of research that require IRB review; the review of ongoing research; the informed consent form. HRA processes and procedures are being modified to accommodate to each of these.

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 (CTO) - Stephen D. Wiviott, MD, Executive Director

Partners Clinical Trials Office provides the MGH research community with contracting and budgetary development for investigators conducting clinical trials with industry sponsors. These service areas are designed to provide clinical researchers with resources to engage in 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.

The Clinical Trials Office achieved a number of important goals in support of MGH investigators and leadership this year. These include a 45% reduction in contracting and budgeting turnaround times since 2016, the continued launch of the Clinical Trials Management System (OnCore), and the negotiation of additional Master Service Agreements. In FY 2015/16 approximately 34 executed Master Service Agreements were in place. Currently the CTO has 44 executed institutional master clinical trial agreements and an additional 41 executed departmental/PI specific master agreements in place to help reduce turnaround times and increase contracting efficiency.

CTO Executed Agreements Volume

Agreement Type	FY17	% change FY17-16	FY16	% change FY16-15	FY15
Clinical Trial Agreements	309	-11%	348	4%	335
Amendments	453	26%	359	13%	318
Support & Other* Agreements	162	-6%	172	26%	137
Confidentiality Disclosure Agreements	493	8%	457	9%	420
Subcontracts	149	107%	72	-11%	81
Total	**1566**	**11%**	**1408**	**9%**	**1291**

**Includeds but is not limited to registry and population study agreements, clinical research support agreements, material transfer agreements and research gift letters.*

CTO contract volume grew 11% over the last year. The number of confidential disclosure agreements grew at a steady pace, and subcontracts and contract amendment volume increased significantly.

Rollout of the OnCore Clinical Trials Management System (CTMS) continues with positive results. Investigators and their study teams find the CTMS aids with data collection and sponsor invoicing. At year end there are 8 MGH Chief of Service units utilizing the technology including Emergency Medicine, Neurology/Neurosurgery and Cardiology. It is anticipated all departments will be active in OnCore by December 2018. In addition, the CTMS completed a 90-day subject stipends payment system that was well-received. The Forte Payments system is scheduled to begin rollout for industry sponsored trials in February 2018 with the expectation that it will be available to the MGH community within the year.

Partners Research Compliance Office (RCO) – Mary Mitchell, Corporate Director

Mary Mitchell leads the Partners Research Compliance Office (RCO); she reports directly to Robert Damiano, Partners Vice President for

Compliance and Audit and has a reporting relationship to Anne Klibanski, MD, Partners Chief Academic Officer. The RCO 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, 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 have become increasingly important to the Partners and MGH research enterprise, the RCO has partnered with Partners Information Security to improve investigator awareness of data/information security regulatory and institutional requirements and policies that go beyond HIPAA. In 2017, the RCO launched a website within the Research Navigator (Partners research portal available to all investigators) that brings together the different Partners data management/integrity sites scattered across various departmental websites. In addition, in order to expand on this electronic information, throughout 2017, the RCO has led development of a data management requirements and guidance document that will be published in early 2018. No comprehensive document currently exists that brings data management information together for the research community in one location. Its publication should aid investigators in their navigation of a complex regulatory and information security environment.

Research Integrity Program. During the past two years, the RCO has been working with senior compliance and legal staff, Research Integrity Officers, and faculty members on an enhanced research integrity program. These efforts culminated in required, online education for Principal Investigators (PI) on Prevention of Research Misconduct (2015) and Financial Stewardship of Grants and Contracts (2016.) Anne Klibanski, MD and Dennis Brown, PhD, served as faculty in the research misconduct prevention module; and Harry Orf, PhD and Merit Cudkowicz, MD served as faculty in the financial stewardship module. To round out the research integrity enhancement activities in 2017, a group of senior Partners faculty (including from MGH: Katrina Armstrong, MD; Elizabeth Austen, MD; Richard Bringhurst, MD; James Brink, MD; and Karen Klahr Miller, MD) also worked with the RCO to develop a Partners Research Code of Conduct and Ethical Standards.

The Research Code is a statement of Partners research principles and expectations of all individuals, employees and non-employees, engaged in research at Partners-affiliated institutions. Adherence to the Research Code is a requirement for participation in a research project and a condition of employment and appointment to the medical staff. Researchers are required to attest to their review of the Research Code on an annual basis. In 2017, the Research Code electronic attestation was launched as part of the annual conflict of interest disclosure process for all researchers responsible for the design, conduct or reporting of research results. The Research Code addresses topics such as scientific integrity and accountability; financial stewardship; research regulations and policies; and staff and fellow supervision and mentoring. It also reiterates the duty of all researchers to report any internal problems that violates its standards to compliance officers or the hospital's Research Integrity Officer.

Training and Education. A key aspect 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 2017 consisted of

- Managing and delivering three Partners Responsible Conduct of Research (RCR) seminars for the 300+ trainees and career awardees across the Partners system
- Developing and offering three RCR seminars each at MGH and BWH
- Animal Research Compliance
- Biological Materials Research Compliance
- Rigor and Reproducibility
- Development of as-needed training in the Foreign Corrupt Practices Act Requirements for PIs and staff of industry-supported clinical trials
- Continued oversight of the PI Research Education series to ensure completion by new PIs

Partners Personalized Medicine (PPM) – Scott Weiss, MD, 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 saving across the system, efficiency, and 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. To date 75,000+ participants consented and 54,000+ collected. In addition, the Biobank has supported over $309M 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:

- Provide serum, DNA, or plasma to Partners investigators
- Provide access to a large cohort of patients who are consented for broad-based research and recontact
- Provide powerful query tools based on clinical data, research data, and specimen data
- Provide rich phenotype data (validated disease populations and calculated healthy controls) as well as additional research data (self-reported survey) in conjunction with consented patients and stored samples
- Provide sample management services
- Provide GWAS Data and Imputed Genomic Data to Investigators
- Participate in NIH-funded longitudinal research program, All of Us, to consent over 90,000 participants in New England (as part of the larger goal of 1M+ participants over next 5 years)

Partners Translational Genomics Core. There are several values that the Partners Translational Genomics Core offers to individual Partners research groups as well as system-wide Partners initiatives such as the Partners Biobank:

- Provide genotyping and Next Gen Sequencing services to Partners Investigators to cost effectively support their research
- Support the use of Biobank samples by providing Partners researchers with DNA analysis and serum/plasma miRNA analysis platforms optimized for sample types collected/extracted from Biobank patients
- Provide sequencing (Next Gen and Sanger) to support the Partners Biobank
- Expand sequencing services through the development of novel sequencing workflows by partnering with Partners investigators as well as identifying 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), Parkinson's biomarkers study using a 7Mb sequencing panel, and 16s microbial sequencing in whole blood (supports use of Biobank samples)
- Provides Partners investigators basic and advanced analysis options for genomic and expression analysis, in partnership with the PMM Bioinformatics department
- Support over $105M Grants annually

Partners Clinical Lab – 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 provide value by supplying IT support for the Biobank, LMM and TGC Core as well as assisting in grant based projects. In addition to this main responsibility, the team devotes effort to develop Health Innovation Platform (HIP). Here are the key IT values/functions:

- Meet the Biobank, LMM's and TGC IT Needs: Support Operations and Maintain application infrastructure
- 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 Partners Translational Genomics Core, such as: Genome/Exome/Panel variant calling and filtration
- Support data processing, analysis, and storage of Genotyping results for Biobank participants' samples
- Develop Health Innovation Platform (HIP) and apps to improve clinical workflows
- Support eMERGE from both lab processing and clinical results delivery perspectives

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

Partners Innovation monetizes the unique assets of MGH and its 2,000 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 114 staff that includes 32 PhDs, 33 MBA/MAs, 13 JDs, 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 FY17 revenue was $130.5 million, a 12% increase from the prior year.
There are more than 215 companies that 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. On October 31, 2017, Partners Innovation Fund II held a final close on $171 million in capital under management, including commitments from Partners HealthCare institutions and $66 million from outside parties, including Astellas Pharma, Eli Lilly and Company, ShangPharma Corporation, and Simcere Pharmaceutical Group. It has invested in more than 30 companies of which more than half a dozen have gone public or been acquired. Other large deals spearheaded by the Innovation team include the 10 agreements with General Electric and the MGH and BWH Center for Clinical Data Sciences.

MGH Outcomes	FY14	FY15	FY16	FY17
Licensing Activity *	113	127	130	133
Material Transfer Agreements	1,073	987	1067	1360
New Disclosures	408	318	365	311
Patents Filed (US)	253	228	528	485
Patents Filed (Int'l)	644	399	382	604
Patents Issued (US)	86	89	109	108
Patents Issued (Int'l)	172	120	190	267
Royalty and Licensing Income	$68.9M	$80M	$77M	$87.7M

The World Medical Innovation Forum will be held April 23-25, 2018, 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 1300 registrants from around the globe are expected with nearly a third being PHS faculty and trainees who will experience first-hand how commercial innovation priorities are set.

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 1200 scientists every year, obtaining over 2400 sets of EHR data supporting over $1.1 billion in healthcare research. A new initiative, 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 and 20 machine-learning disease algorithms gathered on over 75,000 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 both persons who have volunteered through the Research Portal for Patients (clinicaltrials.partners.org), as well as creatively utilizing tools within Epic to message consented patients directly (those who have opted into the Research Opportunities Direct to You). It also supports an efficient provider-approval workflow for studies where direct outreach to patients is not an option.

RISC also launched the Health Innovation Platform (HIP) which 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 capable of leveraging RISC capabilities. These apps can then be used to alter clinical workflows and/or improve decision making. HIP provides a "last mile" capability for deploying big data and machine learning based innovations into the clinical environment.

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 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 (PRM) team. They work in close collaboration with Harry Orf, PhD, Senior Vice President of Research, at MGH and Paul Anderson, MD, Chief Academic Officer and Senior Vice President of Research at BWH, as well as Anne Klibanski, MD, Chief Academic Officer of Partners HealthCare, and Chris Coburn, Chief Innovation Officer.

It was a record-breaking year for research across Partners with over $1.6B in activity. MGH led the way with this success, exceeding the $900M threshold for the first time. Even with the increase in research activity, process improvements continue and have allowed us to leverage existing infrastructure to maintain service levels and even improve turnaround times in some key areas, including contracting. 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.

A major focus of the last year has been on the design and testing of the new INSIGHT grants management system. The new system will significantly improve the user experience with automation in workflows, enhancements to the layout, and more functionality. The updated INSIGHT system is being rolled out in different phases with a go live of December 18th for the agreements and financial modules. This will be followed by the compliance modules, IRB and IACUC, in the spring and summer of 2018. In preparation for the rollout, 55 Principal Investigators have provided feedback. There were 195 demonstrations and feedback sessions across Hospital Departments, as well as 18 hands on training sessions for research support staff.

Research Management provides grants management training to the hospital research community. Over 60 classes are offered throughout the year, covering all aspects of the grants lifecycle. Last year we trained 180 people from the MGH research community. A significant effort to redesign the core grants management training offerings was completed this year. This involved a review of the structure and content and delivery mechanism. The redesign resulted in significantly improved course evaluation scores and more online trainings.

As part of the Partners 2.0 initiative Research Management has actively worked to increase access to data and tools that improve transparency into research support operations. A new dashboard was created that allows Hospital Departments to get up to date information on research activity; submissions, expenses, and financial activity. The dashboard also allows analysis down to the level of individual Principal Investigator. Because of the positive feedback and utilization of this new dashboard by the MGH community we will focus on enhancements to the dashboard during the next year to include additional information such as standard benchmarks for comparison and performance indicators.

With the new NIH requirements related to clinical trial oversight and the mandate for a single IRB, the next year will provide the continued challenge of managing regulations while minimizing the administrative burden on MGH investigators. However, because of the incredible success of the MGH research enterprise and the current infrastructure in place to support it, we should be well positioned to meet the new regulatory challenges.

Partners Office for Interactions with Industry (OII) — 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 Partners 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 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 this past year assumed 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 FY17 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
   - Worked 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 almost two 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

2. Outside Activities – In addition to handling, as part of normal workflow, over 1800 consulting and related agreements:
   - Took advantage of staffing changes to build an entirely new Outside Activities team
   - 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 coordination of multiple management plans
   - Began a comprehensive review of the intake process for outside activities, including the questionnaire that provides information to enable the identification of potential conflicts of interest in outside activities
   - Clarified the status of proctoring and device training under the Partners speaker and training guidelines, and the standards for OII review of confidential disclosure agreements

3. Educational Grants – in addition to handling, as part of the normal workflow, over 300 grants bringing in about $4.7M in funding:
   - Worked with the ERB to find a solution to companies requesting residents' names for travel grants by instead offering companies a unique identifier. This solution saved one residency program from losing out on almost $65,000 a year in travel grants
   - Worked with the ERB to revise several guideline documents to better clarify the policy requirements for trainee travel and offering promotional opportunities
   - Created a new 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. Since March 27, 2017 through the end of FY 17, OII finalized 10 industry gifts for research, totaling over $780,000

4. Systems and Education – in addition to handling, as part of the normal workflow, the distribution and completion of 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 to redesign and launch the Disclosures Module
   - Convened an end-user group of faculty, investigators and Compliance Officers to provide feedback and input on Disclosures 4.0

- 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

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 2017 implementing the strategic plan for research and improving the services that support the Research Institute. Looking ahead to 2018, 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 medical research.

Space. Regarding challenges, the lack of availability of space to grow the research enterprise is among the most pressing. The promise and rapid rise in use of CAR-T cancer therapy will require the hospital to build and operate a sizable GMP facility if it is to maintain its leadership as a premier cancer research and treatment center. And the overall growth of research at MGH over the last decade has far outpaced growth in research space. From 2007 through 2017, research space has growth only 18%, while research employees have grown at twice that rate and research revenues (even when adjusted for inflation) have grown over three times that rate. The IDC density at MGH is approaching $190/sf and is among the highest in the region. Opportunities for building in Charlestown and Nashua Street as well as the possibility of occupying research space at the Medical School are currently being explored.

In addition to finding new research space, new metrics for evaluating the efficiency of use of our current space are being developed. The new metrics directly (and therefore more fairly) relate MTDC and IDC space densities to the grants actually being performed in the space. Also, for the first time, the density of people working in research labs will be tracked against the designed people-capacity of the space.

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 2017, 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.

Catalyst Funding. Another challenge that MGH will face in 2018 is the loss of significant ($3M) Harvard Catalyst funding for the MGH Clinical Research Center. Although the Catalyst grant was recently renewed, policy changes at NCATS now prohibit Catalyst funds from directly supporting CRCs, and this policy changes goes into effect in May, 2018 at Harvard. Fortunately, the hospital had ample warning that this policy change would impact our CRC and provisions were made to provide partial supplemental funding within the hospital operating budget. The remaining budget gap will have to be filled by instituting user fees to investigators for use of the CRC services. Again, investigators were given ample warning so additional fees could be budgeted in their clinical trial grants and operational support within the CRC was streamlined to minimize the size of the new fees.

Diversity and Inclusion in Research. The MGH Diversity and Inclusion (D&I) Committee concluded in 2017 a year-long process to develop a D&I strategic plan across the institution. A research component was included in this plan and a task force was formed to focus on research D&I issues. Two major needs were identified, 1) increase underrepresented minority participation in MGH clinical trials, and 2) organize and better support those conducting research on D&I issues in the hospital. The research task force developed a number of tactics to achieve these objectives and, as of the writing of this report, they are being evaluated for resourcing. Resourcing of objective 1) should be helped by the fact that MGH was recently awarded a highly competitive grant to lead a regional consortium of health care providers that will be enrolling patients into the National Institutes of Health's All of Us Research Program. The program will enroll tens of thousands of patients with a mandate for greater than 30% participation by underrepresented minorities. Meeting this enrollment goal will be a significant challenge but also an extraordinary opportunity for the hospital to strengthen its ties with underrepresented minorities living in our care region.

Capital Campaign. In 2018, MGH will embark on a 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. Within this theme, we have suggested several more targeted programs to promote for major gifts. These include: Investing in our best and brightest (recruitment and retention – Research Scholars and RI Endowed Chairs), Translating discovery to the practice of medicine (an innovation fund for proof of concept, leading to industry partnerships), Leading the digital health revolution (leveraging AI, machine learning, and HIT in imaging, pathology, and beyond), Aging gracefully, prolonging a healthy life (strategies for wellness, disease prevention, and early detection), Personalizing the practice of medicine (bringing genomics, immunotherapy, and stem cell sciences into clinical practice), and Transforming the patient care experience (empowering the patient with tools to integrate them into the caregiving team).

Digital Health. The digital health initiatives described in the MGH Research Policy Updates and Initiatives section above set out a roadmap for

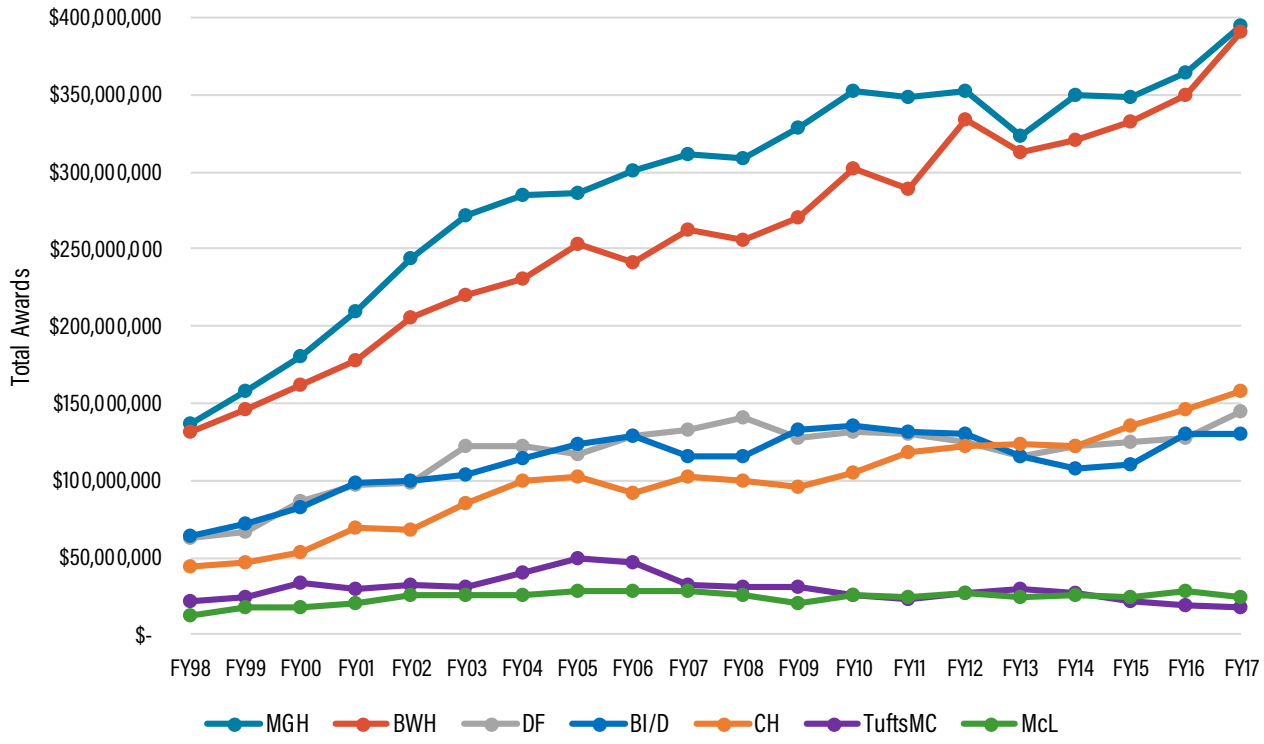
both MGH and Partners to become leaders in this fast-growing field. 2018 will be a pivotal year in which to organize and resource coordinated efforts to leverage the strengths of our AMCs and forge collaborative agreements with major corporate players. While doing so will likely require significant fiscal investment, to not do so will jeopardize our position as a leader in healthcare innovation.

Revitalization of CNY. More than a decade ago, when MGH acquired the Charlestown Navy Yard (CNY) buildings, it established a huge research presence that today serves as home to thousands of MGH researchers, with almost every department represented. In recent years, however, the physical plant has shown signs of wear, and major construction and bridge work in Boston has lengthened the shuttle commute time from 15 minutes to 30-45 minutes. Also, the difficulty of retaining retail food services and other small businesses at CNY has made this research campus less desirable than main campus locations like Simches. To address this concern, hospital leadership has made a commitment to revitalize CNY. Meetings are taking place with the city to streamline the shuttle routes, updated Wi-Fi and video streaming capabilities are being planned for the buildings, new food service options are being explored, and consolidation of several major departmental research programs that will bring senior investigators with established labs to CNY are in process. As this report is being written, a Quality of Life Survey is also being prepared for all CNY researchers to get their input and suggestions on what else the hospital can do to revitalize the research community at CNY.

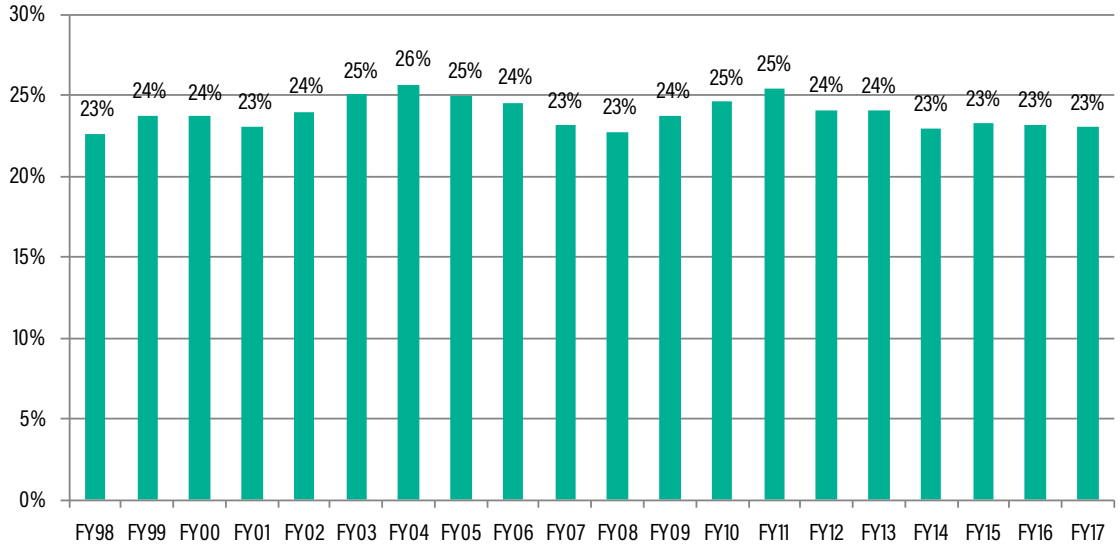
The significant progress has been made in 2017 to promote innovation and improve the services so vital to maintaining our position as a preeminent biomedical research institution have been made by an extraordinary group of hospital and Partners leaders, faculty, and staff. On behalf of the hospital and Research Institute, I express our appreciation for the continued dedication and initiative they offer 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-FY17



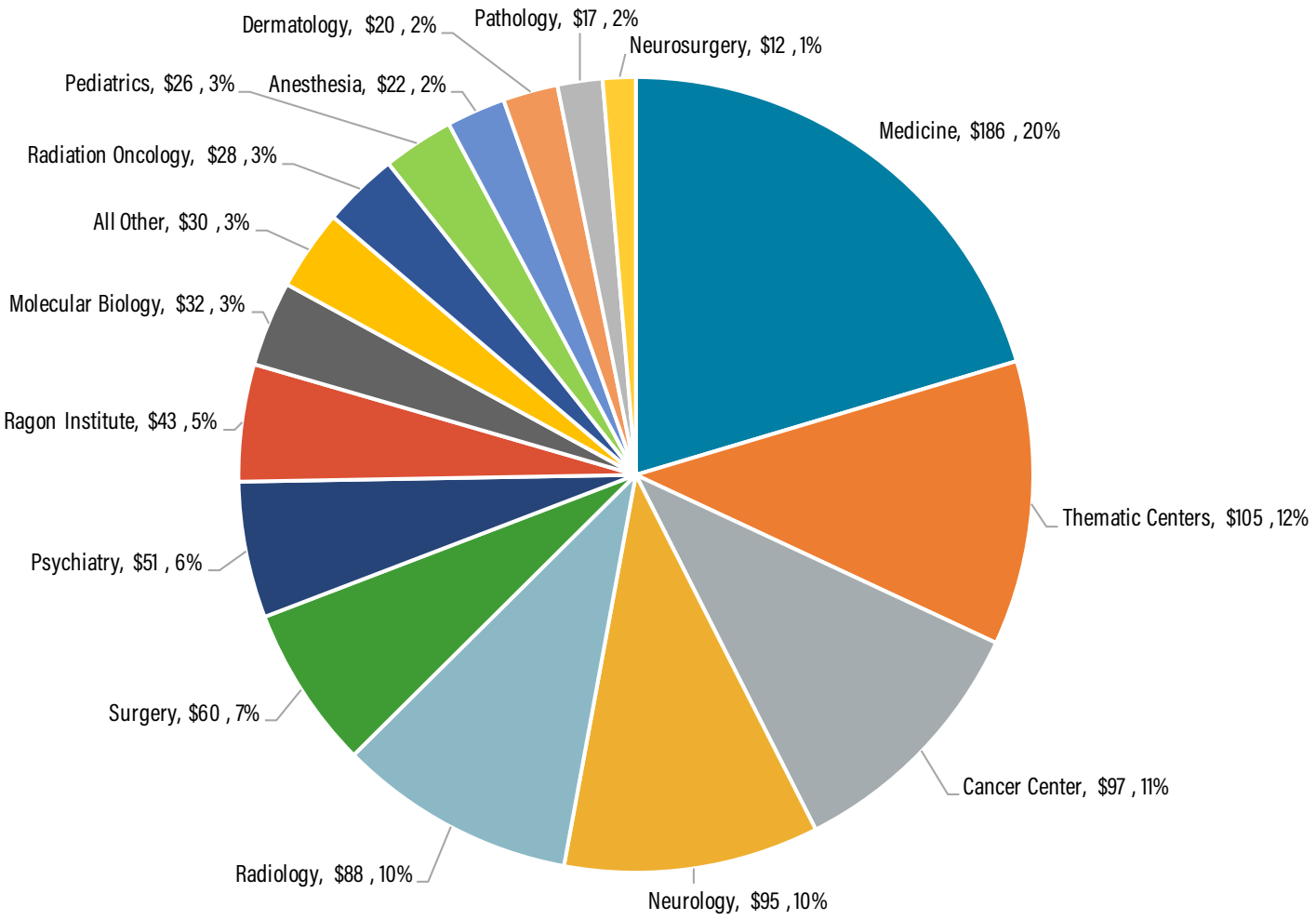
MGH Research Revenue as a Percentage of Total MGH Operating Revenue FY98-FY17



MGH Research Expenditures by Department

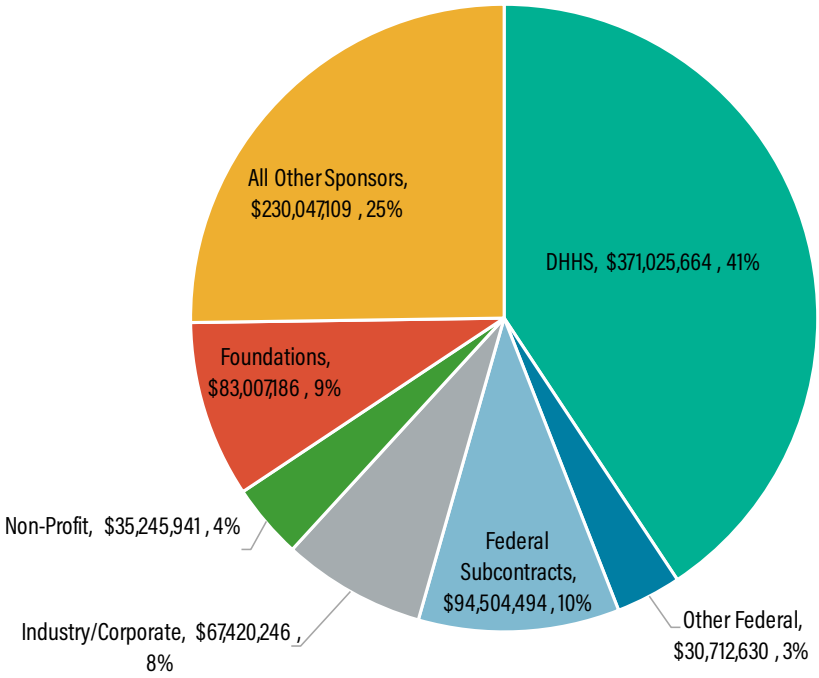
FY17 Direct & Indirect Expenditures - $912M

(shown in Millions)



MGH Research Expenditure by Sponsor

FY17 Direct & Indirect Expenditures - $912M



MGH Research Expenditure by Sponsor

FY07-FY17

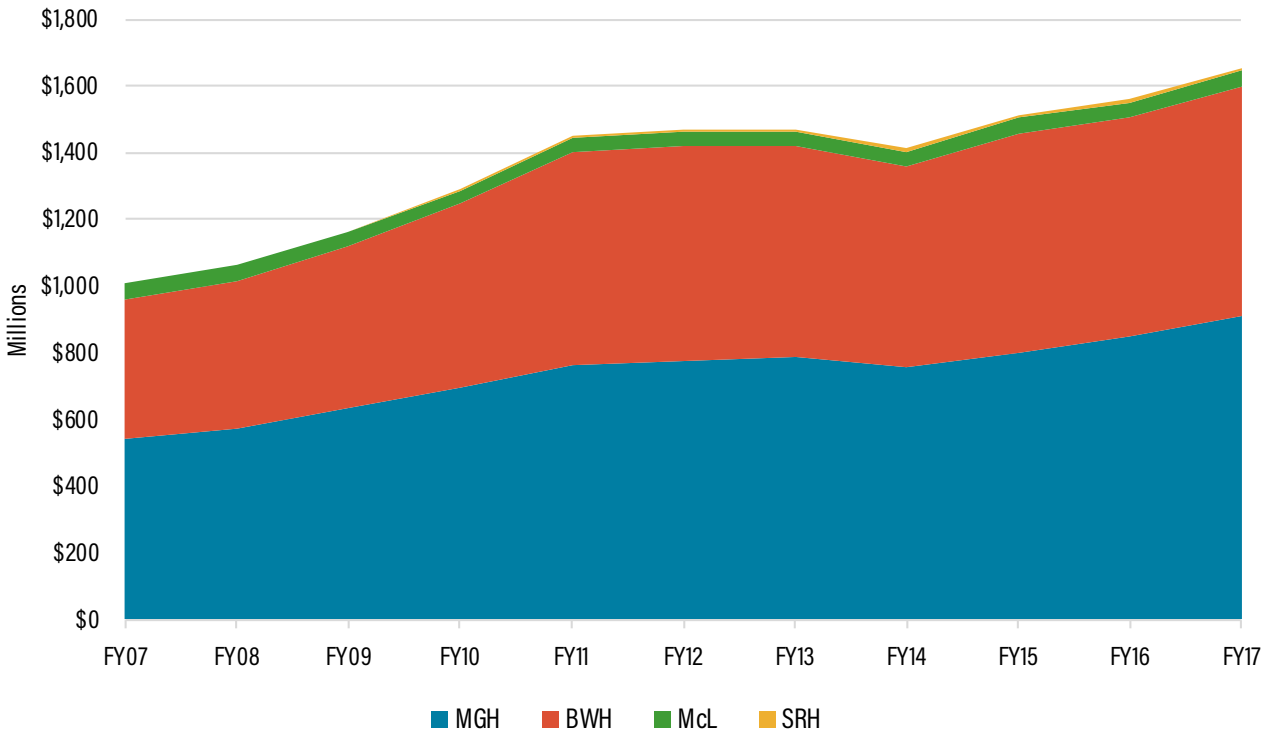
MGH Science Activity by Sponsor

FY17 - 10/1/16 - 9/30/17

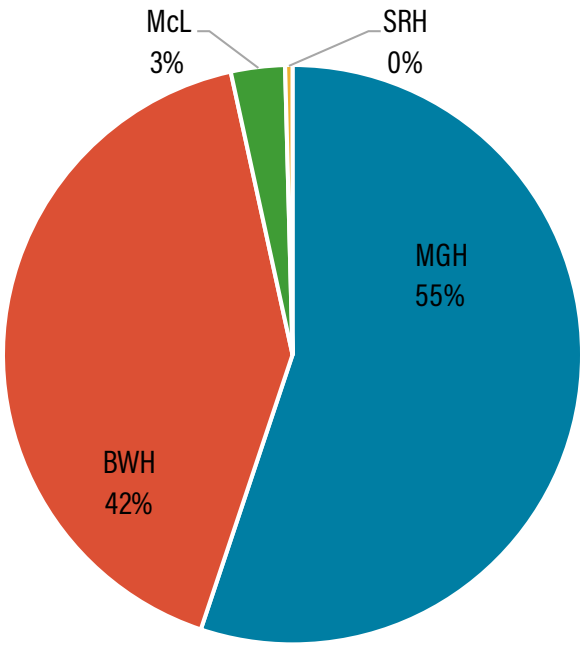
Type of Activity	Direct	Indirect	Total
Federal & State	$ 290,686,622.10	$ 117,073,780.08	$ 407,760,402.18
Non-Federal	$ 414,372,847.54	$ 89,830,020.28	$ 504,202,867.82
Total Expenses FY 17	$ 705,059,469.64	$ 206,903,800.36	$ 911,963,270.00
Federal Activity by Sponsor			
NIH	$ 257,015,472.46	$ 107,214,902.80	$ 364,230,375.26
DOD	$ 14,645,053.09	$ 6,171,491.81	$ 20,816,544.90
DARPA	$ 4,273,566.65	$ 998,541.60	$ 5,272,108.25
HRSA	$ 2,830,390.93	$ 50,259.14	$ 2,880,650.07
NSF	$ 1,054,475.20	$ 609,344.08	$ 1,663,819.28
Other Federal	$ 5,586,887.87	$ 1,285,886.11	$ 6,872,773.98
Total Other Federal Activity	$ 28,390,373.74	$ 9,115,522.74	$ 37,505,896.48
Subtotal Federal	$ 285,405,846.20	$ 116,330,425.54	$ 401,736,271.74
State	$ 5,280,775.90	$ 743,354.54	$ 6,024,130.44
Total State Activity	$ 5,280,775.90	$ 743,354.54	$ 6,024,130.44
Total Federal and State	**$ 290,686,622.10**	**$ 117,073,780.08**	**$ 407,760,402.18**
Non-Federal Activity by Sponsor			
Industry	$ 53,062,412.33	$ 20,888,782.12	$ 73,951,194.45
Foundations	$ 76,233,550.70	$ 7,717,532.43	$ 83,951,083.13
Subcontracts/Other Nonprofit	$ 118,830,918.56	$ 38,225,546.23	$ 157,056,464.79
MGH Endowment & Gifts	$ 165,554,841.09	$ 22,987,352.44	$ 188,542,193.53
Total Non-Federal Activity	$ 413,681,722.68	$ 89,819,213.22	$ 503,500,935.90
Total Expenses	$ 704,368,344.78	$ 206,892,993.30	$ 911,261,338.08
Harvard Medical School	$ 691,124.86	$ 10,807.06	$ 701,931.92
Grand Total	**$ 705,059,469.64**	**$ 206,903,800.36**	**$ 911,963,270.00**

Partners Healthcare Total Research Activity

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



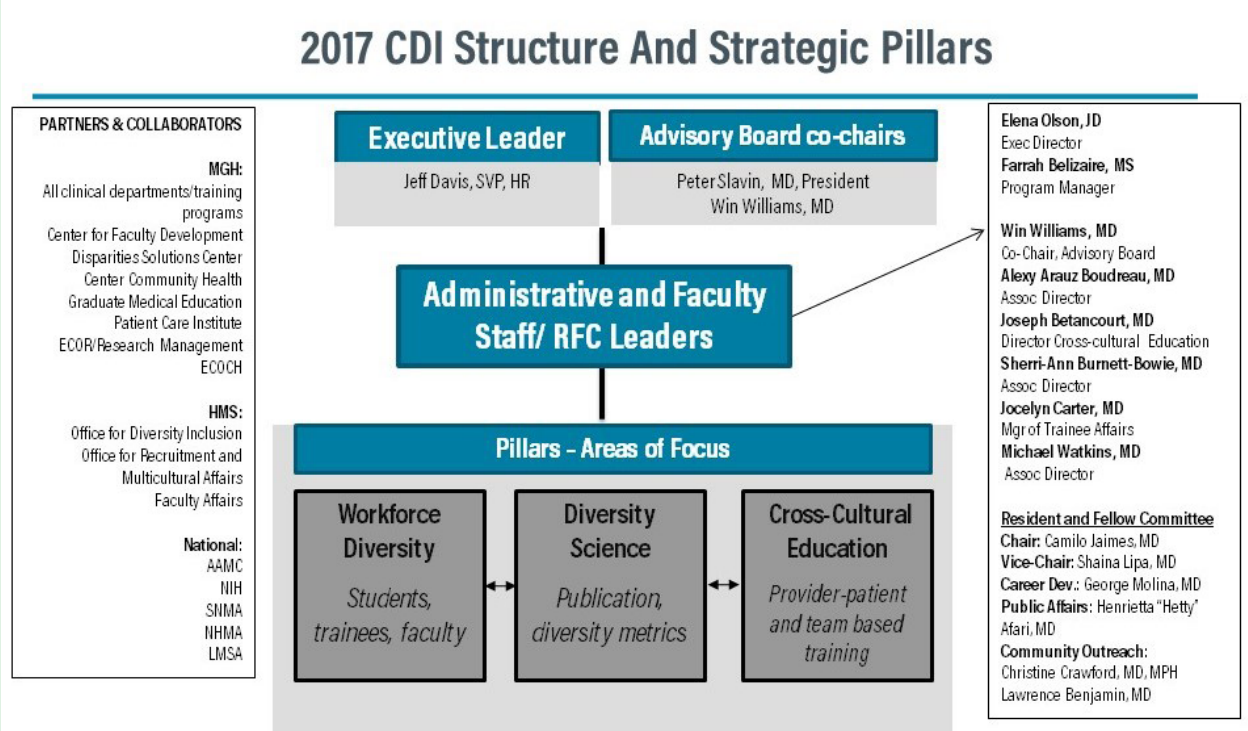
Partners Healthcare Total Research Activity by Institution



Elena B. Olson, JD, Executive Director

1. MISSION

The Center for Diversity and Inclusion (CDI) promotes the recruitment, retention, and advancement of physicians and scientists underrepresented in medicine (URM); as well as helps develop a culturally competent workforce at Mass General. 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.



2. 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
- Advance the science of diversity and inclusion by measuring outcomes of our programs and interventions

3. STRATEGIC PRIORITES

- Integrating CDI focus areas into all MGH mission areas and the fabric of the institution and departments
- Exposing students underrepresented in medicine (URM) to academic research and clinical careers
- Advancing URM trainees and faculty through career development, networking, mentorship and funding
- Channeling health equity, community outreach, and social justice through advocacy and education

4. NOTABLE ACHIEVEMENTS FOR THE 2017 YEAR

4.1. Overall

In 2016-17, CDI met individually with all 19 Chairs and 20 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 to approximately 5,500 physicians, scientists and interdisciplinary teams, focusing on the broader MGH employee community.

4.2. Hospital-wide Diversity Committee

CDI has been key contributor to developing a hospital-wide diversity and inclusion strategic plan in 2017, which identifies priorities for

diversifying the clinical and research workforce and increasing representation of the community research and clinical trials, among many other priorities.

4.3 Professional Leadership and 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. 2017 marked the second 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 11 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. 289 students have participated in SRTP since its founding. Several participating students stayed on in labs and have published their work. 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 2017, 17% (n=43) of the residents who matched in all 21 MGH/integrated residency programs were URM, the highest percentage of URMs matched in MGH history, with several programs exceeding 25%. This is well 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 46 faculty development awards totaling $5.6 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%).

4.4 CDI Led Critical Race and Equity Initiatives

Throughout the 2016-17 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 hospital-wide discussions focused on race, including a Stand Against Racism, exploring different patient and employee scenarios of micro-aggression, stereotype and unconscious bias.

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.

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

Mission
The CFD, Center for Faculty Development, 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 2017 the CFD and its offices again saw continuing success in the integrated approach to providing services and resources to our faculty and trainees. 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 91 professional development programs with 2,973 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 facilitated the implementation of the new Post-Doctoral Division, spearheaded with the OWC the gender parity initiatives supported by the Mass General Physicians' Organization, initiated the needs assessment and requirements for Annual Career Conference Automation, as well as the internal HMS Promotion tracking system. In addition, the CFD created the Chief's Corner to enhance communication and awareness with the Department Chairs.

The CFD collaborated with the MGH Center for Diversity and Inclusion by meeting with a subset of URM Assistant Professors to help them advance their careers.

In addition, 278 individuals visited the CFD and/or one of its offices this past year for a total of 330 office consultations. 255 of these visits were with a CFD staff member (57% faculty, 43% fellows, graduate students, residents and other staff) and 75 met with an external advisor (32% faculty, 68% fellows, graduate students, residents, and other staff). The vast majority of the visits were for career advice, grant funding and promotion.

Strategic Priorities
- 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, 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) 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 with Harvard Medical School

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 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 2017, the ORCD continued to offer individual career counseling, to organize professional development seminars, to provide networking opportunities, and to advocate on behalf of the research community.

Achievements

- Counseled 37 faculty, fellows and research staff in individual meetings aimed at career advice, promotion, and other matters.
- Guided the newly formed Post-Doctoral Division (PDD) to enhance existing programming and career support for MGH research fellows.
- Collaborated with the MGH Development Office to offer 50 individual consultations on identifying research funding opportunities.
- Hosted the largest cohort (42 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 provided information and networking opportunities to support the continued success of the cohort.
- 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.
- Sponsored the 11th 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.
- Offered seminars and workshops to enhance the professional development of research faculty, including sessions on Scientific Communication and Developing a Translational Research Program.
- Coordinated 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.
- Offered the Career Explorations Series, with seminars and panels on careers in academia (both faculty and non-faculty tracks), publishing, and industry research.
- Continued to offer the Career Pathways for Postdocs Internship program, which gives post docs hands-on experience for future career moves.

Strategic Priorities for 2018

- The ORCD will 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 will create programming to assist research faculty in developing new lab management practices that align with the use of digital data.
- The ORCD will work with departments and hospital leadership to clarify the role of Instructors. The office will explore how this entry-level faculty position is used in different departments and determine if there is a set of acceptable definitions for the role of instructors at MGH, that will clarify the role and reduce confusion among early career research faculty.
- 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:
  - ◊ Supporting the use 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).
  - ◊ 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.
- Enhance the ESL offering to include pilot conversation and pronunciation instruction for our highest level learners.

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 500 non-employee PhD students performing their research at MGH. It also provides assistance 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

In the past year the GSD provided 16 educational programs to help graduate students in the following areas: negotiation and conflict management, job search strategy, resume building, interview skills, fellowship applications, and funding opportunities. The GSD expanded efforts to provide individual career counseling and networking opportunities for graduate students here at MGH by counseling 28 graduate students and connecting approximately 17 individuals with an external career consultant to offer a total of 45 office consultations.

In 2017 the MGH Graduate Student Division sponsored the inaugural GSD Mentoring Award to recognize a PI who has demonstrated outstanding contribution in helping graduate students to advance their skills and provide support with academic work. The GSD presented a "Paper of the Year" Award to a student and successfully promoted and advertised the winner's achievement. The GSD continued to offer the international student "Buddy" System to help connect new international graduate students with those who have been at MGH for a longer period. In 2017 the GSD continued successfully run the GSD T-Pass Savings to help graduate students not eligible for the MGH employee discount to defray their T-Pass transportation costs, sponsored and administered the GSD Graduate Student Travel Awards to help graduate students when traveling to an academic/society meeting directly related to their academic advancement. In collaboration with PHS Media the GSD scripted and recorded a MGH Graduate Student Division video to help market and promote opportunities for the graduate students in research offered at MGH. With the help of the GSD Committee members MGH students have a networking community and active presence on social media. Like last year, the GSD maintained its close relationships with local school administrations and participated in the Harvard-MIT HST Faculty Poster session.

Strategic Priorities

- Programming: develop and present a student Panel Discussion an open dialog between the recent graduates or students who recently defended and new PhD students ""How to get through your PhD years? We did it so can you!".
- Communication: enhance GSD visibility by offering GSD Select "Paper of the Year" and enhancing communication with PIs
- Community building: collaborate with PDD and ORCD to connect graduate students with MGH post docs and develop graduate student and post docs mentoring relationships.
- Networking and Education: work with PDD to identify ways to track the careers of MGH PhD students who defended their dissertation and to help foster community with current and new graduate students at MGH.

- Knowledge: continue to facilitate in-person orientation for new graduate students.

In addition, the GSD will continue to:

- Provide educational seminars, social events, and career consultations for MGH graduate students.
- Support scholarly activities of PhD graduate students who are currently doing research at MGH.
- Maintain the relationships with area graduate schools and collaborate with other offices within the CFD to build strong support for the research community at MGH.

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 Post-Doc Policy, including its exception policy.
- Act as central point of contact for post-doc fellows regarding information, resources, and issues.
- Ensure the Annual Career Planning discussion takes place (and that the form is completed).
- Facilitate orientation sessions for newly-arrived post-docs to familiarize them with the MGH.
- Provide individual counseling, advice and support.

Focus

The Post-Doctoral Division serves over 1600 post-doctoral research fellows here at MGH, including administering the MGH Guidelines for Research Fellows and advising the Mass General Postdoctoral Association (MGPA). In 2017, the Division launched its own 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

- Initiated outreach by facilitating four focus groups across the MGH campus and administering a survey to all post docs to assess post doc needs and career goals
- Reviewed feedback, prioritized items, and created a PDD roadmap to address stated needs including career exploration, job search strategy, networking, and writing
- Formed an advisory structure by consolidating the GSD and the PDD Council
- Launched new programming to support post-doctoral career and professional development, including "Welcome to Boston: 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," and a "Scientific Writing Workshop"
- Enhanced communications, outreach and engagement by adopting mobile-friendly email marketing and event registration platforms
- Established PDD Committee from among the 12 post docs who applied for committee membership
- Continued to advise the MGPA and collaborated with leadership to develop programming for each of the sub-committees, including Careers in Academia, Mentoring, Industry Careers, International Medical Graduates, Science Communication, MGH Consulting Club, 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

Strategic Priorities

- Offering 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
- Looking at ways to leverage existing/build an MGH post doc alumni database and build relationships with alumni to help foster community with our current post-doctoral research fellows and better understand the career pathways of our post docs
- Continuing to enhance and streamline communication through digital tools including email and web resources
- Collaborating with internationally-trained MD to continue to develop resources and support for their professional development needs
- Explore ways of supporting postdoctoral fellowship grant applications
- Analyze data on fellowship success rates
- Revamping our orientation and on-boarding process and assessing MGH post doc appointment process

- Creating a mentoring award for PIs

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 2017. Highlights of OWC activity:

- Developed a series of initiatives, supported by the Mass General Physicians Organization (MGPO) designed to enhance gender parity in MGH faculty. Initiatives included:
- An expansion of the Caring for Dependents Travel Awards, which offers up to $500 in expense reimbursement to help faculty parents cover child travel or extra childcare during a scientific/medical conference and the CV assistance program, offering editing and formatting of CVs for HMS promotion.
- 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.
- Celebrated the 20th anniversary of the Claflin Distinguished Scholar Awards, with a special celebration bringing together Claflin alumnae and hospital leadership.
- Continued to partner with individual departments, with a special focus in 2017 on collaborations to support the career development of female trainees. Trainee groups formed in the Departments of Medicine and Surgery, with support and advice from the OWC. The office also sponsored the third annual mentored lunch for women postdocs, in which trainees met in small groups with women faculty to hear advice on trainee-to-faculty transitions.
- Organized the highly successful 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. Redonda Miller, president of Johns Hopkins Hospital.
- Fostered networking with female leader role models with the "Meet and Greet Networking Series."
- 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.
- Sponsored the annual leadership program focused on "Understanding Your Leadership Style."
- 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.
- Counseled 17 women faculty aimed at career advice and supporting gender equity and 8 women faculty sought guidance from an external career consultant. These individuals visited the office for a total of 25 consultations.

Strategic Priorities - 2018

- Continue collaborations with the MGPO to continue the process of identifying and developing initiatives and providing/expanding resources to ensure gender equity; these may include negotiation skill building, publishing programs, as well as academic advancement programs.

- 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 support departmental programs in these areas and others, as identified.
- 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 Workshop 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. Develop new ways for women faculty to network via Facebook and other forms of social media.

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

Mission

The OCC, Office for Clinical Careers, 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 104 faculty and fellows from a cross section of departments in 122 consultation sessions regarding: career advice, CV/cover letter critique, mentoring, and promotion.
- Created new programming content in conjunction with the OCC Advisory Committee: "Making Connections to Get Ahead".
- Sponsored 8 educational programs: Can I Really Write a Book?, Can I/Should I Be Promoted?, Drafting Your Chief's Letter, Positioning Yourself for the Future, Scholarly Writing Seminar, and Teaching: How to Lead Medical Rounds and collaborated with the CFD to hold Crafting Your CV Narrative, promote academic advancement and help to "demystify" the HMS promotions' process.
- Participated in departmental outreach by visiting departmental meetings to present on the Center for Faculty Development and facilitate career advancement seminars.

Strategic Priorities

- Help clinical faculty navigate promotion criteria.
- Help faculty balance between research and patient care responsibilities.
- Enhance the collaboration with the MGPO to work on academic advancement and work life balance issues 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 career and work life balance needs.
- Promote awareness of/celebrate clinical faculty promotions and academic achievements.
- Advise individual clinical faculty on career and academic advancement.
- Collaborate with departmental initiatives and do outreach to departments.
- Implement new strategies to market programs to clinical faculty.

- Conduct Exit Interviews with departing clinical staff to understand reasons for leaving MGH.
- 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 clinical fellow needs.

Center for Computational and Integrative Biology

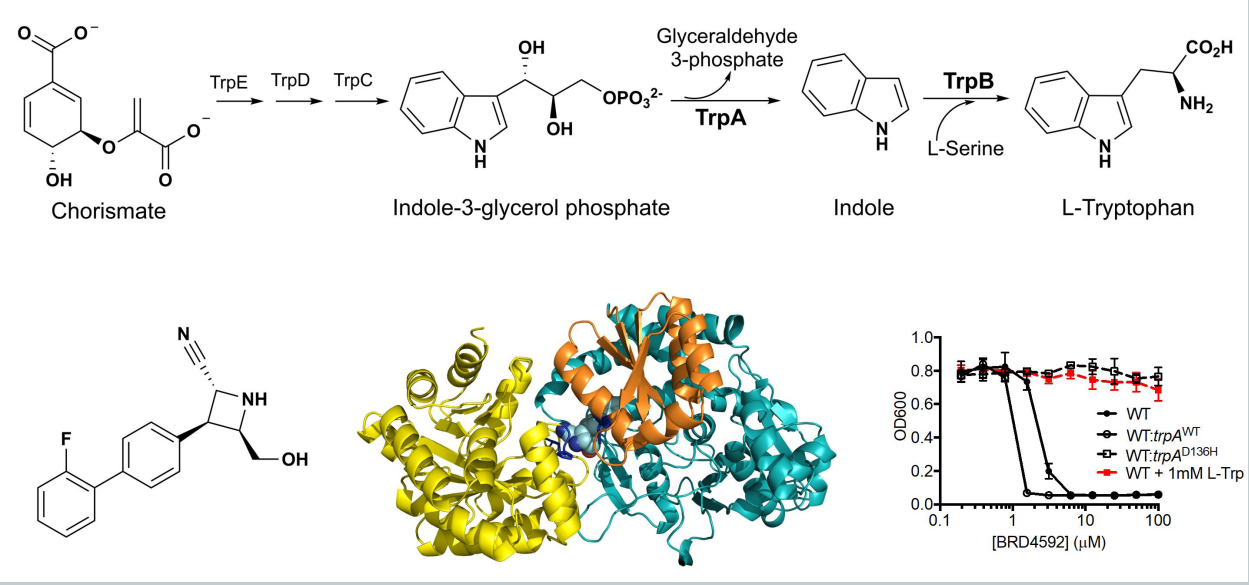
Thematic Center Report

Brian Seed, PhD, Director

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 signalling 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 the unexpected convergence of two groups' interests on tryptophan metabolism and tryptophan metabolites in host-pathogen or host-commensal interactions. We also draw attention to the identification of an unexpected and general connection between nitrate sensing and calcium-mediated signal transduction in plants.

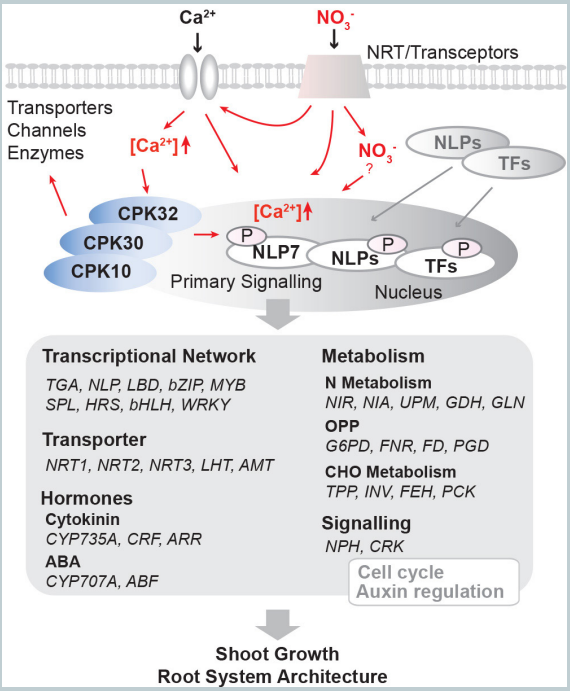
The Hung laboratory has been exploring the creation of new antibiotics with novel targets. Bacteria have numerous essential functions, but only a small fraction of such processes-primarily those involved in macromolecular synthesis-are inhibited by current drugs. The Hung group has identified a synthetic azetidine derivative, BRD4592, that kills Mycobacterium tuberculosis (Mtb) through allosteric inhibition of tryptophan synthase (TrpAB), a previously untargeted, highly allosterically regulated enzyme. BRD4592 binds at the TrpAB α-β-subunit interface and affects multiple steps in the enzyme's overall reaction, resulting in inhibition not easily overcome by changes in metabolic environment. TrpAB is required for the survival of Mtb and Mycobacterium marinum in vivo and this requirement may be independent of an adaptive immune response. The work highlights the effectiveness of allosteric inhibition for targeting proteins that are naturally highly dynamic and that are essential in vivo, despite their apparent dispensability under in vitro conditions, and suggests a framework for the discovery of a next generation of allosteric inhibitors.



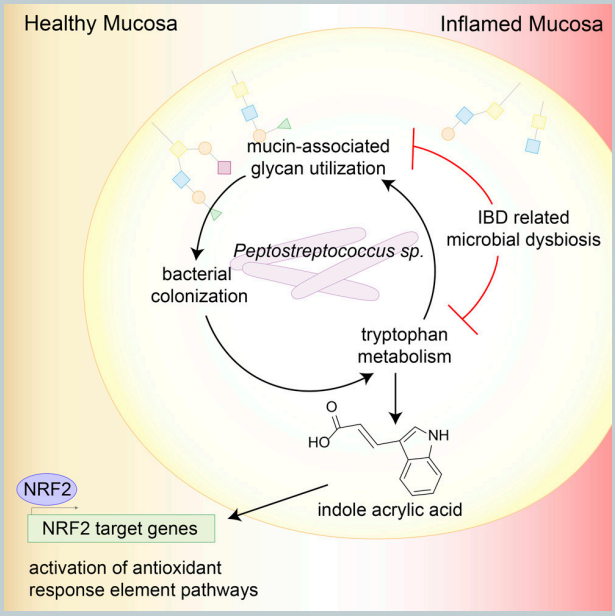
BRD4592 kills Mycobacterium tuberculosis by binding at the TrpAB α-β-subunit interface, affecting multiple steps in the enzyme overall reaction and resulting in an inhibition not easily overcome by changes in the metabolic environment.

The Xavier lab has identified metabolic pathways in enteric bacteria that affect host health. Some commensal bacteria can utilize mucins as an energy source, thus promoting their colonization. However, health conditions such as inflammatory bowel disease (IBD) are associated with a reduced mucus layer, potentially leading to dysbiosis associated with this disease. Several Clostridiales members were found to metabolize intestinal mucins. One of these, Peptostreptococcus russellii, reduces susceptibility to epithelial injury in mice. Several Peptostreptococcus species contain a gene cluster enabling production of the tryptophan metabolite indoleacrylic acid (IA), which promotes intestinal epithelial barrier function and mitigates inflammatory responses. Metagenomic analysis of human stool samples showed that the genetic capability of microbes to utilize mucins and metabolize tryptophan is diminished in IBD patients. Stimulating IA production might promote anti-inflammatory responses and have therapeutic benefits.

The Sheen group identified subgroup III Ca2+-sensor protein kinases (CPKs) as master regulators that orchestrate primary nitrate responses. An engineered mutant CPK10(M141G) was created that could be targeted with a chemical probe, allowing CPK10 to be turned off without embryo lethality and enabling conditional analyses of cpk10 cpk30 cpk32 triple mutants to define comprehensive nitrate-associated regulatory and developmental programs. It was found that nitrate-coupled CPK signalling phosphorylates conserved transcription factors to specify the reprogramming of gene sets for downstream transcription factors, transporters, nitrogen assimilation, carbon/nitrogen metabolism, redox, signalling, hormones and proliferation. The nitrate-coupled Ca2+ signalling network integrates transcriptome and cellular metabolism with shoot-root coordination and developmental plasticity in shaping organ biomass and architecture.



Nitrate-sensitive calcium-dependent kinases phosphorylate conserved transcription factors to specify the reprogramming of gene sets for downstream transcription factors, transporters, nitrogen assimilation, carbon/nitrogen metabolism, redox, signalling, hormones and proliferation.



Peptostreptococcus species contain a gene cluster enabling production of the tryptophan metabolite indoleacrylic acid (IA), which promotes intestinal epithelial barrier function and mitigates inflammatory responses.

Center for Genomic Medicine (formerly Center for Human Genetic Research)

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.

Over the past year, we have collectively gone through a strategic planning process for CGM that has addressed two questions: where do want to go and how will we get there? We seek to build on our considerable strengths in gene discovery and mechanistic research and over the next five years, lead an effort to bring genomics to medicine. We are currently working to implement strategic initiatives in six domains: 1) efforts to build community within CGM and between CGM and other Simches Centers; 2) provide access to pilot/seed funding to catalyze new collaborations ('CGM Catalysis Awards'); 3) develop mechanisms to address bioinformatics analysis needs as well as maintenance of shared equipment; 4) launch three demonstration projects in the area of genomic medicine; 5) recruit new faculty; and 6) develop plans to train the next generation of leaders in human genetics research.

Key CGM achievements fell into four domains:

1. **Science**
   - Organized and completed a joint faculty search with the Department of Pathology
   - Held the 1st cycle of the CGM Catalysis Awards
   - CGM faculty made a number of important scientific observations this past year including:
     - ◊ Landscape of X chromosome inactivation across human tissues. Nature 2017;550: 244-248. Daniel MacArthur, PhD, and his team developed a catalog of X chromosome across tissues and established incomplete XCI as a mechanism that is likely to introduce phenotypic diversity.
     - ◊ Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. Nature2017;544: 235-239. Sekar Kathiresan, MD, and his team identified human 'knockouts' for 1,300 genes and studied the phenotypic consequences of lacking a given gene.
     - ◊ The genomic landscape of balanced cytogenetic abnormalities associated with human congenital anomalies. Nat Genet 2017;49:36-45. Michael Talkowski, PhD, and his team performed whole genome sequencing to understand the spectrum of balanced rearrangements that contribute to congenital anomalies.
     - ◊ Genome-wide association analyses of sleep disturbance traits identity new loci and highlight shared genetics with neuropsychiatric and metabolic traits. Nat Genet 2017; 49: 274-81. Richa Saxena, PhD, and her team performed a genome wide association scan for sleep disturbance traits to find new loci and relationships to metabolic traits.
     - ◊ Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. N Engl J Med 2017; 377:1630-1638. Florian Eichler, MD, and Patricia Musolino, MD, PhD, led a clinical trial of the first successful gene therapy for a progressive disorder of the brain. A hundred years after the first clinicopathological description of childhood cerebral adrenoleukodystrophy, this trial has been able to deliver the corrected gene to CD34+ bone marrow cells and thereby halt progressive inflammation in the brain.

2. **Community**
   - Implemented a bi-monthly CGM newsletter
   - Redesigned and successfully completed the Darwin room renovation into a bioinformatics room capable of seating 21 employees
   - Developed space on Simches 2 to host All of Us Research Program recruitment
   - Created a CGM travel award competition and distributed four $1500 travel awards
   - Organized a monthly volunteering opportunity for staff
   - Organized a monthly networking lunch for staff
   - Developed and launched the new CGM website, logo, letterhead, and email signature

3. **Administration**
   - Hired a new administrative director
   - Hired an IT support technician dedicated to the CGM
   - Formed the CGM Executive committee meeting

- Created a formalized process for Faculty to submit space requests
- Created a formalized process for Faculty to post open job positions within their lab
- Created a formalized process for new employees on their 1st day
- Created an anonymous survey for staff to submit their suggestions/ideas

4. Honors

- Alex Soukas, MD, PhD, Martin Prize for Fundamental Research, MGH
- Daniel MacArthur, PhD, Martin Prize for Clinical Research, MGH
- James Gusella, PhD, William Allan Award, American Society of Human Genetics
- Sekar Kathiresan, MD, Distinguished Scientist Award, American Heart Association
- Richa Saxena, PhD, MGH Research Scholar Award
- Erin Dunn, PhD, National Institute of Mental Health Biobehavioral Research Award for Innovative New Scientists Award
- Vijaya Ramesh, PhD, Promotion to Professor of Neurology, Harvard Medical School
- Roy Perlis, MD, Promotion to Professor of Psychiatry, Harvard Medical School
- Sue Slaugenhaupt, PhD, Election to the Board of Directors of the American Society of Human Genetics
- Rakesh Karmacharya, MD, PhD, National Institute of Mental Health Biobehavioral Research Award for Innovative New Scientists

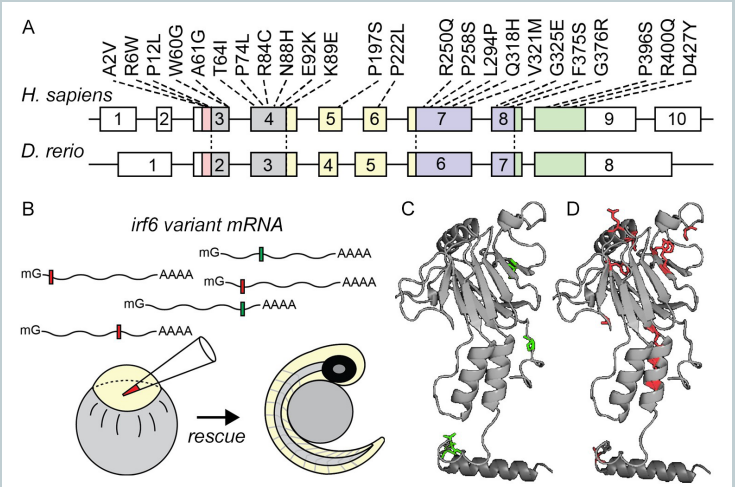
David Scadden, MD, Director

The Center for Regenerative Medicine is dedicated to outstanding stem cell biology informing novel regenerative therapies. The success of this effort requires a collaborative team of scientists and clinicians with diverse areas of expertise and a shared mission.

Laboratory of Eric Liao, MD, PhD

Edward Li, Dawn Truong, Shawn Hallet, Kusumika Mukherjee , Brian Schutte, and Eric Liao. Rapid functional analysis of computationally complex rare human IRF6 gene variants using a novel zebrafish model. PLoS Genet. 2017 Sep 25;13(9):e1007009.

Genetic analysis of craniofacial development - deciphering human protein function in zebrafish model. Tremendous advances in gene sequencing technology has generated a backlog where function of the gene variant or candidate genes are unknown. Study of the candidate genes in an animal or in vitro models are necessary to 1) provide genetic evidence of causality and 2) elucidate the mechanism of gene action. Furthermore, most often whole genome/exome sequencing data identify genetic differences (variants) where it is often unclear from computational predictions whether the variants affect protein function, thereby cataloged as variant of "unknown clinical significance." We exploit the genetic and developmental advantages of the zebrafish model to mechanistically dissect the function of human candidate genes and gene variants implicated in orofacial clefts. Recently, we employed a rescue assay in irf6 zebrafish mutant to determine the pathogenicity of human IRF6 gene variants, where IRF6 is one of the most important genetic determinant of human orofacial clefts. This work highlights the importance of integrating experimental functional analysis with computational predictions in human genetics, a critical step in advancing clinical implementation of personalized medicine.



E

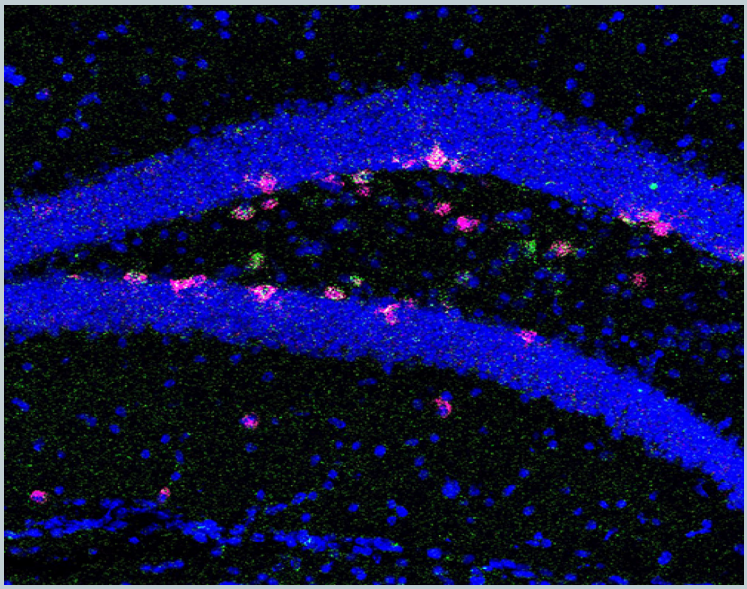
	Computational Agreement (Deleterious)			
Domain	**Human**	**Zebrafish**	**Mutation**	**Result**
N-terminal	R9W	R9	CGT → TGG	Rescued
	P12L	P12	CCA → CTA	Rescued
DNA-binding	K66T	K66	AAA → ACA	Ruptured
	W60G	W60	TGG → GGG	Ruptured
	R84C	R84	CGG → TGC	Ruptured
Mid-linker	P222L	P245	CCA → CTA	Rescued
Protein-binding	L294P	L317	CTT → CCT	Ruptured
	F375S	F398	TTC → TCC	Ruptured
C-terminal	V397A	V420	GTC → GCC	Ruptured
	I423T	I446	ATT → ACT	Rescued
	S424L	S447	AGT → CTT	Ruptured

Application of zebrafish irf6 mutant model to test human IRF6 gene variants. A) diagram of IRF6 transcription factor DNA (grey) and protein binding (blue) domains with representative gene variants B) injection of human IRF6 gene variants into zebrafish irf6 mutant embryos. C and D) secondary structure of IRF6 with residues indicating human variations that are functional (green) or nonfunctional (red). E) computational programs often disagree on prediction of protein function, rendering most sequencing results to be classified as "unknown clinical significance" and not useful for clinical diagnosis. The zebrafish rescue assay can impute protein function and resolve the gene variant to make the information useful for clinical translation.

Laboratory of Amar Sahay, PhD

Tara Raam, Kathleen McAvoy, Antoine Besnard, Alexa Veenema and Amar Sahay . Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. Nature Communications 2017; 8(1): 2001.

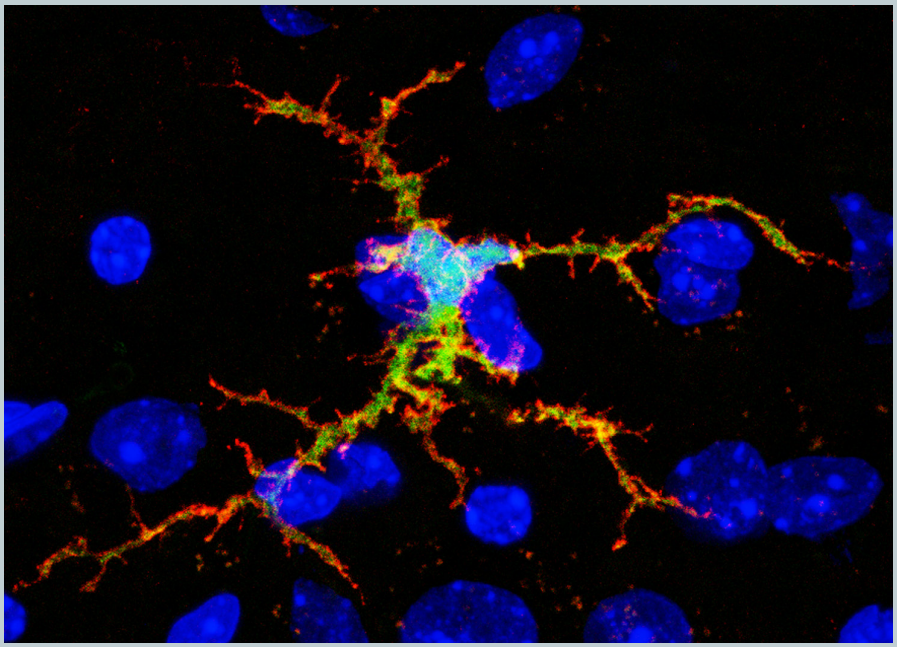
Despite recognition for over 20 years that Oxytocin receptors are expressed in the hippocampus, the physiological contributions of Hippocampal Oxytocin receptors to social cognition remain unknown. The Sahay lab found that hippocampal oxytocin receptors in mice permit distinction of social (familiar vs. novel mouse), but not non-social (two similar objects), memories. Furthermore, these receptors utilize basic population base coding mechanisms to differentiate between social memories. This study illuminates how an ancient neuromodulatory hormone, oxytocin, utilizes a basic memory processing circuit scaffold in the hippocampus to guide social behavior. Alterations in hippocampal circuitry may underlie social memory deficits seen in autism spectrum disorders.



Oxytocin receptors in the hippocampus

Laboratory of David Scadden, MD
Jorg Dietrich, Ninib Baryawno, Naema Nayyar, Yannis K. Valtis, Betty Yang, Ina Ly, Antoine Besnard, Nicolas Severe, Karin U. Gustafsson, Ovidiu C. Andronesi, Tracy T. Batchelor, Amar Sahay, and David T. Scadden. Bone marrow drives central nervous system regeneration after radiation injury. J Clin Invest. 2018 Jan 2;128(1):281-293.

We focus on blood and how modulating hematopoietic cells may alter disease states. In this report, we focused on nervous system injury from cancer therapy involving cranial irradiation, that leaves patients with marked memory and other neurobehavioral disabilities. We demonstrated an unanticipated link between bone marrow and brain in the setting of radiation injury. Specifically, we showed that bone marrow-derived monocytes and macrophages are essential for structural and functional repair mechanisms, including regeneration of cerebral white matter and improvement in neurocognitive function. Using a granulocyte-colony stimulating factor (G-CSF) receptor knockout mouse model in combination with bone marrow cell transplantation, MRI, and neurocognitive functional assessments, we demonstrated that bone marrow-derived G-CSF-responsive cells home to the injured brain and are critical for altering neural progenitor cells and brain repair. Additionally, compared with untreated animals, animals that received G-CSF following radiation injury exhibited enhanced functional brain repair. Together, these results demonstrated that, in addition to its known role in defense and debris removal, the hematopoietic system provides critical regenerative drive to the brain that can be modulated by clinically available agents.



Bone marrow derived GFP+ cells incorporate into and persist in brain after G-CSF treatment. Cells express microglial marker (Iba-1) and macrophage marker (F4/80)(shown).

Center for Systems Biology

Thematic Center Report

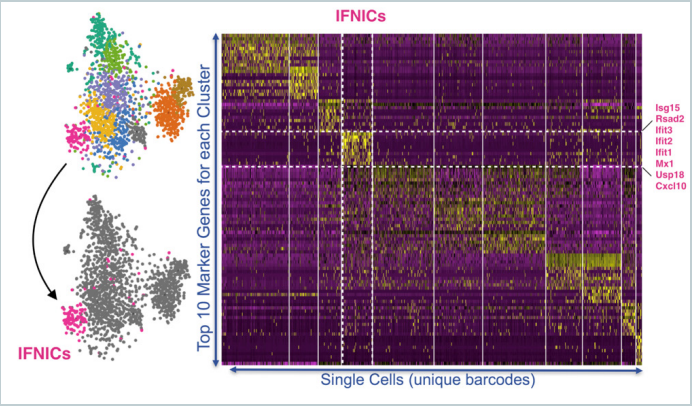
Ralph Weissleder, MD, PhD, Director

The mission of CSB is to analyze at a systems level how biological molecules, proteins and cells 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 disease, diabetes, autoimmune disease, renal disease and reproductive biology. The CSB's mission is enabled by faculty with particular expertise in advanced bioimaging (at all scales), bioengineering, immunology, biology, chemistry, genomics, 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, the Broad Institute, various clinical departments at MGH, as well as with the other MGH Thematic Centers. At the time of writing, the CSB is structured into 13 PI laboratories (Bernstein, Brown, Breton, Higgins, Lee, C. Lin, H. Lin, Miller, Nahrendorf, Naxerova, Pittet, Swirski, and Weissleder), Core Platforms (Bioimaging, Chemical Biology, Biocomputing) and several thematic research programs. The CSB is located within the Simches and CNY Research buildings. There are currently 185 full time employees, including 41 faculty.

Bones and Neutrophils Control Lung Cancer (Science 2017;358:eaal5081)
Tumors are often infiltrated by diverse immune cell types, some of which remain sparsely studied. In a recent study, researchers at CSB uncovered a new type of neutrophil that promotes lung cancer. The production of these neutrophils involves an unexpected remote crosstalk between tumors and bones: lung tumors remotely activate osteocalcin-expressing (Ocn+) osteoblasts; in turn, those bone cells shape immunity by supplying tumors with a distinct type of neutrophil that is defined by expression of the lectin SiglecF. The team further uncovered that the soluble receptor for advanced glycation endproducts (sRAGE) is upregulated in the circulation of tumor-bearing mice and fosters osteoblastic activity and osteoblast-dependent neutrophil maturation in vitro. These findings open new avenues for cancer immunotherapy.

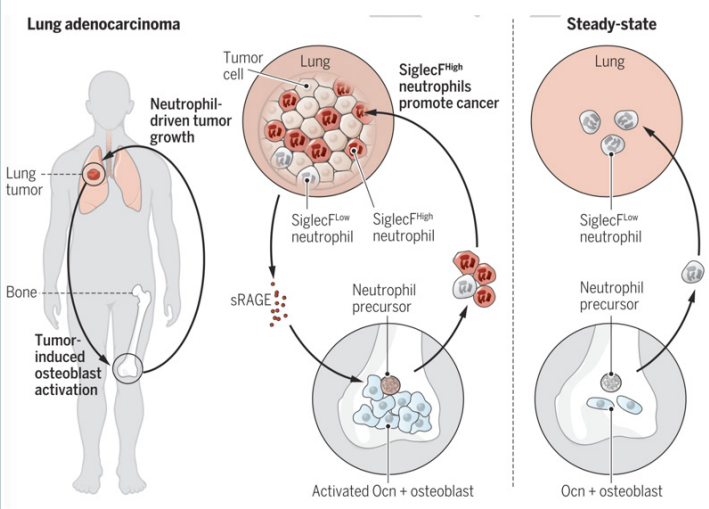
Engblom C, Pfirschke C, Zilionis R, da Silva Martins J, Bos SA, Courties G, Rickelt S, Severe N, Baryawno N, Faget J, Savova V, Zemmour D, Kline J, Siwicki M, Garris C, Pucci F, Liao HW, Lin YJ, Newton A, Yaghi OK, Iwamoto Y, Tricot B, Wojtkiewicz GR, Nahrendorf M, Cortez-Retamozo V#, Meylan E, Hynes RO, Demay M, Klein A, Bredella MA, Scadden DT, Weissleder R, Pittet MJ. Osteoblasts remotely supply lung tumors with cancer-promoting SiglecFhigh neutrophils. Science 2017;358:eaal5081.

Immune cells attend a heart attack masquerade (Nature Med. 2017;:ePub - PMID: 29106401)
Ischemic heart disease is the most common cause of death in the world and it begins with a heart attack. When cells die in the heart, the immune system enters the dead tissue, clears debris, stabilizes and repairs the heart wall. But what is it about dying cells in the heart that is so immune stimulatory? To answer this, researchers at CSB looked deep inside thousands of individual cardiac immune cells and mapped their individual transcriptomes using single cell RNA-Seq. This lead to the discovery that after a heart attack, DNA from dying cells masquerades as a virus and activates an ancient antiviral program called the type I interferon response in specialized immune cells that they term interferon inducible cells (IFNICs). When we blocked the interferon response, either genetically or with a neutralizing antibody given after the heart attack, there was less inflammation, less heart dysfunction, and improved survival. The findings unmask a new potential therapeutic opportunity to prevent heart attacks from progressing to heart failure in patients.



After a heart attack, DNA from dying cells masquerades as a virus and activates an ancient antiviral program called the type I interferon response in specialized immune cells termed interferon inducible cells (IFNICs). Single cell analysis showed that these cells can be molecularly characterized and inhibited. Specifically, when the interferon response is inhibited, either genetically or with a neutralizing antibody given after the heart attack, there was less inflammation, less heart dysfunction, and improved survival. This open up new therapies to preserve myocardium after MI (Nature Med. 2017;:ePub - PMID: 29106401).

King KR, Aguirre AD, Ye YX, Sun Y, Roh JD, Ng Jr RP, Kohler RH, Arlauckas SP, Iwamoto Y, Savol A, Sadreyev RI, Kelly M, Fitzgibbons TP, Fitzgerald KA, Mitchison T, Libby P, Nahrendorf M, Weissleder R. IRF3 and type I interferons fuel a fatal response to myocardial infarction. Nature Med. 2017;:ePub - PMID: 29106401



New immunotherapeutic target cells identified. Systemic cross-talk between lung tumors and bones. Lung adenocarcinomas can remotely activate Ocn+ osteoblastic cells in bones even in the absence of local metastasis. In turn, these osteoblasts supply tumors with SiglecFhigh neutrophils, which exhibit cancer-promoting functions (left). By contrast, the bone marrow in steady state only produces SiglecFlow neutrophils (right; Science Dec, 2017).

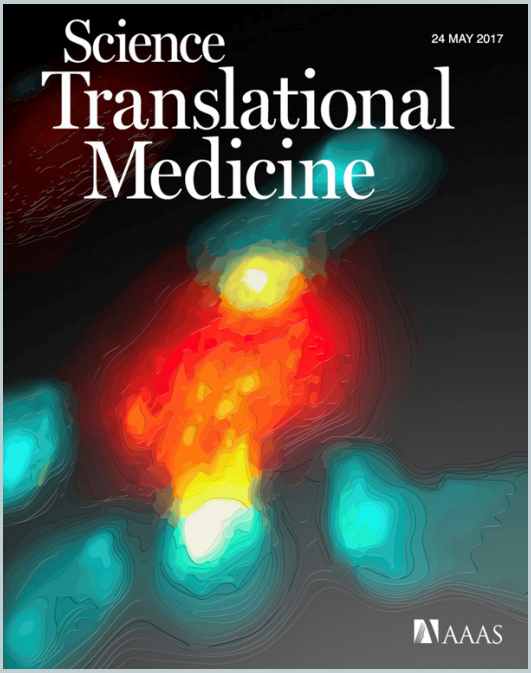
Spotlight on immunotherapy (Science Transl Med. 2017;9(389):eaal3604)
Immunotherapy and especially immune checkpoint blockers (ICBs) are revolutionizing how we treat many cancers. Designed to activate the immune system, these drugs can be extraordinarily effective in some patients. But progress has been slowed by our limited understanding of why ICBs work well in some cancers and patients but not in others. Now, Mikael Pittet and colleagues have used molecular imaging to track ICBs in real time and at high resolution within tumors. Their study, published in Science Translational Medicine, uncovers a previously undiscovered mechanism of treatment resistance, which can be overcome with additional chemical modifications.

Arlauckas SP*, Garris CS*, Kohler RH, Kitaoka M, Cuccarese MF, Yang KS, Miller MA, Carlson JC, Freeman GJ, Anthony RM, Weissleder R, Pittet MJ. In vivo imaging reveals a tumor-associated macrophage–mediated resistance pathway in anti–PD-1 therapy. Science Transl Med. 2017;9(389):eaal3604 - PMID: 28490665

A signature achievement (Science Transl Med. 2017;9(391):eaal3226)
Pancreatic ductal adenocarcinoma is one of the deadliest types of tumors, in part because it is usually detected at a late stage. To facilitate the diagnosis of this tumor, researchers at CSB have developed a multiplexed nanoplasmonic assay to analyze extracellular vesicles in blood of patients. While some blood biomarkers have previously been proposed, none of them have proven sufficiently accurate in clinical practice. We have now identified a new five-marker signature that yielded the most accurate diagnosis in a large cohort of patient samples.

Yang KS*, Im H*, Hong S, Pergolini I, Del Castillo AF, Wang R, Clardy S, Huang CH, Pille C, Ferrone S, Yang R, Castro CM, Lee H, Del Castillo CF, Weissleder R. Multiparametric plasma EV profiling facilitates diagnosis of pancreatic malignancy. Science Transl Med. 2017;9(391):eaal3226 - PMID: 28539469

Cardiac macrophages charging ahead (Cell. 2017;169:510-522)
While we knew for a while that the healthy heart contains tissue resident macrophages, these cells' organ specific functions were unknown. Triggered by a serendipitous finding of ECG abnormalities during a cardiac MRI scan of a mouse after macrophage ablation, a CSB team of investigators now describes previously unknown electrical properties of macrophages. When coupled to myocytes via gap junctions, macrophages depolarize in sync with conducting cells. In a sink-source relationship, electric current flows back and forth between macrophages and cardiomyocytes. Macrophages influence conduction through the atrioventricular node, the electrical connection between the heart's chambers. When macrophages are manipulated, the flow of electricity slows down, and may even cease altogether. Such a condition requires pacemaker treatment in humans. These surprising findings, published in Cell, jolt the field of electrophysiology and may lead to new therapeutic opportunities for patients with cardiac arrhythmias. The collaborative effort was spearheaded by teams at MGH but also involved investigators at the BWH and in Freiburg, Germany.



Antibodies against immune checkpoint proteins such as PD-1 keep antitumor T cells from becoming exhausted and can greatly improve the survival of cancer patients, but even this therapy is not always effective, and a paper by Arlauckas et al. demonstrates one reason why. Using intravital imaging to track individual cells and antibodies, the authors observed macrophages removing anti–PD-1 antibodies from T cells, thus inactivating them. This cover image shows an example of this interaction, with a macrophage (red) directly contacting T cells (blue) and removing the anti–PD-1 antibody (yellow; Sci Transl Med. 2017;9(389):eaal3604 - PMID: 28490665).

Hulsmans M, Clauss S, Xiao L, Aguirre AD, King KR, Hanley A, Hucker WJ, WÃ¼lfers EM, Seemann G, Courties G, Iwamoto Y, Sun Y, Savol AJ, Sager HB, Lavine KJ, Fishbein GA, Capen DE, Da Silva N, Miquerol L, Wakimoto H, Seidman CE, Seidman JG, Sadreyev RI, Naxerova K, Mitchell RN, Brown D, Libby P, Weissleder R, Swirski FK, Kohl P, Vinegoni C, Milan DJ, Ellinor PT, Nahrendorf M. Macrophages Facilitate Electrical Conduction in the Heart. Cell. 2017;169:510-522 - PMID: 28431249 - PMCID: PMC5474950

A new trick for macrophages (Science Transl Med.2017;9(392):eaal0225)
Macrophages, immune cells in our body, have a long to-do list. They defend us from bacteria, are essential in wound healing, keep the heart beating and perform other vital tasks. In a new twist, these cells are now shown to dramatically accumulate on the outside of cancer microvessels following radiation therapy. There, they elicit dynamic and focally localized bursts of capillary leaks. This in turn enhances drug delivery, especially of nanomaterials. These new insights have implications for the design of next- generation tumor targeted nanomaterials and clinical trials for adjuvant strategies.

Miller MA, Ravi Chandra R, Cuccarese MF, Pfirschke C, Engblom C, Stapleton S, Adhikary U, Kohler RH, Mohan JF, Pittet MJ, Weissleder R. Radiation therapy primes tumors for nanotherapeutic delivery via macrophage-mediated vascular bursts, Science Transl Med. 2017;9(392):eaal0225

For a complete list of ~ 135 publications from CSB in 2017, please see here: https://csb.mgh.harvard.edu/publications?year=2017

Keychain sensor for food allergens. More than 50 million Americans suffer from food allergies and each year there are an estimated 20,000 food allergy-related emergency department visits in the United States, including 90,000 cases of anaphylaxis. The best way to manage food allergy is to avoid products that contain allergen. But avoidance isn't always possible because food can be mislabeled or cross-contaminated. Meet iEAT (integrated Exogenous Antigen Testing) a $40 portable allergen-detection system that consists of a disposable kit to extract allergens from food and an electronic keychain analyzer for allergen detection. In less than 10 minutes, the iEAT completes food analyses and sends the results to a cloud server. The prototype was used to detect five model allergens from wheat, peanuts, hazelnuts, milk and egg white. Testing on food items from local restaurants revealed unexpected findings such as gluten in "gluten-free" dishes and egg protein in beer. The technology is being expanded to detect additional allergens, pesticides and environmental hormones (ACS Nano. 2017;11(10):10062-10069 - PMID: 28792732)

R. Rox Anderson, MD, Director

Our mission is to improve people's lives through research, development, innovation, and education. Photomedicine encompasses all of light's beneficial, harmful, diagnostic, therapeutic, surgical, medical and technological aspects in biology and medicine. Our prevalent research topics include: point-of-care optical diagnostics for coronary artery disease, upper GI, coagulopathy and infections; novel immunization strategies; light-activated cancer treatments; trauma interventions; photobiomodulation; melanoma genetics and treatment strategies; bio-inspired optical technologies; pain control.

Strategic priorities

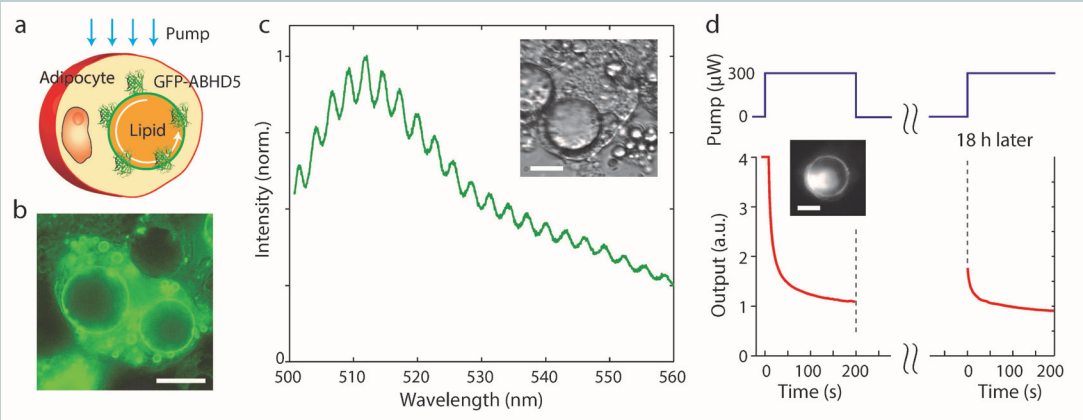
- Leadership in the field of photomedicine. We are the world's largest research center in this rapidly expanding field, with over 250 personnel, and an annual budget near $30M. Our work also extends well beyond the theme of photomedicine.
- Innovation for medical impact. In 2017, we were the leading source of MGH and Partners royalty income. A ~$25M investment fund was established to foster tech transfer from the Center. Ten percent of this fund is available for discovery and feasibility-stage research at Wellman Center and MGH. A dozen early projects were supported at Wellman and MGH from this new fund during 2017.
- World Health. We are pursuing collaborative research on every continent, with emphasis on trauma, malnutrition, infection and cancer in developing countries.
- Education. We offer courses, regular seminar and lecture series, student and postdoctoral fellow education, a summer undergraduate school, and the Bullock Fellowships. This year, Wellman led the creation of two endowed full-time research fellowships that honor two physicists whose work here had high impact. These are the Tom Deutsch Fellowship (linked to Optical Society of America) and the Franz Hillenkamp Fellowship (linked to the SPIE society).
- Return value to MGH. Wellman is non-departmental and highly collaborative.

A Sample of 2017 Research Highlights

We published about 160 research papers and received about 20 new US patents in 2017.

Live, bio-inspired lasers. Professor (congratulations!) Andy Yun's lab created the world's first living laser several years ago, and has recently developed intracellular whispering-galley-mode (WGM) laser particles capable of uniquely tagging up to billions of individual cells. His group recently demonstrated the first fully self-assembled WGM intracellular laser by transducing GFP into adipocytes whose spherical lipid droplets allow WGMs. The WGMs transfer optical pump energy via evanescent optical waves to GFP as the optical gain medium. In essence this is the world's first living, self-assembled laser device.

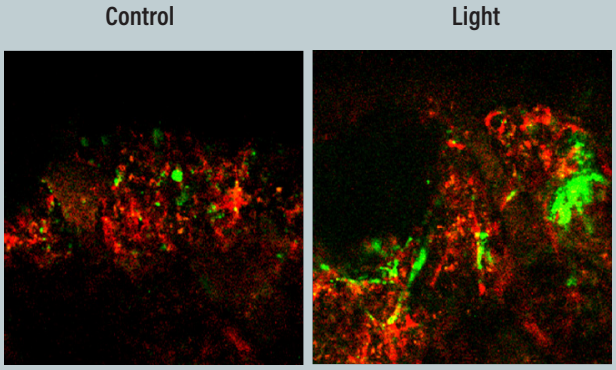
Humar M, Yun SH. Whispering-galley-mode emission from biological luminescent protein microcavity assemblies. Optica 2017;4(2):222-228



Mature adipocytes created by differentiation of GFP-transformed precursor cells (a), when pumped by blue light, are living lasers (b). The cytoplasmic lipid droplets have high refractive index, allowing WGMs (spectrum, c) that couple pump energy to adjacent GFP molecules.

Near-infrared light restores platelet production, lifetime, and function

Mei Wu's laboratory has discovered that exposure to ~800 nm near infrared light stimulates bone marrow to produce more platelets, prolongs platelet lifetime in storage, and increases platelet function under stress. Based on efficacy for treating radiation and immune thrombocytopenia



Femoral marrow (mouse) exposed to low levels of 810 nm near-infrared light shows megakaryocyte activation (green cells), with subsequent increased platelet output.

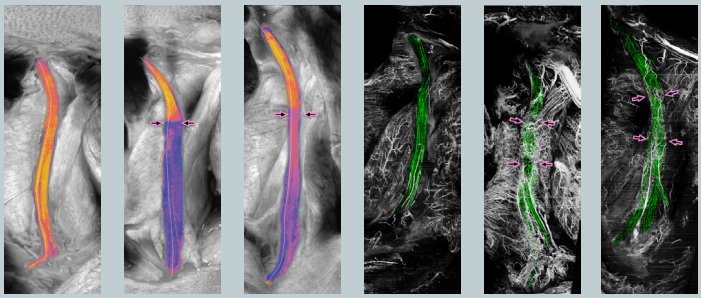
in animal models, clinical studies are planned. The mechanism involves endogenous mitochondrial photochemistry in megakaryocytes and platelets.

Zhang Q, Dong T, Li P, Wu MX. Noninvasive low-level laser therapy for thrombocytopenia. Science Translational Medicine 2017; 349(8):349 ra101

Seeing nerve injury and repair

Benjamin Vakoc's laboratory is developing powerful new stain-free versions of optical coherence tomography that image the natural birefringence of nerves (correlated to myelin structure), while also imaging microvasculature by optical doppler shifts, very rapidly and at high resolution. The images below show degeneration and repair after nerve crush injury. Angiogenesis is a key event preceding micro-anatomic nerve recovery.

Nam AS, Chico-Calero I, Easow JM, Villager M, Welt J, Winograd JM, Randolph MA, Redmond RW, Vakoc BJ. Assessment of vascularization and myelination following peripheral nerve repair using angiographic and polarization sensitive optical coherence tomography. SPIE Proc 10053 (2017).



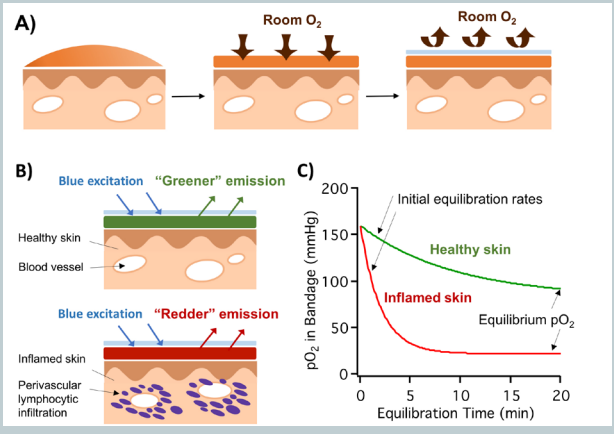
A nerve is shown *in vivo* before, 7 days and 1 month after crush injury and repair by autologous nerve grafting. Images at left show myelination (orange); images at right show microvasculature (green). No biopsies, stains or dyes were used. Angiogenesis precedes nerve recovery.

Mapping and understanding tissue p02

Conor Evans' laboratory has synthesized novel oxygen-sensing phosphorescent probes and incorporated these into bandages that accurately track tissue p02, and can be read with a smartphone. The technology has many potential applications, including detection of changes in metabolism with inflammation and wound healing. A clinical trial is underway for surgical wounds.

Li Z, Navarro-Alvarez N, Keeley DJ, Howell NH, Goncalves BM, Huang CA, Evans CL. Non-invasive monitoring of skin inflammation using an oxygen-sensing paint-on bandage. Biomed Opt Express 2017 8(10):4640-4651.

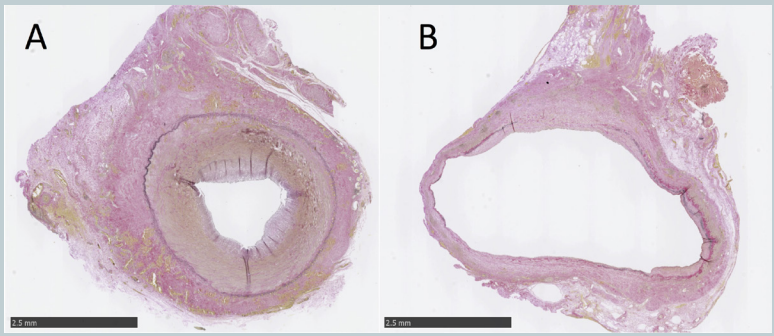
When a spray-on, oxygen-sensing optical reporter dressing (a) is placed on skin and stimulated by blue light (b), the rate of local 02 consumption is immediately measured (c). Inflammation and active wound healing consume oxygen, whereas the metabolic demand of necrotic tissue is zero. This novel "dressing" can also map and monitor tissue p02. A phase I clinical trial is underway for surgical wounds.



Photochemical "passivation" improves vascular surgery

Vein grafting is widely used for repairing peripheral and central arterial diseases. Robert Redmond and Irene Kochevar previously discovered that Rose Bengal, a vital diagnostic dye already used in humans, potently crosslinks tissue collagens upon in situ activation by green light. Treated veins immediately become mechanically strong enough to withstand arterial blood pressure. This novel strategy may have strong clinical impact.

Salinas HM, Khan SI, McCormack MC, Fernandes FU, Gfrerer L, Watkins MR, Redmond RW, Austen WG Jr. Prevention of vein graft intimal hyperplasia with photochemical tissue passivation. J Vasc Surg 2017 65(1):190-196.

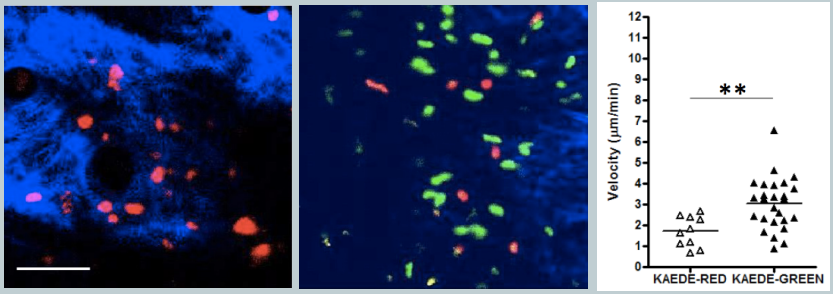


When a grafted vein is exposed to arterial blood pressure, intimal hyperplasia occurs, restricting blood flow (A). Photochemical tissue passivation is a rapid local treatment that prevents this response (B). The treatment consists of one brief exposure to green light after local application of Rose Bengal during surgery.

Tracking the course of T cells in immune response

Charles Lin's laboratory, a joint effort of MGH Wellman Center and Systems Biology Center, has developed advanced cell tracking microscopies employing in situ immediate labeling of cells using photo-convertible chromophores. Normal cutaneous response to infection requires development of both long-lived resident memory T cells, and influx of specific transient T cells upon subsequent exposure. This process was studied in detail for candida infection in mice, by imaging resident and transient T cell populations.

Park CO, Fu X, Jiang X, Pan Y, Teague JE, Collins N, Tian T, O'Malley JT, Emerson RO, Kim JH, Jung Y, Watanabe R, Fuhlbrigge RC, Carbone FR, Gebhardt T, Clark RA, Lin CP, Kupper TS. Staged development of long lived TCRαβ Th17 resident memory T cell population to Candida albicans after skin infection. J Allergy Clin Immunol. 2017;:ePub - PMID: 29128674 - DOI: 10.1016/j.jaci.2017.09.042



All dermal T4 lymphocytes were photo-convertible labelled in situ (red cells, left image). A day later, resident (red) cells are still seen, while newly-arrived migrating T cells (green) appear and interact.

Anesthesia, Critical Care and Pain Medicine

Department Report

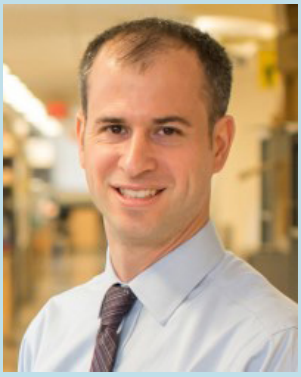
Jeanine Wiener-Kronish, MD, Chief

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 2017. (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.

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 2017:

Dr. Warren Zapol's laboratory designed, constructed and tested a lightweight, economical, portable electric nitric oxide (NO) generator in both lambs and humans with pulmonary hypertension. Inhaled NO therapy is a life-saving treatment for newborn babies with pulmonary hypertension. Inhaled NO therapy is unavailable in many parts of the world and is not readily available in patients' homes due to current cumbersome delivery systems and associated high costs (approximately $14,000 for 5 days of treatment for one newborn). The system designed by Dr. Zapol's lab makes inhaled NO therapy more widely available. Their system produces a therapeutic range of NO (5-80 ppm) from air, using a pulsed electrical discharge. Their research at MGH demonstrated that electrically generated NO is equivalent to NO delivered from a standard NO/N2 cylinder- the current clinical gold standard. This new, economical technology for NO inhalation therapy will liberate patients from costly, cumbersome tanks and complicated delivery systems and will facilitate long-term, home use of inhaled NO. The researchers in Dr. Zapol's lab anticipate that the availability of this device will also permit investigators to identify novel indications for NO inhalation therapy in pulmonary hypertension, including the treatment of chronic lung diseases and congestive heart failure. These findings were published in Science Translational Medicine.



Brian Wainger, MD, PhD, recipient of NIH Director's New Innovators Award

Dr. Brian Wainger's lab developed and used stem cell technology to model diseases affecting sensory and motor neurons. He defined a technique to derive nociceptor neurons from fibroblasts using transcription factor lineage reprogramming. Using existing approaches to differentiate motor neurons from induced pluripotent stem cells, Dr. Wainger demonstrated that motor neurons derived from patients with amyotrophic lateral sclerosis (ALS) were hyperexcitable compared to motor neurons derived from healthy controls. Using the FDA-approved antiepileptic retigabine, which increases potassium currents, he showed that treatment with the drug both reduced the hyperexcitability and increased the in vitro survival of the ALS motor neurons. These findings were published in Nature Neuroscience and Stem Cell.

Dr. Brian Wainger was also a recipient of the NIH Director's New Innovators Award for his project *A Human Stem Cell-Derived Neuromuscular Junction Model for Amyotrophic Lateral Sclerosis*. Dr. Wainger'slab research focuses on modeling motor and sensory neuron diseases using stem cell technology and electrophysiology. Congratulations!

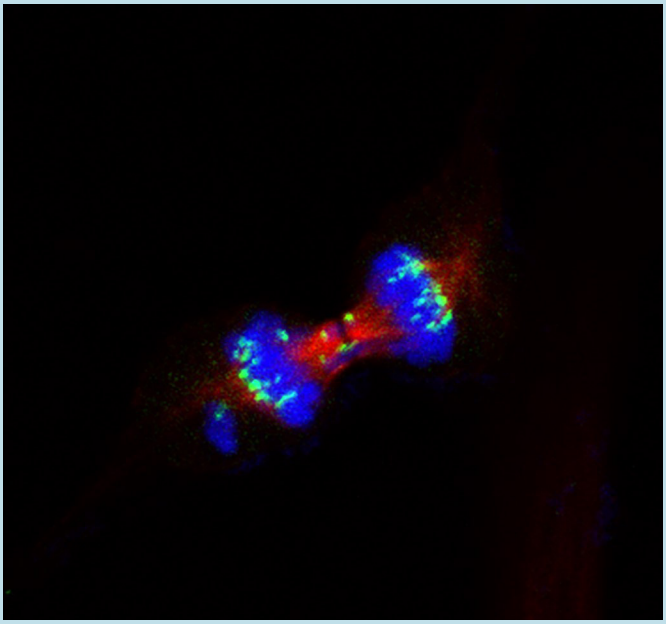
Dr. Patrick Purdon recently published his research in the Proceedings of the National Academy of Sciences that detailed the characterization of electroencephalogram (EEG) changes during Propofol-induced general anesthesia, as a patient loses consciousness and recovers consciousness. Dr. Purdon's work demonstrates that there are specific EEG signatures associated with different levels of unconsciousness. Tracking these signatures during the administration of anesthesia provides a clinically useful way to identify a patient's level of unconsciousness.

Dr. Shiqian Shen and his research team recently found a unique role of gut microbiota in the development of chemotherapy-induced neuropathic pain. Chemotherapy-induced pain is a dose-limiting condition that affects 30% of patients undergoing chemotherapy. Dr. Shen and colleagues found that gut microbiota promotes the development of chemotherapy-induced mechanical hyperalgesia. Their findings demonstrate that oxaliplatin is not only dependent on gut microbiota to exert its tumor-killing effect, but gut microbiota also has a crucial impact on the development of mechanical hyperalgesia. This role of gut microbiota likely results from its permissive effect on dorsal root ganglion inflammatory responses mounted by the chemotherapy agent, oxaliplatin used in these experiments. This work was published in Nature Neuroscience.

Cancer Center

Department Report

Daniel A. Haber, MD, PhD, Director



Indirect immunofluorescence image of a human RPE-1 exiting mitosis with several missegregation events. Cell was stained for microtubules (red), centromeres (green) and DNA (blue). Image credit: Lilian Kabeche, PhD, Zou Laboratory. (Kabeche et al, Science 359:6371, 2017)

The mission of the Massachusetts General Hospital Cancer Center (MGH Cancer Center) is to advance knowledge and 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 technologies to enable early blood-based detection of cancer, establishing paradigms for precision oncology using genetically-informed small molecule inhibitor therapies, and creating a leading cancer immunology program, including checkpoint inhibitors and engineered T cell therapies, integrated within our translational research enterprise. In addition to these major thematic areas of emphasis, we will continue to support fundamental, investigator initiated discovery, which we believe to be the centerpiece of our successful research enterprise. For the purposes of this review, research highlights are presented for 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. Nick Dyson serves as Scientific Director (CCR) and Dr. David Ryan is Chief of Hematology/Oncology and Clinical Director of the Cancer Center. Total annual research expenditures for CCR and Hematology/Oncology in FY17 was $96 million (including industry clinical trials contracts). In 2017, 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 of first-in-human drugs).

Highlighted accomplishments for the Cancer Center during 2017 are grouped into four thematic areas:

1. Master regulators of cell fate and tumorigenesis:
Using transcription-factor-induced reprogramming as a screening assay, Dr. Konrad Hochedlinger and colleagues identified the RNA-processing factor Nudt21 as a novel regulator of cell fate change, modulating the generation of induced pluripotent stem cells and their differentiation into myeloid precursors (Brumbaugh et al, Cell 8674:31370, 2017). Dr. Leif Ellisen et al reported that the ACTL6A and p63 genes collaborate in regulating cell fate in epithelial cells, driving head and neck squamous cell carcinoma and mediating activation of YAP (Saladi et al, Cancer Cell 31:35, 2017). Dr. Mario Suva and colleagues used single cell RNA sequencing of gliomas to define distinct cell lineages within IDH-mutant brain cancers, characteristic of altered differentiation pathways in this genetic subtype (Tirosh et al, Science 539:309, 2017), and Dr. Miguel Rivera's lab used Chip-Sequencing technologies to identify novel master transcriptional regulators in Ewings Sarcoma (Boulay et al, Cell 171:163, 2017).

2. Cancer Immunology:
Dramatic responses to immune checkpoint therapies have revolutionized the treatment of metastatic melanoma, but tumors may acquire resistance leading to partial responses or tumor recurrence. By sequencing longitudinally collected biopsies from patients on clinical trials of anti-PDI and anti-CTLA4, Dr. Nir Hacohen and colleagues at MGH and the Broad Institute identified inactivation of beta-2 microglobulin (b2M), an essential component of MHC class I antigen presentation whose loss makes tumor cells "invisible" to the immune system (Sade-Feldman et al, Nature Comm. 8:1136, 2017). In a separate study using single cell RNA sequencing of immune cells, Dr. Hacohen's team also classified six subtypes of human dendritic cells and four monocyte subtypes, providing new tools for immune monitoring and immune stimulation (Villani et al, Science 356:6335, 2017), and in a tour de force for the creation of therapeutic personal vaccines in melanoma, Dr. Hacohen and collaborators at Dana Farber, Broad and MGH reported their first results with tumor sequencing-derived neo-epitope vaccination (Ott et al, Nature 547:217, 2017). Following up on her work with Dr. Carl June at U. Pennsylvania, Dr. Marcela Maus and her colleagues reported a first-in-human study

of chimeric antigen receptor (CAR) T cells targeting the epidermal growth factor receptor variant III (EGFRvIII) in patients with recurrent glioblastoma (O'Rourke et al, Science Transl Med. 9:399, 2017).

3. Targeted Therapies and Drug Resistance:
Dr. Lee Zou and colleagues discovered that ATR kinase, a master regulator of genomic integrity during DNA replication, also plays an unexpected role during mitosis, pointing to new applications of ATR inhibitors in cancer cells undergoing mitotic stress (Kabeche et al, Science 359:6371, 2017). In breast cancer, Dr. Gaddy Getz and colleagues at the Broad Institute and MGH reported on the landscape of non-coding regulatory mutations in breast cancer (Rheinbay et al, Nature 547:55, 2017), and Dr. Leif Ellisen and his colleagues identified novel intergenic fusions involving the estrogen receptor gene in as many as 14% of women with advanced HR+ breast cancer, pointing to new mechanisms mediating resistance to hormonal therapy and potential new therapeutic targets (Matissek et al, Cancer Discovery 17:0535, 2017).Along similar lines, Drs. Lipika Goyal, Andrew Zhu, Nabeel Bardeesy and colleagues reported the acquisition of anti-FGFR drug resistance mutations in FGFR2-fusion positive intrahepatic cholangiocarcinoma (Goyal et al, Cancer Discovery 7:252, 2017). Dr. Othon Iliopoulos and his team discovered the effectiveness of Glutaminase 1 (GLS1) inhibitors in von Hippel–Lindau (VHL)- deficient renal cell cancers (RCC) pointing to new potential therapeutic combinations (Okazaki et al, J Clin Invest. 127:1631, 2017). Dr. Keith Flaherty and his colleagues reported on the five-year analysis of combination BRAF inhibitor dabrafenib and MEK inhibitor trametinib versus monotherapy for patients with BRAF V600-mutant metastatic melanoma, demonstrating durable long term overall survival in a subset of patients (Long et al, J Clin Oncol. 74:1025 2017).

4. Quality of Care and Palliative Therapy:
Drs. Jennifer Temel and Areej El-Jawahri conducted a randomized clinical trial of early and focused palliative care in patients with hematologic malignancies, demonstrating a remarkable and sustained improvement in symptoms of depression and post-traumatic stress at six months following bone marrow transplantation (Lage et al, J. Clin Oncol. 35: 3714, 2107). This study builds on their paradigm-shifting clinical studies on the benefit of early integration of palliative care interventions in cancer treatment.

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.

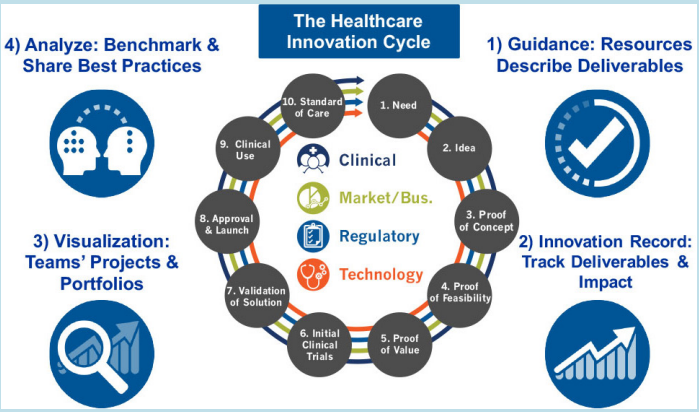
CIMIT leadership and its funded investigators conducted a Clinical Impact Study to assess the outcomes of supported projects and learn how to improve innovation in healthcare. The first study was conducted in 2012 (CIS; http://cimit.org/web/cimit/clinical-impact) and was updated in 2014. Based on the 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 one or more team members.

Joint Warfighter Program continued with incremental funding to CIMIT of $2.4M of direct costs towards the research of MGH investigators in cutting-edge, commercializable projects: Robert Redmond, Julian Goldman, Rajiv Gupta, and Mark Ottensmeyer.

CIMIT's participation in B-BIC. John Parrish, CIMIT CEO, is a co-Principal Investigator for the NHLBI-funded Boston Biomedical Innovation Center (B-BIC) and CIMIT Accelerator Executive Paul Tessier served on its Technology Assessment and Development Group. In that capacity, Paul provided coaching to investigators on commercialization of translational research and in preparing B-BIC grant applications.

CIMIT's CRAASH Course

In 2017, CIMIT continued to hold healthcare commercialization boot camps. 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.



GAITS builds on the Healthcare Innovation Cycle as a foundation to support teams and portfolio managers so they can learn and use best practices with four interrelated functions: guidance, innovation record, visualization, and analysis.

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. 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 ten 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

MGH Dermatology has a long and distinguished role in the history of modern dermatology. This has manifested itself in the delivery of 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, with outstanding medical care that is tightly linked to our commitment to move our understanding of skin diseases into new frontiers of understanding and innovation. Our department houses an extremely busy dermatology clinic that cares for >1000 patients per week. In additional to general dermatology 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 Consult Team. 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 (CBRC), which houses laboratories of 14 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. 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 2017, research and scholarly activities undertaken by faculty in the Department of Dermatology gave rise to 254 publications, as well as 259 speaking engagements. $18.2M 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 with researchers across Harvard Medical School. A research program in Cancer Immunotherapy was recently initiated as a partnership with MGH Cancer Center. Our Dermatologic Epidemiology Program includes active partnership with Harvard Medical School's Population Medicine Department. 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, 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.

Cunningham TJ, Tabacchi M, Eliane JP, Tuchayi SM, Manivasagam S, Mirzaalian H, Turkoz A, Kopan R, Schaffer A, Saavedra AP, Wallendorf M, Cornelius LA, Demehri S. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. J Clin Invest. 2017 Jan 3;127(1):106-116. doi: 10.1172/JCI89820. Epub 2016 Nov 21.

Actinic keratosis are common pre-malignant lesions of the skin which can progress to squamous cell carcinomas. This study utilized a combination of genetically engineered mouse models as well as a prospective double-blind human clinical trial to mechanistically dissect and test a small molecule inducer of TSLP, as a topical immunotherapy approach to treat these lesions. The study demonstrated 87% efficacy in actinic keratosis reduction in the test group vs 26% reduction in the control arm ($p < 0.0001$). This work thus identified a clinically available novel mechanism-based immunotherapy for treatment of early skin neoplasms.

Kawakubo M, Demehri S, Manstein D. Fractional laser exposure induces neutrophil infiltration (N1 phenotype) into the tumor and stimulates systemic anti-tumor immune response. PLoS One. 2017 Sep 18;12(9):e0184852. doi: 10.1371/journal.pone.0184852. eCollection 2017.

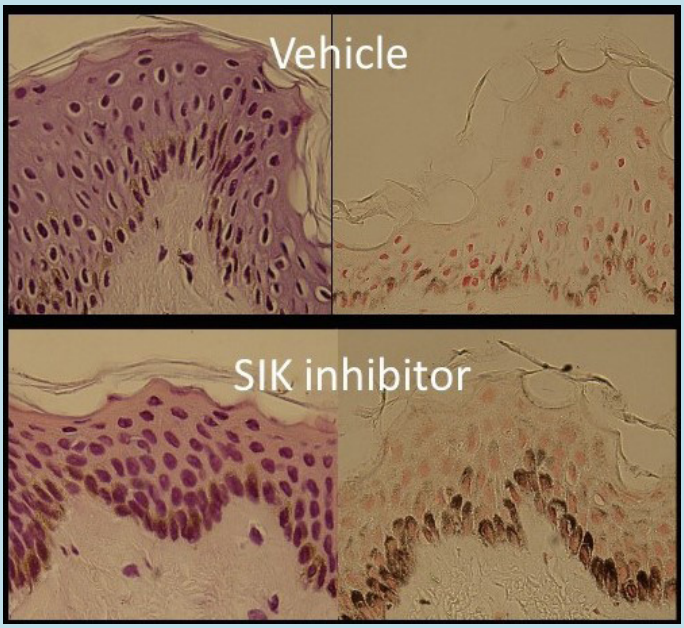
Despite the excitement of immunotherapy as a clinically successful modality in the treatment of melanoma, lung cancer, and other tumor types, many human malignancies remain profoundly resistant to the current set of immune checkpoint inhibitors. The current study utilized a specific laser device invented at MGH/Wellman, to trigger localized immune infiltration within a tumor that otherwise exhibited minimal immune treatment responses. The net effect was production of systemic immunity, manifest by the ability to clear distant lesions and to resist re-challenge by the autologous cancer. The mechanism involved eradication of Treg cell populations.

Kim DE1, Procopio MG1, Ghosh S1, Jo SH2, Goruppi S2, Magliozzi F1, Bordignon P1, Neel V3, Angelino P4, Dotto GP5,2. Convergent roles of ATF3 and CSL in chromatin control of cancer-associated fibroblast activation. J Exp Med. 2017 Aug 7;214(8):2349-2368. doi: 10.1084/jem.20170724. Epub 2017 Jul 6.

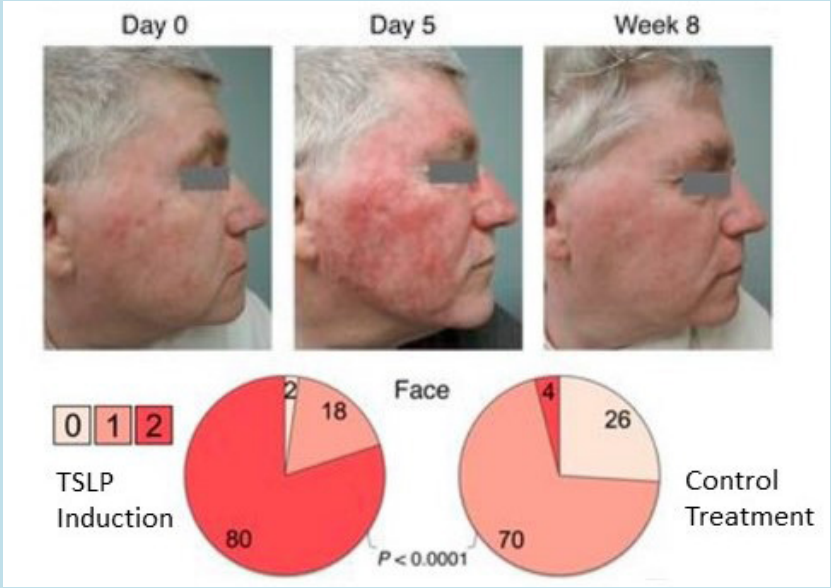
The tumor microenvironment is well known to confer significant growth properties on both tumor initiation and promotion. This study identifies a mechanistic convergence of two key modulators which suppress activation of cancer-associated-fibroblasts: the stress-responsive transcriptional repressor ATF3 and the Notch pathway antagonist CSL. Here ATF3 and CSL are shown to be epigenetically and functionally related to each other and to CAF activation. Further, bromodomain/BET inhibitor treatments are shown to counteract the effects of ATF3 or CSL loss on CAF-tumor-promoting properties in an in vivo model of squamous cancer stromal expansion.

Mujahid N, Liang Y, Murakami R, Choi HG, Dobry AS, Wang J, Suita Y, Weng QY, Allouche J, Kemeny LV, Hermann AL, Roider EM, Gray NS, Fisher DE. A UV independent topical small molecule approach for melanin production in human skin. Cell Reports 2017; 19(11):2177-2184.

The vast majority of human skin cancers arise are associated with UV carcinogenesis, and arise within skin that is largely lacking dark/eumelanin pigmentation. Individuals with "easy" UV-tanning dose-response capacity typically carry lower skin cancer risk than people who are unable to tan, or tan with difficulty. This study identified a small molecule target called Salt Inducible Kinase (SIK) as a druggable candidate for stimulation of human skin pigmentation following administration of topical kinase inhibitors designed for human skin penetration. The resulting skin darkening was potent, reversible, and mechanistically linked to a genetically validated pathway controlling eumelanin synthesis.



Histologic examination of human skin treated with topical small molecule SIK inhibitor. The left images show H&E staining, with minimal changes noted. The right images show control/vehicle (top) as compared to SIK inhibitor-treated (bottom) using a melanin stain (Fontanna-Masson). Strong eumelanin induction is noted by SIK inhibitor, and the melanin is also seen to be exported from melanocytes to perinuclear location of overlying keratinocytes within the basal epidermis, thereby mimicking UV-induced pigmentation.



Results of a clinical trial testing topical application of the TSLP inducing agent calcipotriol to produce regression of actinic keratosis lesions. Facial images demonstrate the anticipated inflammatory induction at 5 days followed by striking clearance by 8 weeks. The lower pie charts quantify degrees of purposefully induced erythema, which are significantly enhanced by the TSLP inducing treatment.

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 life-threatening 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 injury and illness. 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 healthcare policy.

The Emergency Medicine Clinical Research team. The EM Clinical Research leadership seated in front, from left to right, are: Nick Giordano, MS; Michael Filbin, MD, MSc (Research Director); Blair Alden Parry, CCRC, BA (Senior Manager); and John T. Nagurney, MD, MPH.

Over the past year we have continued to broaden our research portfolio to include more studies on pediatrics, geriatrics, vascular emergencies, 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 2018
1. Develop 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. Leverage Epic to enable automated data acquisition methods where possible, as well as develop reliable data collection and storage methods when automation not possible, to support both interventional and observational investigations. Develop automated alerts in Epic to assist in screening for clinical trials.

3. Identify and implement alternative staffing models (for both clinical investigator coverage & research staff) to optimize efficiency in subject recruitment to allow growth of our diverse departmental research portfolio.

Achievements
1. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant C, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. BMJ 2017; 356: i6583. doi: 10.1136/bmj.i6583. PMID: 28202713.

This international collaboration examined the overall effect of vitamin D supplementation on risk of acute respiratory infection, and identified factors modifying this effect. Individual participant data were obtained from ~11,000 participants in 25 eligible randomized controlled trials worldwide. Vitamin D supplementation was safe and protected against acute respiratory infection overall (adjusted OR 0.88, 95%CI 0.81-0.96; P for heterogeneity <0.001). Patients who were very deficient (25OHD <25 nmol/L or <10 ng/ml) and those not receiving bolus doses experienced the most benefit.

2. Zeleznik OA, Poole EM, Lindstrom S, Kraft P, Van Hylckama Vlieg A, Lasky-Su JA, Harrington LB, Hagan K, Kim J, Parry BA, Giordano N, Kabrhel C. Metabolomic Analysis of 92 Pulmonary Embolism Patients from a Nested Case-control Study Identifies Metabolites Associated with Adverse Clinical Outcomes. J Thromb Haemost. 2017 Dec 29. doi: 10.1111/jth.13937. PMID: 29285876.

Little is known about metabolic changes that differentiate low-risk from high-risk pulmonary embolisms (PEs). Kabrhel et al. put together the first ever high-throughput metabolomic analysis of PE risk. Comparing metabolites of low-risk and intermediate/high risk PE patients we identified significant differences in 50 metabolites after multiple testing correction, specifically in the following metabolic pathways: TCA Cycle, Fatty Acid Metabolism (Acyl Carnitine), and Purine Metabolism, (Hypo)Xanthine/Inosine Containing. The results from this study suggest that modern metabolomics can provide insight into the pathophysiology of PE and that metabolites may be useful in the risk stratification of PE.

3. Pruitt P, Van Ornam J, Borczuk P. A Decision Instrument to Identify Isolated Traumatic Subdural Hematomas at Low Risk of Neurological Deterioration, Surgical Intervention or Radiographic Worsening. Acad Emerg Med. 2017; 24(11): 1377–1386.

Subdural hematomas (SDH) are the most common type of hemorrhagic intracranial injury seen after head trauma. While the clinical presentation of SDH is heterogeneous and can vary from mild headache to coma, the disposition of all these patients has been uniform and include transfer to a level one trauma center for neurosurgery consultation with observation. This study identifies a very low risk group of patients who are unlikely to suffer any serious consequences or interventions as well as validates this model on an independent patient cohort. Individuals with a Glasgow coma score of 15, a SDH <= 5mm in thickness, no evidence of midline shift on CT, and who are not on warfarin or clopidogrel form such a group who do not need transfer to a level 1 trauma center.

4. Sri-On J, Tirrell GP, Bean JF, Lipsitz LA, Liu SW. Revisit, Subsequent Hospitalization, Recurrent Fall, and Death Within 6 Months After a Fall Among Elderly Emergency Department Patients. Ann Emerg Med. 2017 Oct;70(4):516-521.e2.

The importance of geriatric medicine and addressing the needs of this ever-increasing subset of our population is evident in the practice of medicine. The impact of the aging population on healthcare is felt particularly in the Emergency Department. Elderly falls constitute an emerging public health issue that has been Dr. Liu's primary research focus. This investigation highlights the prognostic importance associated with an ED visit for fall, and the high incidence of 6-month adverse events. This work provides justification for focusing resources on this vulnerable patient population and providing adequate outpatient resources to address the risk.

Dr. Clark, Dr. Sriram and selected nurses from Victoria Hospital traveled from Prince Albert, Saskatchewan, Canada, to Kenya to be trained on the Every Second Matters – Ketamine (ESM-Ketamine) package in December 2017. Sagam Community Hospital staff led the training, with oversight from Dr. Thomas F. Burke, Founder and Chief of the MGH Division of Global Health and Human Rights.

The Emergency Medicine Network (EMNet) research team. EMNet was founded in 1996 and has a mission to advance public health objectives through diverse projects in emergency care, particularly multicenter clinical research. The EMNet leadership seated in front, from left to right, are: Kohei Hasegawa, MD, MPH; Ashley Sullivan, MS, MPH (Associate Director); Carlos Camargo, MD, PhD (Director); and Janice Espinola, MPH.

Medicine

Department Report

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

As the largest of the MGH Departments, the Department of Medicine is integral to the MGH mission statement:
"Guided by the needs of our patients and their families, we aim to deliver the very best health care in a safe, compassionate environment; to advance that care through innovative research and education; and to improve the health and well-being of the diverse communities we serve."

The Department plays a key role in the MGH and MGPO strategic and operational priorities, including the ongoing commitment to high quality care, population health, and workforce diversity. In addition, the Department and faculty leaders are central to the implementation of the recent MGH/MGPO strategic plan recommendations including the establishment of an MGH Research Institute, optimization of inpatient flow, and development of a specialized services center to grow international and other business.

The Department of Medicine Roadmap for the next decade was designed to synergize with the MGH/MGPO priorities by identifying cross-cutting Departmental goals that link to the four missions of clinical care, research, education, and community health. Each goal supports the overall priorities of the MGH and MGPO and enables the development of Departmental activities that span one, two, three or even all four missions. Having cross-cutting goals serves to create connections and collaboration across the Department, to increase the efficiency of Departmental support, and to assist with resource prioritization.

In the **Cardiology Division**, Ahmed A. Tawakol defined a mechanism linking stress to adverse cardiovascular events. His study demonstrates for the first time that resting metabolic activity within the amygdala significantly associates with the risk of developing cardiovascular disease (CVD) independently of other established risk factors (1). Further, it found that a) the link between amygdalar activity and CVD events was substantially mediated by arterial inflammation, and b) the link between amygdalar activity and arterial inflammation was substantially mediated by upregulated bone marrow activity. These observations provide new and important insights, specifically that: 1) the amygdala may be a key structure in the mechanism linking stress to CVD events, and 2) up-regulation of hematopoietic tissue activity and increased atherosclerotic inflammation are additionally implicated in a neural-hematopoietic-arterial axis resulting in CVD. The observations of the current study provide heretofore unrecognized answers to an important medical question that has long been shrouded in mystery, namely, how stress causes physical illness. In other noteworthy work in the Cardiology Division, Ik-Kyung Jang in a prospective study, tested the hypothesis that patients with acute coronary syndromes (ACS) might be treated differently depending on their underlying pathophysiology (2). In 25% (103/405) of patients with ACS, the underlying mechanism was plaque erosion which was diagnosed by optical coherence tomography. When these patients with erosion were treated with effective anti-thrombotic therapy without stent implantation, 78% of them met the primary endpoint (> 50% reduction of intracoronary thrombus volume) and 40% had no residual thrombus at one month. While we tend to treat ACS as a "one size fits all", this study suggests advanced imaging can provide clinically meaningful insights into ACS mechanisms and differing plaque biology, that ultimately may enable us to individualize the treatments we offer our patients.

In interdisciplinary work from a team of cardiologists and immunologists at the **Cardiovascular Research Center** and Center for Systems Biology, David Milan, Patrick Ellinor, Matthias Nahrendorf described a completely new participant in cardiac conduction: the macrophage (3). This comes as a surprise, because normally these leukocytes are associated with innate immune functions such as phagocytosis of bacteria. Triggered by the serendipitous observation that macrophage depletion causes atrioventricular block in mice, the team describes that these cells are a numerous presence in the murine and human cardiac conduction system. Macrophages couple electrically to cardiomyocytes via gap junctions, leading to rhythmic depolarization of macrophages in sync with neighboring cells. In a sink-source relationship, electric current flows back and forth between macrophages and cardiomyocytes. When macrophages are manipulated, the flow of electricity slows down, and may even cease altogether. Such a condition requires pacemaker treatment in humans. These findings jolt the field of electrophysiology and may lead to new therapeutic opportunities for patients with cardiac arrhythmias. The data were obtained with the latest technologies available at MGH, including many "firsts": among them are single cell RNA sequencing of AV node macrophages, multiphoton imaging of optically cleared mouse and human AV nodes, patch clamp of cardiac macrophages and the first application of optogenetics to macrophages.

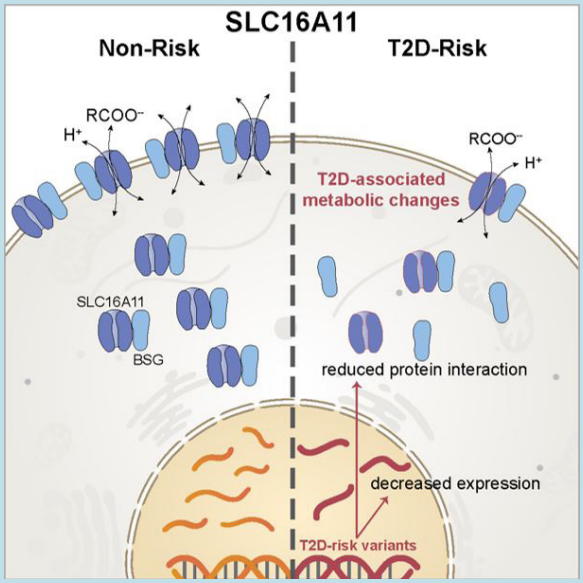
The **Clinical and Translational Epidemiology Unit**, a new research unit in the Department of Medicine, studied whether patients who have been diagnosed with colorectal cancer would benefit from high fiber consumption. In a study published in JAMA Oncology in November 2, 2017, Mingyang Song examined post-diagnosis fiber intake in relation to long-term survival outcomes, among 1,575 patients with nonmetastatic colorectal cancer drawn from two large Harvard cohort studies. It was found that each 5-g increment in fiber intake per day was associated with 22% lowered risk of dying from colorectal cancer and 14% lowered risk of dying from any cause. Patients who increased their fiber intake after diagnosis from levels before diagnosis had a substantially better survival. When different food

sources of fiber were examined, cereal fiber and whole grains appeared to be the driving source for the beneficial effect. These observational provide the first line of scientific evidence for a potential benefit of high-fiber diet on colorectal cancer survivorship. Compelling evidence has implicated a mediating role for the gut microbiome, the population of microbes living in the large intestine, in human health and disease. However, many of these studies are limited in their design – specifically, many are cross-sectional or restricted by the number of individuals or type of patient population that contributes to the analysis. In 2012, Andrew Chan set out to prospectively collect stool samples from more than 300 elderly men nested within the Health Professionals Follow-up Study. Using state-of-the-art computational approaches in collaboration with Dr. Curtis Huttenhower's group at the Broad Institute, their initial characterization of the whole shotgun metagenomic and metatranscriptomic sequencing data (deeper profiling than 16S profiling) was published in two companion manuscripts with Nature Microbiology. Raaj Mehta, a 2nd year internal medicine resident at MGH, and Galeb Abu-Ali, of the Broad Institute, worked to demonstrate that gut organismal composition and metagenomic profiles remain highly personalized over time, whereas metatranscriptomic profiles were much more variable. However, further characterization of the metatranscriptome led them to discover that there is "core" metatranscriptome, or a subset of microbial pathways primarily involved in housekeeping functions, that is constitutively and stably expressed between individuals and across time, even when that function is being provided by different microbes. The remaining "variable" metatranscriptome is enriched for specialized processes including secondary metabolism and stress adaptation, which may vary due to different exposures or health states in an individual over time. Combined, these results support single-time point assessment as a representative measure of a person's microbiome using metagenomes, however, multiple time point assessments may be needed to accurately measure metatranscriptome elements. Moving forward, these findings lay the groundwork towards implementing population-scale stool collection efforts to prospectively determine the role of the gut microbiome in health outcomes.

The **Disparities Research Unit** successfully completed an ambitious clinical trial funded by the Patient Centered Outcomes Research Institute. The results of this study are in press in JAMA Psychiatry. The study is the first of its kind, as a randomized controlled trial conducted with ethnic/racial minorities in behavioral healthcare, focused on improving shared decision-making (SDM) and quality of care. We tested the effectiveness of a patient (DECIDE-PA) and provider (DECIDE-PC) intervention in improving SDM, and patient-perceived quality of care among white, Black, Latino, and Asian patients. We enrolled more than 300 patients and nearly 80 providers in the trial, spanning 13 behavioral health clinics throughout Massachusetts. The results suggest that the provider intervention could improve SDM with minority populations and the patient intervention can help improve patient reported quality of care - both by incorporating patient preferences. The Disparities Research Unit also finalized one of the only longitudinal studies of Puerto Rican adolescents growing up in two contexts, and one of the few studies following children into young adulthood to address the development of Depression and Anxiety disorders. This National Institute of Mental Health-funded study addresses the long-term effects of early experiences of minority status and neighborhood context on Latino young-adult behavioral health by comparing the experiences of Puerto Rican youth growing up in Puerto Rico and in the South Bronx. The study follows up a cohort of 2000 youth as young as 5-13 years old in the original first wave of the Boricua Youth Study, through the fourth wave of data where they are young adults (mean age of 23). Our follow-up rates for the study exceeded our goal, with an 82.78% response rate for eligible youth and a 73.57% response rate for eligible parents who were interviewed in Wave 1 of the original study. Our findings provide important data on the development of depression and anxiety among youth growing up in different social contexts and how the experience of minority status can be a risk factor for behavioral health problems in young adulthood.

The **Endocrine Division** has a robust and diversified research program. Within the Division, Murat Bastepe from the Endocrine Unit recently reported a major advance towards understanding the role of XLαs, an imprinted variant of the stimulatory G protein alpha-subunit (Gsα), which mediates the actions of numerous endogenous agonists via generation of cAMP (4). XLαs and Gsα are both encoded by the GNAS complex locus, mutations of which are found in many tumors and several inherited diseases. Following a proteomic screen, they found that XLαs interacts with sorting nexin-9 (SNX9) and dynamins, which play essential roles during clathrin-mediated endocytosis, a fundamental cellular process necessary for nutrient uptake and regulation of cell signaling. Their investigations using a series of methods involving CRISPR/Cas9-mediated gene editing and transgenic mice revealed that XLαs acts as an inhibitor of clathrin-mediated endocytosis and, thereby, plays a critical role in tissue iron uptake. This action of XLαs is most remarkable in the heart and skeletal muscle, where it is abundantly expressed. As expected, XLαs also inhibits the agonist-induced internalization of G protein-coupled receptors, which depends on clathrin-mediated endocytosis. Additional experiments suggested that the action of XLαs in endocytosis does not depend on its G protein function and involves alterations of endogenous SNX9 levels. This study thus provides novel insights into the regulation of iron metabolism and the mechanisms regulating endocytosis. In another noteworthy discovery from the Endocrine Unit, Hank Kronenberg found that once daily administration of teriparatide increases the number of osteoprogenitor cells in vivo (5). Teriparatide is a recombinant form of parathyroid hormone, approved for the treatment for osteoporosis that increases the rate of bone formation. While teriparatide increases osteoblast numbers by suppressing osteoblast apoptosis and activating bone-lining cells it had been unclear whether teriparatide also acts on osteoprogenitor cells in vivo. They also discovered that teriparatide increases the numbers of early cells of the osteoblast lineage, hastens their differentiation into osteoblasts, and suppresses their differentiation into adipocytes in vivo.
Steven Russell from the **Diabetes Unit** of the Endocrine Division has been developing an integrated closed-loop device (the 'bionic pancreas')

that can manage insulin and glucagon infusions, resembling the native endocrine organ, solely in response to glucose levels. A critical problem in the care of patients with type 1 diabetes, who require round-the-clock insulin treatment, is maintaining an adequate level of glycemic control. While maintaining glucose in the normal range is crucial to avoid long-term complications, doing so too aggressively can cause life-threatening hypoglycemia. Thus there is a narrow therapeutic range, and insulin needs are constantly altered by carbohydrate intake and energy expenditure. The development of new technologies such as continuous insulin pumps or continuous glucose sensors can help, but require a tremendous amount of mental effort on the part of patients wearing these devices. Earlier this year they tested their device and algorithm in a cross-over clinical trial in adults, in comparison with the most advanced standard of care (conventional or sensor-augmented insulin pump therapy) (6). While participants wore the new 'bionic pancreas' they experienced less hyperglycemia and fewer hypoglycemic episodes, effectively maintaining their glucose in the very narrow therapeutic range. The device was only initialized with body mass information and used the participants' own physiology to calibrate its function, without the need to intervene with carbohydrate counting or other forms of constant user attention, other than initial placement. This device has the potential to revolutionize the way care is delivered to patients with type 1 (and possibly type 2) diabetes. This clinical trial was pivotal in demonstrating efficacy and safety, and suggests that approval and marketing are imminent. In 2014, Jose Florez from the Diabetes Unit and the SIGMA T2D Consortium identified a new genetics risk factor for type 2 diabetes (T2D) of relatively strong effect in a locus containing an uncharacterized solute carrier, SLC16A11. Earlier this year, Jose Florez and his collaborators at the Broad Institute built upon the previously reported genetic association at the SLC16A11 locus and took the first key steps toward establishing the biological mechanism by which genetic variation at this locus impacts T2D risk, which is essential for clinical translation of genetic discoveries (7). To elucidate the function of this previously uncharacterized solute carrier, they established that SLC16A11 is a proton-coupled monocarboxylate transporter, and described two independent mechanisms through which variants at this locus reduce SLC16A11 activity: a) the T2D risk haplotype contains a cis-eQTL affecting SLC16A11 expression in human liver, reducing levels by approximately 42% in individuals heterozygous for the risk allele and 66% in homozygous carriers; and b) the T2D associated coding variants in SLC16A11 disrupt a crucial interaction with a chaperone protein, basigin, leading to a 60% reduction in SLC16A11 at the cell surface and reduced function of the transporter. They estimated that homozygous carriers may have up to ~85% less SLC16A11 at the cell surface and this is likely to be the causal mechanism underlying increased T2D risk. This work represents a major advance in translating the genetic association at 17p13, identifying SLC16A11 as the causal gene, liver as a relevant tissue, and two independent mechanisms acting in the same direction of effect. The results raise the therapeutic hypothesis that increasing SLC16A11 activity might be beneficial in treating T2D. More generally, this paper illustrates how investigators may traverse the arduous path from genetic association to causal variant, disease mechanism and clinical impact.



Therapeutics that enhance SLC16A11 levels or activity may be beneficial for type 2 diabetes (Ruso et al. Cell 2017, ref 7)

Studies from **Reproductive Endocrine Unit** have identified TCF12 as critical transcriptional regulator of Gonadotropin-releasing hormone (GnRH) neuronal development. Whole exome sequencing analysis in 300 individuals with Kallmann Syndrome (KS; an anosmic form of human GnRH deficiency) revealed six unrelated KS individuals harboring autosomal dominant loss-of-function mutations in the TCF12 gene which encodes a basic-helix-loop-helix transcription factor. Tcf12 loss of function modeling in zebrafish larvae perturbed GnRH neuronal patterning with concomitant attenuation of the expression of several genes that are both mutated in other syndromic forms of KS, mapping a novel TCF12 network. Restoration of STUB1 mRNA, one of the genes in the TCF12 affinity network, rescued loss of Tcf12 in vivo. This work is in review and was awarded the 2017 MGH Clinical Research Day Clinical Translational Research Award. These findings uncover a previously unknown TCF12 affinity network that regulates the development of the GnRH axis in humans. Since TCF12 mutations have been previously implicated in syndromic craniosynostosis, these data now highlight a novel genetic link between GnRH ontogeny and craniofacial patterning. Other studies from the Reproductive Endocrine Unit tested provocative neuropeptide stimulation in children to uncover the pathophysiology of pubertal delay. Delayed puberty, which has long term health consequences, presents a clinical challenge. The most common cause of delayed puberty is constitutional delay, a self-limited condition in which puberty starts late but progresses normally. However, a small proportion of children presenting with delayed puberty have idiopathic hypogonadotropic hypogonadism (IHH), a lasting reproductive endocrine deficit caused by defective secretion or action of GnRH. The challenge lies in distinguishing between these two diagnoses. Currently, there is no method to predict whether a given patient will eventually enter puberty; a definitive diagnosis can only be made retrospectively, when the patient is found to enter puberty or not. To address this long standing, unmet clinical need, investigators in the Reproductive Endocrine Unit conducted

a "first-in-child" study to probe GnRH neuronal physiology in children. Their research team administered kisspeptin, an experimental drug, to children with delayed puberty under the umbrella of United States Food and Drug Administration's Investigational New Drug (IND) program. They showed that children with pubertal delay are either kisspeptin responders or non-responders. No other human population (healthy or diseased) that has received kisspeptin has shown this degree in variation in kisspeptin responsiveness. Thus, being a kisspeptin responder vs. a non-responder may be clue to the underlying pathophysiology of delayed puberty. Moreover, this data represents the possibility for the development of a future a future diagnostic test that can distinguish self-limited constitutional delay of puberty from abiding IHH.

Research in the **Division of Gastroenterology** made noteworthy progress in intestinal biology, inflammatory bowel disease (IBD) and liver disease. Studies from Ramnik Xavier's laboratory from the GI Unit and Aviv Regev from the Broad Institute used single cell RNA sequencing techniques to describe for the first time the cell circuitry of the small intestine that offers the promise of understanding the disruption of this circuitry in intestinal diseases (8). In the realm of IBD, genetic variants previously identified by GI Unit investigators (CARD9) that predispose to IBD were effectively targeted Dr. Xavier using small molecule screening approaches thus opening up ways to translate this discovery to the clinic (9). Studies by Kate Jeffrey clarified a functional role for the epigenetic reader SP140, a polymorphism of which is found in Crohn's disease, in maintaining macrophage transcriptional programs and innate immunity in the intestinal tract (10). Important work was also done in liver disease by Greg Lauer's group. Transcriptional profiling of CD8 T cells early in acute hepatitis C virus infection revealed divergence of profiles of T cells associated with development of chronic persistent infection as compared with spontaneous clearance of infection. These profiles thus reveal the early events associated with failure to control infection (11). Additional work capitalizing on the use of a novel assay for the induction of quiescence of activated hepatic stellate cells, the prime mover in hepatic fibrosis, for a high throughput small molecule screen, performed by Alan Mullen revealed that tricyclic antidepressants can inhibit activated stellate cells through inhibition of acid ceramidase and alterations in the sphingolipid pathway, a heretofore untapped and promising antifbrotic therapeutic target (12). This work reveals the promise of unbiased discovery approaches in simultaneously opening new pathways for therapeutics development and disease pathogenesis.

The Division of **General Internal Medicine** had several noteworthy publications this year. Anne Thorndike demonstrated that a simple choice architecture intervention to improve the visibility and quality of fresh produce resulted in increased purchase of fruit and vegetables by corner store customers participating in the WIC program, based on objective state-level data (13). In the future, the United States Department of Agriculture might consider policies for WIC and SNAP-certified stores that encourage displaying fruit and vegetables and other healthy choices in highly visible locations, such as the front of the store. These policies could help improve healthy food choices and reduce disparities in obesity in low-income families. Daniel Singer performed a systematic review of cohort studies and randomized trials and found highly heterogeneous estimates of overall and CHADS-VASc stratified stroke risks (14). For example, for a CHADS-VASc score of 2, 27% of studies reported stroke rates below 1%/year and 40% reported stroke rates between 1 and 2%/year, where rates of 2+ %/year are needed for anticoagulants to confer net clinical benefit. Rates differed markedly between adjacent countries (Sweden vs Denmark) arguing that methodologic differences were a major source of heterogeneity. These results call into question the scientific basis of leading guidelines "risk-based" recommendations for use of anticoagulants in patients with AF. James Meigs published a study demonstrating how new genetic information can inform public health efforts to reduce health disparities and control the current diabetes epidemic (15). A large international genetics research team (named MAGIC – Meta Analysis of Glucose and Insulin Consortium) identified 60 gene variants – 42 for the first time – that influence blood levels of Hemoglobin A1c (A1C), used both to diagnose and manage diabetes. Together, 60 variants had modest influences on A1C in white Americans, but just one variant found only in African Americans (in the gene for the red blood cell enzyme G6PD) significantly reduced the accuracy of A1C testing in carriers, such that the research team estimated about 650,000 African Americans would be missed if screened for diabetes using HbA1c alone.

Rachel LaRocque from **Division of Infectious Diseases** used data from Global TravEpiNet, a CDC-supported consortium of 24 sites that provide pretravel medical advice, to describe how providers assessed the measles immunity status and reasons given for nonvaccination among those considered eligible to receive the measles-mumps-rubella (MMR) vaccine (16). Measles outbreaks in the US persist due to imported cases of under-vaccinated U.S. travelers who acquire infection with measles while abroad and infect others following their return to the U.S. The study included 40,810 adult travelers, of whom providers considered 6,612 (16%) to be eligible for MMR vaccine at the time of pretravel consultation. Of the MMR-eligible travelers, more than half (53%) were not vaccinated at the visit due to traveler refusal (48%), provider decision (28%), or health systems barriers (24%). Most MMR-eligible travelers who were not vaccinated were evaluated in the South or at nonacademic centers. Findings highlight that measles immunity could be improved among US international travelers, which should substantially reduce the risk of measles importation and, by extension, decrease the number of new measles cases seen due to transmission within the U.S. Measles education strategies should also be targeted to both providers and travelers and should focus on geographic regions with low uptake of MMR vaccination for international travelers.

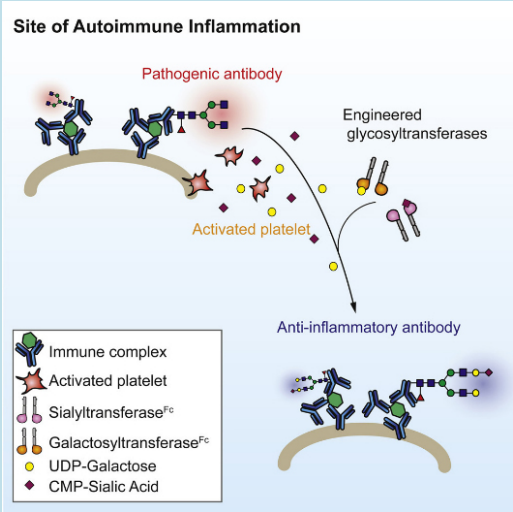
Medical Practice Evaluation Center investigator Rochelle Walensky used a computer model to estimate the risk of dying from lung cancer among people with HIV, according to whether they smoke as over 40% of people with HIV in the US smoke cigarettes. HIV itself increases the

risk of lung cancer. Her team found that those who take antiretroviral medicines but smoke have a nearly 25% risk of dying from lung cancer, approximately 10 times higher than their risk of dying from HIV/AIDS (17). They projected that nearly 10% of all people in HIV care in the US will die from lung cancer if smoking patterns do not change. Smoking cessation should be a priority in HIV care. Potential contractions in international funding may force resource-limited nations to scale back their public health responses to HIV. This team also used a simulation model to forecast the clinical, epidemiologic, and budgetary outcomes resulting from alternative scale-back strategies in two such nations: South Africa and Côte d'Ivoire. At 10 years, we found that these strategies would result in budgetary savings of up to 30% and increases in HIV deaths of up to 39%. The most efficient strategies would save $600-900 for each year of life lost. Scaling back international aid would have severe adverse health consequences. Certain strategies resulted in less clinical and public health harm than others; these may represent better options for HIV program reduction if recipient nations are forced to respond to cutbacks in foreign aid.

In the **Division of Nephrology**, Jodie Babitt made important contributions to understanding how the liver senses body iron levels and erythropoetic demands to control production of the main iron regulatory hormone hepcidin, thereby maintaining systemic iron homeostasis and an adequate iron supply for erythropoiesis. Based on its ability to donate and accept electrons, iron has a critical role in many fundamental biological processes including oxygen and electron transport, cellular respiration, and DNA synthesis, making iron essential for nearly all living organisms. However, this same property makes excess iron toxic by generating free radicals that can lead to cell death. Dysregulation of iron homeostasis leads to many common diseases such as anemia, thalassemia, and the iron overload disorder hemochromatosis that in aggregate affect nearly 1 billion people. The Babitt lab discovered that liver endothelial cells are the main source of bone morphogenetic protein 6 (BMP6), a critical signaling molecule that has paracrine effects to control the transcription of hepcidin in hepatocytes (18). Moreover, she discovered that in addition to BMP6, endothelial cell derived BMP2 is also a critical regulator of hepcidin production (19). Finally, she demonstrated that erythroferrone, a signaling molecule released by proliferating erythrocyte precursors in the bone marrow, targets the SMAD signaling pathway to control hepatic hepcidin production in response to erythropoietic demands (20). These findings reveal important insights into how cells and tissues communicate to control systemic iron homeostasis to provide adequate iron for growth and survival but to limit the toxicity of iron excess. In other work in the Nephrology Division, a basic scientist Teodor Paunescu and a clinical researcher Sagar Nigwekar established an innovative collaboration and led a clinical research program that quantified odor identification, odor threshold, and subjective odor perception in a prospective cohort (n=161) comprising 36 participants with chronic kidney disease, 100 participants with end-stage kidney disease, and 25 controls (21). Olfaction is fundamental to optimal nutrition. Anorexia and malnutrition are major contributors to morbidity and mortality in kidney disease, but whether the olfaction-nutrition axis in these patients is modifiable is unknown. The mean odor identification score was lower in patients with chronic kidney disease (75.6%) and end-stage renal disease (66.8%) than in controls (83.6%), whereas all groups had similar scores for subjective smell assessment. A reduction in odor identification score was associated with higher subjective global assessment score and lower serum total cholesterol, low-density lipoprotein cholesterol, and albumin concentrations. In a 6-week, open-label clinical trial, intranasal theophylline increased odor identification score in 71% patients with end-stage renal disease. In conclusion, this study demonstrated that patients with kidney disease have olfactory deficits that influence their nutritional status and these deficits may be corrected using nasal theophylline.

In the **Division of Pulmonary and Critical Care Medicine**, David Lagares had two important publication this year. In one of these studies published in Nature Medicine, he uncovered a new molecular mechanism of tissue fibrogenesis by demonstrating that targeting the ADAM10-sEphrin-B2 pathway in scar-forming myofibroblasts prevents lung fibrosis and restores organ function (22). These findings reveal novel therapeutic targets for the treatment of a variety of human fibrotic diseases, such as idiopathic pulmonary fibrosis, systemic sclerosis, liver cirrhosis, kidney fibrosis and desmoplastic tumors. The identification of novel therapeutic strategies aiming at reducing tissue fibrosis and promoting the regeneration of damaged tissues is a major unmet clinical need in regenerative medicine. 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. David Lagares also demonstrated that fibroblast-to-myofibroblast differentiation driven by matrix stiffness increases the mitochondrial priming (proximity to the apoptotic threshold) of these activated cells (23). 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, we demonstrate 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, these findings elucidate the potential efficacy of targeting myofibroblast antiapoptotic proteins with BH3 mimetic drugs in scleroderma and other fibrotic diseases.

In the **Division of Rheumatology, Allergy & Immunology** and Center for Immunology & Inflammatory Diseases, Robert Anthony sought to convert endogenous IgG to anti-inflammatory mediators in vivo by engineering solubilized glycosyltransferases that attach galactose or sialic acid (24). Self-reactive IgGs contribute to the pathology of autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. Paradoxically, IgGs are used to treat inflammatory diseases in the form of high-dose intravenous immunoglobulin (IVIG). Distinct glycoforms on the IgG crystallizable fragment (Fc) dictate these divergent functions. IgG anti-inflammatory activity is attributed to sialylation of the Fc glycan. When both enzymes were administered in a prophylactic or therapeutic fashion, autoimmune inflammation was markedly attenuated in vivo. The enzymes worked through a similar pathway to IVIG, requiring DC-SIGN, STAT6 signaling, and Fcg RIIB. Importantly, sialylation was highly specific to pathogenic IgG at the site of inflammation, driven by local platelet release of nucleotide-sugar donors. These results underscore the therapeutic potential of glycoengineering in vivo. Self-reactive IgGs contribute to the pathology of autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. Paradoxically, IgGs are used to treat inflammatory diseases in the form of high-dose intravenous immunoglobulin (IVIG). Distinct glycoforms on the IgG crystallizable fragment (Fc) dictate these divergent functions. IgG anti-inflammatory activity is attributed to sialylation of the Fc glycan. The Anthony lab therefore sought to convert endogenous IgG to anti-inflammatory mediators in vivo by engineering solubilized glycosyltransferases that attach galactose or sialic acid. When both enzymes were administered in a prophylactic or therapeutic fashion, autoimmune inflammation was markedly attenuated in vivo. The enzymes worked through a similar pathway to IVIG, requiring DC-SIGN, STAT6 signaling, and Fcg RIIB. Importantly, sialylation was highly specific to pathogenic IgG at the site of inflammation, driven by local platelet release of nucleotide-sugar donors. These results underscore the therapeutic potential of glycoengineering in vivo and were published in Cell in February 2018 (24).



Glycosyltransferase fusion proteins convert endogenous IgG into anti-inflammatory IgG (Pagan et al. Cell 2017, ref 25)

In rheumatoid arthritis (RA), immunological triggers at mucosal sites, such as the gut microbiota, have been postulated to promote autoimmunity that affect joints. Allen Steere who are also member of our Center for Immunology and Inflammatory Diseases, recently demonstrated the relevance of the immune responses to Prevotella copri, a gut microbe, in RA patients (22). They recently published the first information linking microbial immunity and autoimmunity in joints in RA patients. Using discovery-based proteomics to detect HLA-DR-presented peptides in synovia or peripheral blood mononuclear cells, they identified two, novel autoantigens, N-acetylglucosamine-6-sulfatase (GNS) and filamin A (FLNA), as targets of T and B cell responses in 52% and 56% of RA patients, respectively. Both GNS and FLNA were highly expressed in synovia. These autoantibody responses were not found in patients with other rheumatic diseases or in healthy subjects. The HLA-DR-presented GNS peptide has marked sequence homology with epitopes from sulfatase proteins of Prevotella sp. and Parabacteroides sp., whereas the HLA-DR-presented FLNA peptide has homology with epitopes from proteins of Prevotella sp. and Butyricimonas sp., another gut commensal. Patients with T cell reactivity with each self-peptide also had responses to the corresponding microbial peptides, and the levels correlated directly. Furthermore, HLA-DR molecules encoded by RA shared-epitope alleles were predicted to bind these self and microbial peptides strongly, and these responses were more common in RA patients with shared-epitope alleles. Thus, sequence homology between T cell epitopes of two self-proteins and a related order of gut microbes may provide a link between mucosal and joint immunity in RA patients.

Literature Cited

1. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, Truong QA, Solomon CJ, Calcagno C, Mani V, Tang CY, Mulder WJ, Murrough JW, Hoffmann U, Nahrendorf M, Shin LM, Fayad ZA, Pitman RK. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet 2017; 389: 834-845.
2. Jia H, Dai J, Hou J, Xing L, Ma L, Liu H, Xu M, Yao Y, Hu S, Yamamoto E, Lee H, Zhang S, Yu B, Jang IK. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomogragphy-based management in plaque erosion (the EROSION study). European Heart Journal 2017;38:792-800.
3. Hulsmans M, Clauss S, Xiao L, Aguirre AD, King KR, Hanley A, Hucker WJ, Wülfers EM, Seemann G, Courties G, Iwamoto Y, Sun Y, Savol AJ, Sager HB, Lavine KJ, Fishbein GA, Capen DE, Da Silva N, Miquerol L, Wakimoto H, Seidman CE, Seidman JG, Sadreyev RI, Naxerova K, Mitchell RN, Brown D, Libby P, Weissleder R, Swirski FK, Kohl P, Vinegoni C, Milan DJ, Ellinor PT, Nahrendorf M. Macrophages Facilitate Electrical Conduction in the Heart. Cell 2017;169:510-522.
4. He Q, Bouley R, Liu Z, Wein MN, Zhu Y, Spatz JM, Wang CY, Divieti Pajevic P, Plagge A, Babitt JL, Bastepe M. Large G protein α-subunit XLαs limits clathrin-mediated endocytosis and regulates tissue iron levels in vivo. Proc Natl Acad Sci U S A. 2017;114:E9559-E9568

5. Balani DH, Ono N, Kronenberg HM. Parathyroid hormone regulates fates of murine osteoblast precursors in vivo. J Clin Invest. 2017;127:3327-3338.
6. El-Khatib FH, Balliro C, Hillard MA, Magyar KL, Ekhlaspour L, Sinha M, Mondesir D, Esmaeili A, Hartigan C, Thompson MJ, Malkani S, Lock JP, Harlan DM, Clinton P, Frank E, Wilson DM, DeSalvo D, Norlander L, Ly T, Buckingham BA, Diner J, Dezube M, Young LA, Goley A, Kirkman MS, Buse JB, Zheng H, Selagamsetty RR, Damiano ER, Russell SJ. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. Lancet. 2017;389:369-380.
7. Rusu V, Hoch E, Mercader JM, Tenen DE, Gymrek M, Hartigan CR, DeRan M, von Grotthuss M, Fontanillas P, Spooner A, Guzman G, Deik AA, Pierce KA, Dennis C, Clish CB, Carr SA, Wagner BK, Schenone M, Ng MCY, Chen BH; MEDIA Consortium; SIGMA T2D Consortium, Centeno-Cruz F, Zerrweck C, Orozco L, Altshuler DM, Schreiber SL, Florez JC, Jacobs SBR, Lander ES. Type 2 Diabetes Variants Disrupt Function of SLC16A11 through Two Distinct Mechanisms. Cell 2017;170:199-212.e20.
8. Haber AL, Biton M, Rogel N, Herbst RH, Shekhar K, Smillie C, Burgin G, Delorey TM, Howitt MR, Katz Y, Tirosh I, Beyaz S, Dionne D, Zhang M, Raychowdhury R, Garrett WS, Rozenblatt-Rosen O, Shi HN, Yilmaz O, Xavier RJ, Regev A. A single-cell survey of the small intestinal epithelium. Nature 2017;551:333-339.
9. Leshchiner ES, Rush JS, Durney MA, Cao Z, Dančík V, Chittick B, Wu H, Petrone, A, Bittker JA, Phillips A, Perez JR, Shamji AF, Kaushik VK, Daly MJ, Graham DB, Schreiber SL, Xavier RJ. Small-molecule inhibitors directly target CARD9 and mimic its protective variant in inflammatory bowel disease. Proc Natl Acad Sci USA 2017;114:11392-11397.
10. Mehta S, Cronkite DA, Basavappa M, Saunders TL, Adiliaghdam F, Amatullah H, Morrison SA, Pagan JD, Anthony RM, Tonnerre P, Lauer GM, Lee JC, Digumarthi S, Pantano L, Ho Sui SJ, Ji F, Sadreyev R, Zhou C, Mullen AC, Kumar V, Li Y, Wijmenga C, Xavier RJ, Means TK, Jeffrey KL. Maintenance of macrophage transcriptional programs and intestinal homeostasis by epigenetic reader SP140. Sci Immunol. 2017;2. pii: eaag3160.
11. Wolski D, Foote PK, Chen DY, Lewis-Ximenez LL, Fauvelle C, Aneja J, Walker A, Tonnerre P, Torres-Cornejo A, Kvistad D, Imam S, Waring MT, Tully DC, Allen TM, Chung RT, Timm J, Haining WN, Kim AY, Baumert TF, Lauer GM. Early Transcriptional Divergence Marks Virus-Specific Primary Human CD8+ T Cells in Chronic versus Acute Infection. Immunity 2017;47:648-663.
12. Chen JY, Newcomb B, Zhou C, Pondick JV, Ghoshal S, York SR, Motola DL, Coant N, Yi JK, Mao C, Tanabe KK, Bronova I, Berdyshev EV, Fuchs BC, Hannun Y, Chung RT, Mullen AC. Tricyclic Antidepressants Promote Ceramide Accumulation to Regulate Collagen Production in Human Hepatic Stellate Cells. Sci Rep. 2017;7:44867.
13. Thorndike AN, Bright O, Dimond M, Fishman R, Levy DE. Choice architecture to promote fruit and vegetable purchases by families participating in the Special Supplemental Program for Women, Infants and Children (WIC): randomized corner store pilot study. Public Health Nutrition 2017:20:1297-1305.
14. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide Variation in Reported Rates of Stroke Across Cohorts of Patients with Atrial Fibrillation. Circulation 2017:135:208-219.
15. Wheeler E, Leong A, …., Meigs JB. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis. PLoS Med. 2017;14:e1002383.
16. Hyle EP, Rao SR, Jentes ES, Parker Fiebelkorn A, Hagmann SHF, Taylor Walker A, Walensky RP, Ryan ET, LaRocque RC. Missed opportunities for measles, mumps, rubella vaccination among departing U.S. adult travelers receiving pretravel health consultations. Ann Intern Med. 2017;167:77-84.
17. Reddy KP, Kong CY, Hyle EP, Baggett TP, Huang M, Parker RA, Paltiel AD, Losina E, Weinstein MC, Freedberg KA, Walensky RP. Lung Cancer Mortality Associated With Smoking and Smoking Cessation Among People Living With HIV in the United States. JAMA Intern Med. 2017;177:1613-1621.
18. Walensky RP, Borre ED, Bekker LG, Hyle EP, Gonsalves GS, Wood R, Eholié SP, Weinstein MC, Anglaret X, Freedberg KA, Paltiel AD. Do Less Harm: Evaluating HIV Programmatic Alternatives in Response to Cutbacks in Foreign Aid. Ann Intern Med. 2017;167:618-629.
19. Canali S, Zumbrennen-Bullough KB, Core AB, Wang CY, Nairz M, Bouley R, Swirski FK, Babitt JL. Endothelial cells produce bone morphogenetic protein 6 required for iron homeostasis in mice. Blood. 2017;129:405-414.
20. Canali S, Wang CY, Zumbrennen-Bullough KB, Bayer A, Babitt JL. Bone morphogenetic protein 2 controls iron homeostasis in mice independent of Bmp6. Am J Hematol. 2017;92(11):1204-1213.
21. Wang CY, Core AB, Canali S, Zumbrennen-Bullough KB, Ozer S, Umans L, Zwijsen A, Babitt JL. Smad1/5 is required for erythropoietin-mediated suppression of hepcidin in mice. Blood. 2017;130:73-83.
22. Nigwekar SU, Weiser JM, Kalim S, Xu D, Wibecan JL, Sougherty SM, Mercier-Lafond L, Corapi KM, Eneanya ND, Holbrook EH, Brown D, Thadhani RI, Paunescu TG. Characterization and Correction of Olfactory Deficits in Kidney Diseases. J Am Soc Neprhol. 2017;28:3395-3403.
23. Lagares D, Ghassemi-Kakroodi P, Tremblay C, Santos A, Probst CK, Franklin A, Santos DM, Grasberger P, Ahluwalia N, Montesi SB, Shea BS, Black KE, Knipe R, Blati M, Baron M, Wu B, Fahmi H, Gandhi R, Pardo A, Selman M, Wu J, Pelletier J-P, Martel-Pelletier J, Tager AM, Kapoor M. ADAM10-mediated ephrin-B2 shedding promotes myofibroblast activation and organ fibrosis. Nature

Medicine 2017; 23:1405–1415.
24. Targeted apoptosis of myofibroblasts with the BH3 mimetic ABT-263 reverses established fibrosis
25. Lagares D, Santos A, Grasberger PE, Liu F, Probst CK, Rahimi RA, Sakai N, Kuehl T, Ryan JR, Bhola P, Montero J,Kapoor M, Baron M, Varelas X,Tschumperlin DJ, Letai A, Tager AM. Sci. Transl. Med. 9, eaal3765.
26. Pagan JD, Kitaoka M, Anthony RM. Engineered Sialylation of Pathogenic Antibodies In Vivo Attenuates Autoimmune Disease. Cell 172: 1-14; 2018.
27. Pianta A, Arvikar SL, Strle K, Drouin EE, Wang Q, Costello CE, Steere AC. Two rheumatoid-arthritis-specific autoantigens correlate microbial immunity with autoimmune responses in joints. J Clin Invest 2017;127:2946-2956.

Molecular Biology

Department Report

Robert E. Kingston, PhD, Chief

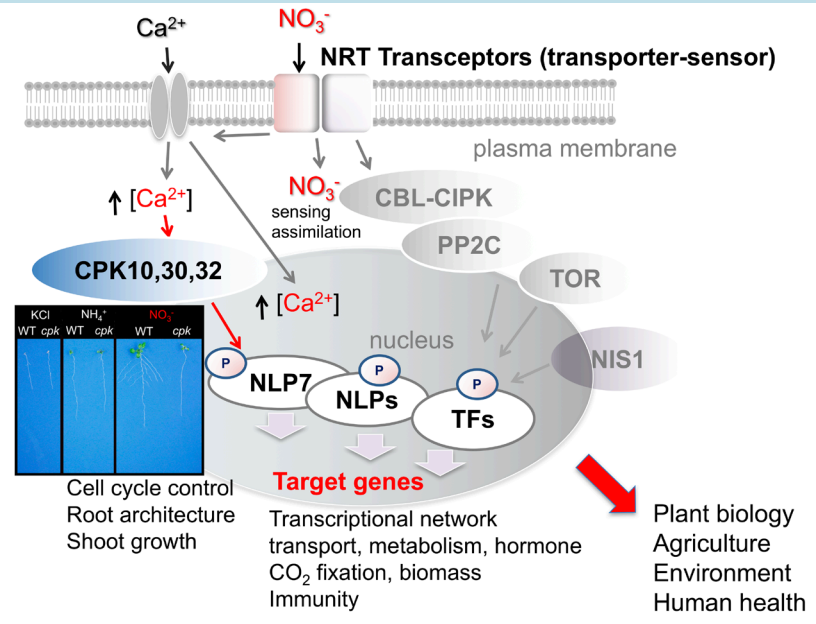
The Department of Molecular Biology at Massachusetts General Hospital is a part of both the research community of the hospital and the Division of Medical Sciences of the Harvard Graduate School of Arts and Sciences. We also have a strong connection with the Department of Genetics at HMS, where most 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 advance scientific breakthroughs for the benefit of MGH's patients and the worldwide community. Our central strategic priority is to hire the very best early-career scientists, and help them to build and leverage next-generation technologies to generate fundamental advances in biomedicine.

At present, approximately 200 people, including 15 faculty, about 150 postdoctoral fellows and graduate students, and about 35 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 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).
- Synapse formation, transmission, and trafficking (Kaplan).
- miRNA and RNAi pathways. Aging in C. elegans. Search for extraterrestrial life (Ruvkun).

The Department of Molecular Biology congratulates Radhika Subramanian, who is the recipient of a 2017 National Institutes of Health Director's New Innovator Award. The award, which funds high-risk, high-reward projects, was granted in recognition of Radhika's pioneering efforts in reconstructing the spatial organization of intracellular signaling during cell-division. This is the second prestigious award for Radhika in the past two years: she was also selected as a Pew Biomedical Scholar in 2016.

We focus on enhancing the understanding of biology and disease through the pursuit of cutting edge fundamental and translational research. Over the course of the past year, our faculty have published several highly regarded publications in a variety of fields. For example, The Mootha lab recently published a study that demystifies the role of a mitochondrial protein known as CLYBL. This protein is expressed in all vertebrates, in all tissues, yet its function was previously unknown, and, intriguingly, 3-5% of the human population have nonfunctional copies of the CLYBL gene, but they seem to be healthy. So, what is CLYBL, and why has a substantial fraction of the population lost the functioning gene?

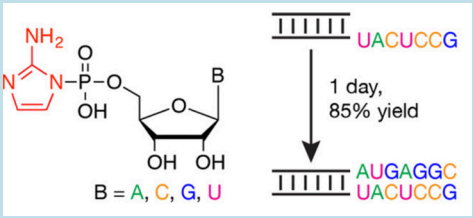


Elucidation of the function of the CLYBL protein. In a 2017 paper from Vamsi Mootha's lab, Shen and colleagues were able to define the metabolic role of the CLYBL protein, which until recently had an unknown function.

The Mootha lab and their collaborators described the function of CLYBL in their November 2017 paper in Cell (Shen et al, Cell. 2017 Nov 2;171(4):771-782.e11. doi: 10.1016). They found that CLYBL breaks down the metabolite citramalyl-CoA (see Figure 1). As a result of that activity, CLYBL detoxifies the metabolic precursor of citramalyl-CoA, itaconyl-CoA. Further, Shen et al discovered that itaconyl-CoA inactivates coenzyme B12 in the human enzyme MUT (methylalonyl-CoA mutase). These

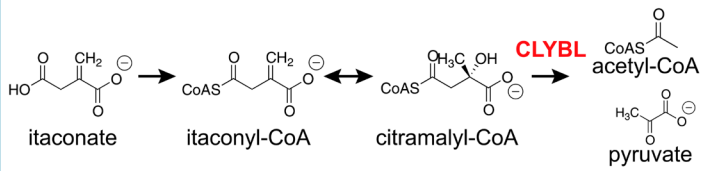
discoveries shed some understanding on the role of CLYBL, its ubiquitous expression, and the interesting association between the loss of CLYBL function and lower levels of coenzyme B12. But perhaps this work provides us with something more interesting: a basis for studying the deeper mystery of why 3-5% of the population has lost its CLYBL function.

Showcasing the breadth of research topics in the Department, a recent study by Jen Sheen's lab provides us with a new understanding of how nutrient signals affect gene expression, metabolism, and growth in plants. Liu et al (Nature. 2017 May 18;545(7654):311-316. doi: 10.1038) discovered that nitrate, the primary source of nitrogen for most plants and a growth-limiting nutrient, triggers calcium signaling via Ca2+-sensor protein kinases (CPKs), which act as "master regulators" to control gene expression programs. CPKs were found to phosphorylate the NIN-like protein (NLP) transcription factors, which, in turn, affect the expression of a broad spectrum of genes that function in nitrate metabolism, tissue growth, and organ development (Figure 2). This work provides a detailed view into the remarkable ability of plants to sense, uptake, and assimilate inorganic nutrients.



New insights in plant nutrient signaling. A study from Jen Sheen's lab illuminates the complex mechanism plants use to respond to nitrate, a growth-limiting nutrient.

Jack Szostak's lab has focused its effort on what must be the most fundamental question in biology: how did molecules coalesce to form primitive cells, and how did those primitive cells evolve complex molecular machinery? Because of its chemical, structural, and catalytic properties, RNA is thought to have played a central role in the development of early cells, but RNA is a polymer that must be built from its ribonucleotide precursors. RNA polymerases catalyze that polymerization process in our cells, but how could this polymerization have occurred at the dawn of life, before the first protocells acquired polymerases and other protein enzymes?



Efficient nonenzymetic replication of RNA. Jack Szostak's lab found conditions that lead to efficient nonenzymetic RNA polymerization, which is thought to be a necessary step in the early development of cells. Their work details a plausible mechanism for the establishment of catalytic RNAs.

A recent paper by Li and colleagues (J Am Chem Soc. 2017 Feb 8;139(5):1810-1813. doi:10.1021) details a plausible mechanism for efficient non-enzymatic polymerization of ribonucleotides. By activating ribonucleotides with a molecule called 2-aminoimidazole, Li et al were able to achieve fast, non-enzymatic copying of short, mixed RNA template sequences. Interestingly, 2-aminoimidazole is chemically related to another molecule called 2-aminooxazole, which is thought to be involved in the prebiotic syntheses of the pyrimidine ribonucleotides (the "C" and "T" components of DNA, and the "U" component of RNA). This work puts forth one reasonable pathway for the establishment of the "RNA world", in which RNA polymers catalyzed the chemical reactions that presumably gave way to protein enzymes and other complicated cellular machinery.

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 increased 10% over the prior year, bringing in $108.6M in total research revenue.

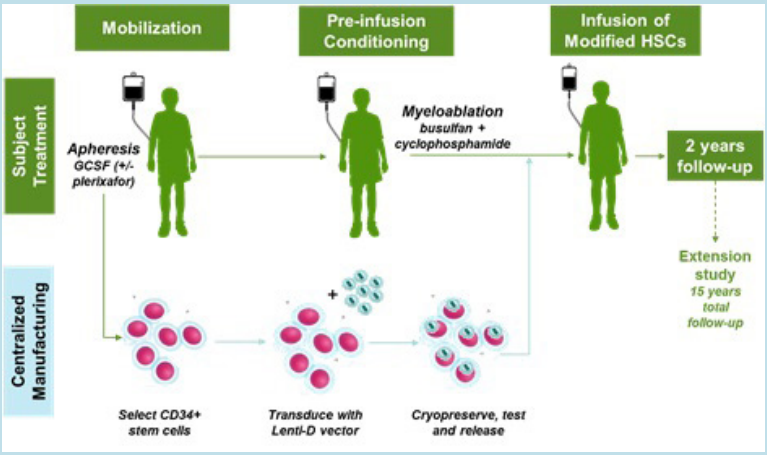
Departmental Strategic Research Priorities

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

Breakthroughs in Research and Therapeutics

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

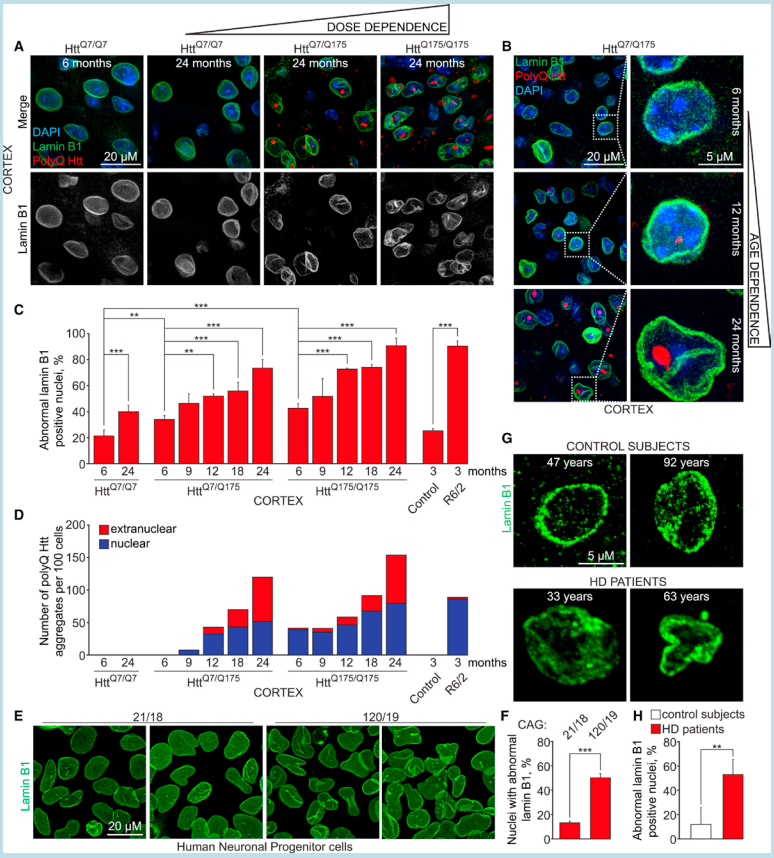
In recent New England Journal of Medicine published research led by Dr. Florian Eichler, Director of the Leukodystrophy Service, Director of the Center for Rare Neurological Diseases, and Associate Professor of Neurology, X-linked adrenoleukodystrophy is studied for a possible therapy. In X-linked adrenoleukodystrophy, mutations in ABCD1 lead to loss of function of the ALD protein. Cerebral adrenoleukodystrophy is characterized by demyelination and neurodegeneration. Disease progression, which leads to loss of neurologic function and death, can be halted only with allogeneic hematopoietic stem-cell transplantation. They enrolled boys with cerebral adrenoleukodystrophy in a single-group, open-label, phase 2–3 safety and efficacy study. Participants were required to have early-stage disease and gadolinium enhancement on magnetic resonance imaging (MRI) at screening. The investigational therapy involved infusion of autologous CD34+ cells transduced with the elivaldogene tavalentivec (Lenti-D) lentiviral vector. In this interim analysis, participants were assessed for the occurrence of graft-versus-host disease, death, and major functional disabilities, as well as changes in neurologic function and in the extent of lesions on MRI. The primary end point was being alive and having no major functional disability at 24 months after infusion. Their results included a total of 17 boys that received Lenti-D gene therapy. At the time of the interim analysis, the median follow-up was 29.4 months (range, 21.6 to 42.0). All the participants had genemarked cells after engraftment, with no evidence of preferential integration near known oncogenes or clonal outgrowth. Measurable ALD protein was observed in all the participants. No treatment-related death or graft-versus-host disease had been reported; 15 of the 17 participants (88%) were alive and free of major functional disability, with minimal clinical symptoms. One participant, who had had rapid neurologic deterioration, had died from disease progression. Another participant, who had had evidence of disease progression on MRI, had withdrawn from the study to undergo allogeneic stem cell transplantation and later died from transplantation-related complications. Their conclusions found that early results of this study suggest that Lenti-D gene therapy may be a safe and effective alternative to allogeneic stem-cell transplantation in boys with early-stage cerebral adrenoleukodystrophy. Additional follow-up is needed to fully assess the duration of response and long-term safety. (Funded by Bluebird Bio and others; STARBEAM ClinicalTrials.gov number, NCT01896102; ClinicalTrialsRegister.eu number, 2011-001953-10.)



Eichler F, Duncan C, Musolino PL, Orchard PJ, De Oliveira S, Thrasher AJ, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. N Engl J Med. 2017;377(17):1630-8. Epub 2017/10/04. doi: 10.1056/NEJMoa1700554. PubMed PMID: 28976817; PubMed Central PMCID: PMCPMC5708849.

Polyglutamine-Expanded Huntingtin Exacerbates Age-Related Disruption of Nuclear Integrity and Nucleocytoplasmic Transport

Dr. Clotilde Lagier-Tourenne, Assistant Professor of Neurology, recently published her research in Neuron that discusses the onset of neurodegenerative disorders, including Huntington's disease, which is strongly influenced by aging. Hallmarks of aged cells include compromised nuclear envelope integrity, impaired nucleocytoplasmic transport, and accumulation of DNA double-strand breaks. Dr. Lagier-Tourenne and her team show that mutant huntingtin markedly accelerates all of these cellular phenotypes in a dose- and age-dependent manner in cortex and striatum of mice. Huntingtin-linked polyglutamine initially accumulates in nuclei, leading to disruption of nuclear envelope architecture, partial sequestration of factors essential for nucleocytoplasmic transport (Gle1 and RanGAP1), and intranuclear accumulation of mRNA. In aged mice, accumulation of RanGAP1 together with polyglutamine is shifted to perinuclear and cytoplasmic areas. Consistent with findings in mice, marked alterations in nuclear envelope morphology, abnormal localization of RanGAP1, and nuclear accumulation of mRNA were found in cortex of Huntington's disease patients. Overall, their findings identify polyglutamine-dependent inhibition of nucleocytoplasmic transport and alteration of nuclear integrity as a central component of Huntington's disease. Analogous work by Dr. Hyman's lab shows that a similar mechanism is in play in Alzheimer's disease as well.



Expanded PolyQ Huntingtin disrupts neuronal nuclear envelope morphology in a dose- and age-dependent manner

Gasset-Rosa F, Chillon-Marinas C, Goginashvili A, Atwal RS, Artates JW, Tabet R, et al. Polyglutamine-Expanded Huntingtin Exacerbates Age-Related Disruption of Nuclear Integrity and Nucleocytoplasmic Transport. Neuron. 2017;94(1):48-57.e4. doi: 10.1016/j.neuron.2017.03.027. PubMed PMID: 28384474; PubMed Central PMCID: PMCPMC5479704.

Early detection of consciousness in patients with acute severe traumatic brain injury

In recently published work, Dr. Brian Edlow, Associate Director of the Center for Neurotechnology and Neurorecovery (CNTR), Director of the Laboratory for NeuroImaging of Coma and Consciousness (NICC), Director of the Critical Care Research Neuroimaging Patients, and Assistant Professor of Neurology, discusses patients with acute severe traumatic brain injury and how they may recover consciousness before self-expression. Without behavioral evidence of consciousness at the bedside, clinicians may render an inaccurate prognosis, increasing the likelihood of withholding life-sustaining therapies or denying rehabilitative services. Task-based functional magnetic resonance imaging and electroencephalography techniques have revealed covert consciousness in the chronic setting, but these techniques have not been tested in the intensive care unit. Dr. Edlow and his team prospectively enrolled 16 patients admitted to the intensive care unit for acute severe traumatic brain injury to test two hypotheses: (i) in patients who lack behavioral evidence of language expression and comprehension, functional magnetic resonance imaging and electroencephalography detect command-following during a motor imagery task (i.e. cognitive motor dissociation) and association cortex responses during language and music stimuli (i.e. higher-order cortex motor dissociation); and (ii) early responses to these paradigms are associated with better 6-month outcomes on the Glasgow Outcome Scale-Extended. Participants underwent functional magnetic resonance imaging on post-injury Day 9.2 ± 5.0 and electroencephalography on Day 9.8 ± 4.6. At the time of imaging, behavioral evaluation with the Coma Recovery Scale-Revised indicated coma (n = 2), vegetative state (n = 3), minimally conscious state without language (n = 3), minimally conscious state with language (n = 4) or post-traumatic confusional state (n = 4). Cognitive motor

dissociation was identified in four patients, including three whose behavioural diagnosis suggested a vegetative state. Higher-order cortex motor dissociation was identified in two additional participants. Complete absence of responses to language, music and motor imagery was only observed in coma patients. In participants with behavioral evidence of language function, responses to language and music were more frequently observed than responses to motor imagery (62.5–80% versus 33.3–42.9%). Similarly, in 16 matched healthy subjects, responses to language and music were more frequently observed than responses to motor imagery (87.5–100% versus 68.8–75.0%). Except for one participant who died in the intensive care unit, all participants with cognitive motor dissociation and higher-order cortex motor dissociation recovered beyond a confusional state by 6 months. However, 6-month outcomes were not associated with early functional magnetic resonance imaging and electroencephalography responses for the entire cohort. These observations suggest that functional magnetic resonance imaging and electroencephalography can detect command-following and higher-order cortical function in patients with acute severe traumatic brain injury. Early detection of covert consciousness and cortical responses in the intensive care unit could alter time-sensitive decisions about withholding life-sustaining therapies.

Brian L Edlow, Camille Chatelle, Camille A Spencer, Catherine J Chu, Yelena G Bodien, Kathryn L O'Connor, Ronald E Hirschberg, Leigh R Hochberg, Joseph T Giacino, Eric S Rosenthal, Ona Wu; Early detection of consciousness in patients with acute severe traumatic brain injury, Brain, Volume 140, Issue 9, 1 September 2017, Pages 2399–2414, https://doi.org/10.1093/brain/awx176

The melanoma-linked "redhead" MC1R influences dopaminergic neuron survival

In recently *Annals of Neurology* research, Dr. Xiqun Chen, Assistant Professor of Neurology, explains that individuals with Parkinson disease are more likely to develop melanoma, and melanoma patients are reciprocally at higher risk of developing Parkinson disease. Melanoma is strongly tied to red hair/fair skin, a phenotype of loss-of-function polymorphisms in the MC1R (melanocortin 1 receptor) gene. Loss-of-function variants of MC1R have also been linked to increased risk of Parkinson disease. The present study is to investigate the role of MC1R in dopaminergic neurons in vivo. During Dr. Chen and her team's research, genetic and pharmacological approaches were employed to manipulate MC1R, and nigrostriatal dopaminergic integrity was determined by comprehensive behavioral, neurochemical, and neuropathological measures. Their results showed that MC1Re/e mice, which carry an inactivating mutation of MC1R and mimic the human redhead phenotype, have compromised nigrostriatal dopaminergic neuronal integrity, and they are more susceptible to dopaminergic neuron toxins 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Furthermore, a selective MC1R agonist protects against MPTP-induced dopaminergic neurotoxicity. Their findings reveal a protective role of MC1R in the nigrostriatal dopaminergic system, and they provide a rationale for MC1R as a potential therapeutic target for Parkinson disease. Together with its established role in melanoma, MC1R may represent a common pathogenic pathway for melanoma and Parkinson disease.

Chen X, Chen H, Cai W, Maguire M, Ya B, Zuo F, et al. The melanoma-linked "redhead" MC1R influences dopaminergic neuron survival. Ann Neurol. 2017;81(3):395-406. Epub 2017/01/23. doi: 10.1002/ana.24852. PubMed PMID: 28019657.

Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease

Drs. Andy Cole, Director of the MGH Epilepsy Service and Professor of Neurology, and Alice Lam, Instructor in Neurology, recently published their research in Nature that describes how they directly assessed mesial temporal activity using intracranial foramen ovale electrodes in two patients with Alzheimer's disease (AD) without a history or EEG evidence of seizures. They detected clinically silent hippocampal seizures and epileptiform spikes during sleep, a period when these abnormalities were most likely to interfere with memory consolidation. The findings in these index cases support a model in which early development of occult hippocampal hyperexcitability may contribute to the pathogenesis of AD.

Lam AD, Deck G, Goldman A, Eskandar EN, Noebels J, Cole AJ. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. Nat Med. 2017;23(6):678-80. Epub 2017/05/01. doi: 10.1038/nm.4330. PubMed PMID: 28459436; PubMed Central PMCID: PMCPMC5461182.

NeuroNEXT

In Oct 2011, NINDS awarded the Clinical Coordinating Center (CCC) grant to MGH – Neurology Clinical Research Institute the Data Coordinating Center (DCC) grant to the University of Iowa, and Clinical Study Sites (CSS) grants to 25 academic institutions, including MGH/BWH. Three novel initiatives to increase the efficiency of conducting clinical trials in the Network were proposed: (1) utilization of a Central IRB (CIRB) of record, (2) establishment of Master Clinical Trial Agreements (MCTA) with all CSS, and (3) availability of experienced trial design staff to assist principal investigators. The overall goal of the Network was to conduct 5 – 7 studies over a 7-year grant period. As the CCC, MGH faculty and staff developed the first CIRB for a NINDS supported network, and is a role model for improving trial efficiencies.

The Network worked with investigators from academia, industry and foundations, to design studies for a variety of pediatric and adult

neurologic indications and submitted over 35 grant applications. The barrier for bringing forward novel therapeutic ideas was significantly lowered as the MGH CCC and the DCC faculty help train and support new investigators. To date, 9 studies have been approved for funding and several more are in the pipeline. Three of the investigators funded to date had little or no experience in grant writing or conducting multicenter clinical research studies, which is in line with the mission of the Network to train and mentor new clinical trialists. All studies are enrolling ahead or on schedule. The first four studies are complete. The first study, a biomarker study in infants with SMA, provided key information to the FDA for review of novel gene therapies. It also rapidly enrolled healthy children and children with SMA. A baseline data manuscript was published, the primary results manuscript accepted for publication, a manuscript describing muscle function testing is under review, and the data from this study were shared with FDA to inform regulatory review of investigational agents for SMA. The Network provided significant training and support to a first-time clinical investigator that led to both his success in leading the study and professional growth. The second study, ibudilast in progressive MS, demonstrated a 50% slowing of cerebral brain atrophy, providing key data to design the pivotal Phase III trial. The trial successfully enrolled on time, completing enrollment in June 2015. A baseline data manuscript was published. Follow-up was completed in May 2017, and the study is currently undergoing closeout with a plenary presentation of primary study results planned for the 2017 European Committee for Treatment and Research in Multiple Sclerosis meeting. This trial was the first Network industry collaboration (Medicinova) with high quality imaging data and standardization, and a collaboration for data.

Previously published data have reported mean times for contract execution and site IRB approval of 105 and 125 days, respectively (Atassi et al 2013). Within the NeuroNEXT Network, the master contract was set up prior to the start of any study, eliminating the need for contract negotiation for each study. Based on data from the first 4 studies, the median time for IRB approval of each protocol has been 50 days. Thus, in comparison to historical data, there has been a reduction from 105 to 0 days for contract negotiation and from 125 to 50 days for IRB approval.

The Network met or exceeded enrollment milestones to date with seminal projects including four studies that have completed enrollment and four that are currently enrolling patients. Based upon the success of these initiatives, the NCRI has piloted the use of a Central IRB and master contracting for studies conducted in other disease networks including v the Northeast ALS Consortium (NEALS) Network. To date 34 NEALS sites have formally agreed to rely on the Central IRB and three studies are actively utilizing this program.

Innovative and Collaborative Departmental Centers

Center for Neurotechnology and Neurorecovery (CNTR)

The Center for Neurotechnology and Neurorecovery (CNTR) led by Dr. Leigh Hochberg and Dr. Sydney Cash, the Center of Neurotechnology and Neurorecovery (CNTR) develops, tests, and deploys novel neurotechnologies to improve the care of people suffering from diseases or injuries of the nervous system. Established in 2009 as the Neurotechnology Trials Unit in the MGH Department of Neurology, the CNTR is dedicated to improving the care of people with diseases or injuries of the nervous system such as traumatic brain injury, spinal cord injury, stroke, epilepsy, and ALS. CNTR research and patient care benefit from a synergy of four domains of expertise:

Research and Development: A team of clinicians, scientists and engineers work collaboratively to design new clinical neurotechnologies and perform high resolution neurophysiology research. CNTR provides scientific expertise in the analysis and integration of complex neurophysiologic and neuroimaging data, and lead the field in research into neurologic devices, neuroprosthetics, seizure detection and prediction, disorders of consciousness, and neurorecovery.

Neurologic Device Clinical Trials: Complementing CNTR's scientific capabilities are strengths in the coordination of multi-site neurologic device clinical trials, execution of investigator-initiated and industry-sponsored clinical trials in neurologic devices, and interactions with clinical and research regulatory bodies.

Clinical Consultation: The CNTR also provides inpatient neurologic consultation for patients with severe disorders of consciousness or locked-in syndrome.

Education: The CNTR provides predoctoral and postdoctoral training in neurotechnology and neurorecovery. This will be supported by our recently award T32 training program grant from NINDS which will bring together a strong set of laboratories to address a substantial need for novel treatments for patients with acute brain injuries, such as, stroke and traumatic brain injury. The program will focus on recovery and restoration of brain function, an area of which there are few training programs. This will be a joint effort between MGH Neurology and Physical Medicine and Rehabilitation, Spaulding Rehabilitation Center, and the School of Engineering and Brown Institute for Brain Science at Brown University.

MGH Clinical Data Animation Center (CDAC)

The mission of CDAC is to enhance the utility of patient data at MGH, to enable better clinical care, and to advance medical knowledge across all clinical disciplines. Led by Dr. Brandon Westover, the CDAC is a strategic initiative that has three large goals. First, the CDAC strives to provide critical infrastructure, data management, and data mining tools to enable prospective clinical trials, particularly in the inpatient setting. Second, CDAC aims to enable quality improvement projects. Finally, the CDAC seeks to enable new large scale, highly granular retrospective and

prospective studies using MGH's massive data archives and continual acquisition of new data.

Prestigious Awards

Merit Cudkowicz, MD, MSc
Dr. Merit Cudkowicz is this year's recipient of the Forbes Norris Award. This award was first presented in 1994 by the International Alliance of ALS/MND Associations to recognize excellence in the ALS/MND community. It honors the memory of Dr. Forbes "Ted" Norris (1928-1993), a neurologist who dedicated his career to helping people with ALS/MND. The purpose of this award is to recognize a combination of two important qualities: management of and advances in our understanding of ALS/MND, to the benefit of people living with the disease. Additionally, Dr. Cudkowicz is so the 2018 recipient of the Pinnacle Award from the Greater Boston Chamber of Commerce. This award honors nine leading Greater Boston women for outstanding achievement in the workplace, leadership that has made a difference, and a commitment to enhance the quality of life in the region.

Dr. Cudkowicz was awarded both of these awards for her contributions in the field of ALS and Neurology at both MGH and at large. Furthermore, she was received these awards for her outstanding leadership, her mastery of clinical trials, her generous mentorship of others and her exceptional dedication to her patients.

Clotilde Lagier-Tourenne, MD, PhD
Dr. Clotilde Lagier-Tourenne was the recipient of the 2017 Grass Foundation - ANA Award in Neuroscience. This award was established in 2007 to recognize outstanding young physician-scientists conducting research in basic or clinical neuroscience. The Grass Foundation was established in 1955 by Albert and Ellen Grass to advance research and education in neuroscience, with a special focus on investigators early in their careers.

Dr. Lagier-Tourenne's laboratory performs patient-oriented research to understand the molecular mechanisms driving neurodegeneration in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and Huntington's disease. Recently, Clotilde Lagier-Tourenne's group has uncovered a new disease mechanism central to neurodegeneration in Huntington's disease. The transport between the nucleus and cytoplasm of affected neurons is impaired leading to abnormal accumulation of proteins and RNAs. This phenomenon is observed in normal aging but strikingly exacerbated in Huntington's disease and in ALS with C9ORF72 expansion disease. Her group is investigating whether similar disruption of nucleocytoplasmic transport is involved in neuronal death leading to other forms of ALS. Indeed, it appears that exacerbation of normal aging is a common feature in neurodegeneration and the Lagier-Tourenne's team explores the therapeutic potential of strategies targeting abnormal cellular compartmentalization. This work is what led her to receive this year's Grass Foundation Award.

Bradley Hyman, MD, PhD
Dr. Hyman, a physician scientist, and Katie Brandt, a caregiver advocate, were named to the National Alzheimer Project Act's Advisory Committee. This national committee consists of leaders of the governmental and private agencies that have joined together for the national response to the Alzheimer epidemic. Two physician scientists and two caregiver advocates were named as representatives to the Committee.

Dr. Hyman was also named as chair of the Executive committee of the Alzheimer Disease Research Centers, the organization that coordinates efforts of the community of the national NIH P50 and P30 Alzheimer Research Centers.

Yakeel Quiroz, PhD
Dr. Yakeel Quiroz received the Tony Wong Award for 2017. This award is given to NAN members who have made a significant contribution to the field of multicultural neuropsychology. The NAN Diversity Committee was impressed by a number of her accomplishments in the field.

Bob S. Carter, MD, PhD, Chief

The mission of the Department of Neurosurgery is to advance an understanding of the nervous system and to use this to advance therapy. The Department focuses on clinical care, basic research and translational studies taking research from the bench to the bedside.
Strategic priorities of the Department align with major clinical areas and include: 1) functional neurosurgery with particular attention to brain:machine interface, 2) neurosurgical oncology including understanding of the genetic underpinnings of central nervous system tumors and experimental therapeutics, 3) cerebrovascular biology of aneurysm formation and risk factors for aneurysm rupture, 4) spinal outcomes research, and 5) pediatric cranial trauma.

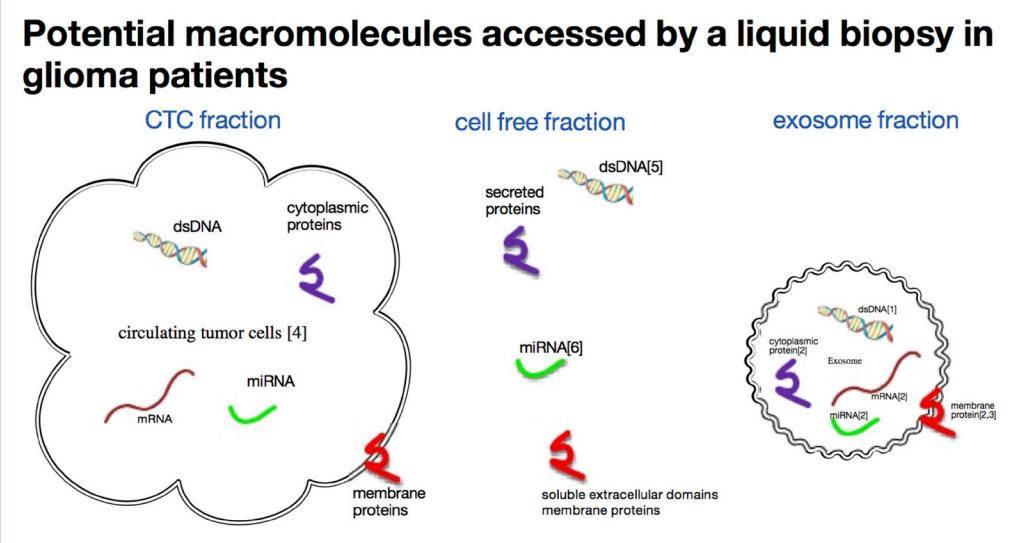
A few highlights of the Departments research program are noted below.

Neurosurgical Oncology

In 2017, the Department and the Simches Brain Tumor Center continued major efforts to better understand and target genetic alterations in central nervous system gliomas. Drs. Cahill, Brastianos, Shankar and Barker continued their groundbreaking work analyzing the molecular underpinnings of meningioma. Noting that meningiomas fall into a relative restricted set of mutational groups, clinical trials have been launched to target these mutations establishing MGH as the leading center for novel chemotherapeutic treatments for meningioma and other benign tumors. Drs. Carter, Nahed, Balaj and Stott have also had a major focus on liquid biopsy for brain tumors, publishing the results of a large trial of detection of EGFRvIII mutation in brain tumors in CSF.

Functional Neurosurgery

Drs. Williams, Fried, and Pezaris in close collaboration with the Departments of Psychiatry and Neurology have contined to explore the physiology and therapeutic manipulation of brain circuitry. Advances this year included the Fried laboratory's development of a new implantable microcoil for magnetic cortical stimulation and the Pezaris lab work in developing a visual prosthetic based on lateral geniculate stimulation.



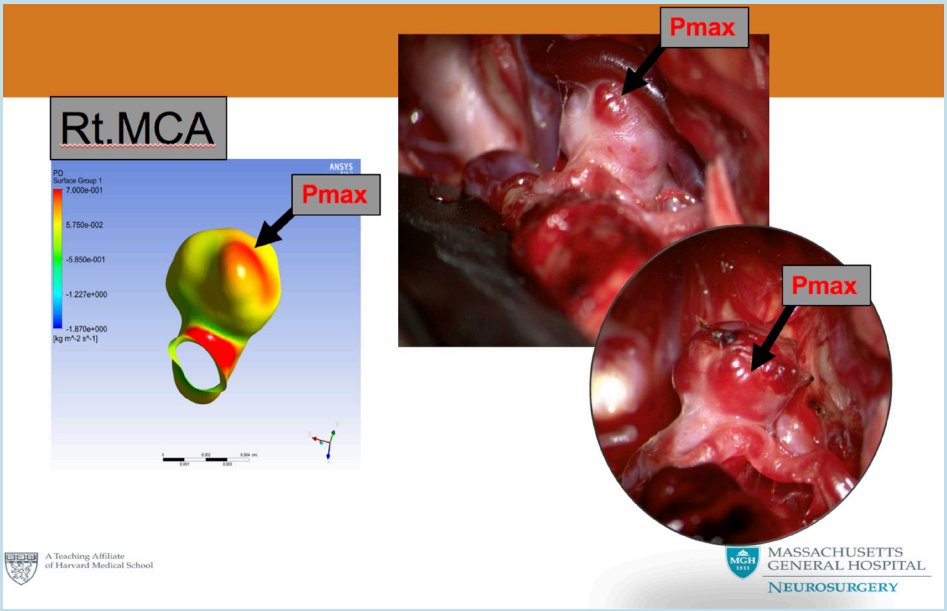
Carter/Nahed Laboratory Groups: The Brain Tumor Liquid Biospy Center is pursuing multiple avenues to interrogate brain tumors using blood and cerebrospinal fluid including circulating tumor cells, cell free DNA and exosomes.

Vascular Neurosurgery

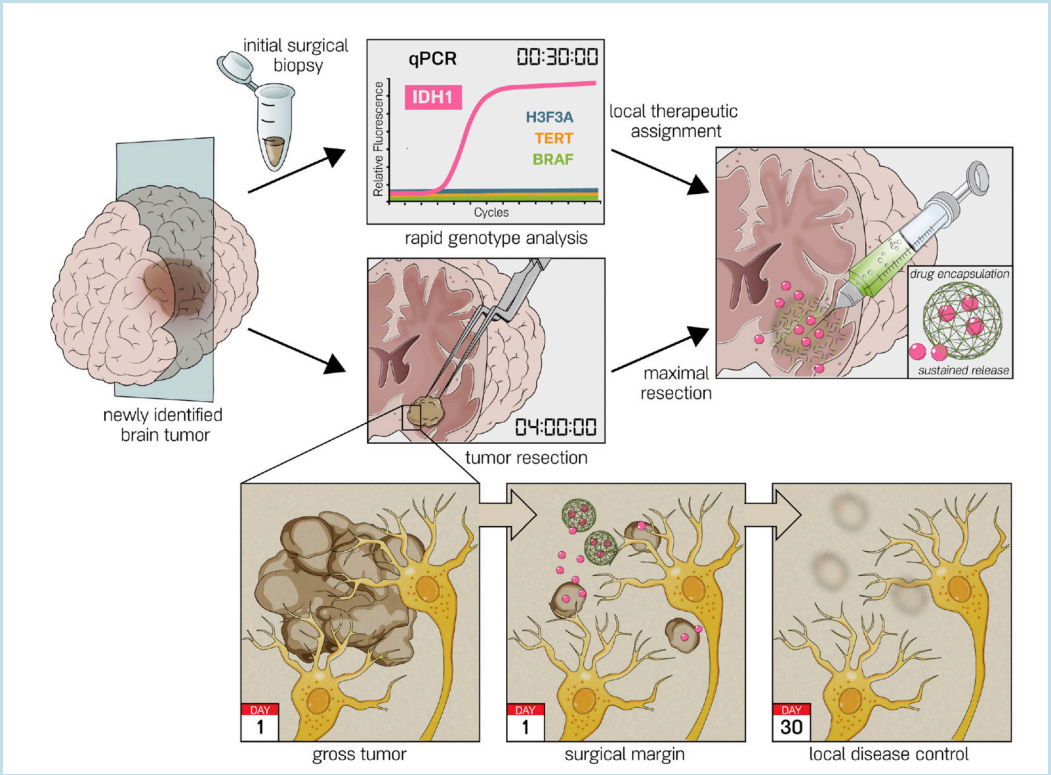
The Patel laboratory has used flow modeling to correlate virtual representations of intra-aneurysmal stress with intraoperative detection of aneurysm dome rupture points. It is anticipated that this work will lead to a better understanding of predictive factors for aneurysm rupture and improved stratification of patients for elective treatment of aneurysms.

Spine Neurosurgery

The spinal neurosurgery group has launched a spinal tumor tissue biobanking program in collaboration the Department of Pathology and a novel nanoparticle based chemotherapeutic strategy for intraspinal tumors. Drs. Shin, Cahill, and Shankar hope to develop rapid intraoperative genotyping to guide the intraoperative delivery of targeted nanoparticles in the context of these tumors.



Patel Laboratory: Virtual representation of maximal wall stress (left) correlates with intraoperative determination of aneurysmal bleb (right).



Shankar/Cahill Laboratory: Novel paradigm for delivering intraoperatively determined genotype-directed local therapy during neurosurgical resection to target nanoparticle based therapy against remaining disease burden at the surgical margin.

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

The Yvonne L. Munn Center for Nursing Research has continued to advance a research agenda across the MGH community and promote opportunities for nurse researchers to develop and extend their own programs of research. The Munn Center has expanded its infrastructure to collaborate more effectively with other disciplines to promote innovation and mobilize resources to support research initiatives that advance clinical practice and optimize quality patient-centered outcomes.

Research within the Munn Center is supported by internal and external resources and funding opportunities. In addition to philanthropy, external funding for nurses has been secured from the NIH, HRSA, and NIOSH (OSHA) as well as the American Nurses Foundation, and Sigma Theta Tau International. This funding supports research that impacts: a) health behaviors in women with HIV and heart disease; b) interventional strategies to improve pain management; c) wound care that accelerates healing and reduces hospital acquired pressure injuries; d) interventions to decrease falls and the risk for falls; e) improved assessment of pain in infants; f) interventional strategies to accelerate growth in premature infants; and g) continued development of instruments and evaluation strategies to increase workplace satisfaction and the health of clinicians. These initiatives lead to outcomes that help articulate nursing's impact on high quality, safe, and cost-effective health care.

Munn Center
GOAL 1: Facilitate MGH nurses' participation in and development of nursing knowledge that aligns with the goals of MGH and Patient Care Services.
GOAL 2: Foster opportunities within the MGH Research Institute to enhance the unique contributions of nursing science.
GOAL 3: Partner with academic and clinical settings and industry to improve the health and well-being of the communities we serve.
GOAL 4: Expand the impact of nursing science through the development of financial resources that improve patient care delivery and outcomes.
GOAL 5: Strengthen nursing's contributions to patient care outcomes through improved selection, storage, retrieval and evaluation of large data sets.

Workforce Evaluation
The Munn Center continues to participate in the distribution and oversight of the evaluation of professional practice across patient care services at MGH. In the spring of 2017, the Munn Center evaluation team distributed over 5,000 Professional Practice Environment Surveys to all providers within patient care services at the MGH, clinics and primary health care sites. The survey contains multiple instruments, several developed at the MGH, to evaluate clinician's overall satisfaction with the work environment at MGH. The survey results (both quantitative and qualitative themes) reflect a satisfied to highly satisfied workforce who are responding to the complex challenges of health care delivery. 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.

American Nurses Credentialing Center (ANCC) Magnet visit
Members of the nursing research community were active participants in the fourth Magnet Redesignation Site visit, held in November 2017. In addition to a significant amount of research evidence provided by the Munn Center staff and scholars across the MGH community, site visitors also met with staff from across the MGH community as well as academic partners to discuss the impact and overall effectiveness of nursing research at the MGH. One site visitor noted, "...there is no other hospital setting doing nursing research like the MGH". The final evaluation is forthcoming in 2018 .

Achievements of Munn Center Staff (2017)
Gaurdia Banister, PhD, RN, NEA-BC, FAAN was appointed Director of the Munn Center for Nursing Research and became the first recipient of the newly developed Connell-Jones Endowed Chair in Nursing and Patient Care Research to advance her research related to health care and diversity. The creation of the endowed chair also shined a spotlight on Dorothy Jones EdD, RNC, ANP, FAAN, FNI the first director and senior nurse scientist of the Munn Center and professor of nursing at the Boston College Connell School of Nursing, one of the chair's namesakes. Dr. Jones EdD, was also named the 2017 Living Legend by the ANA MA Nursing Association for overall contributions to professional nursing. She maintains an active program of research in

Featured in the picture from the Connell – Jones Endowed Chair for Nursing and Patient Care Research Celebration

workforce evaluation and knowledge development.

Diane Carroll, PhD, RN, FAAN was inducted into the Sigma Theta Tau Research Nursing Research Hall of Fame. Inductees are nurses who have achieved significant and sustained national and international recognition for their work, and whose research has influenced the profession and the people it serves. Dr. Carroll maintains a program of research in cardiovascular patient populations and patient safety, specifically in fall prevention and smart pump technology.

Jane Flanagan, PhD, RN, AHN-BC, ANP-BC FNI was inducted into the American Academy of Nursing was inducted into the American Academy of Nursing, a prestigious organization of nursing's most accomplished leaders in education, management, practice, and research. Her program of research explores the post hospital disposition of older adults; the efficacy of holistic, complementary interventions for women with breast cancer; and the feasibility and efficacy of implementing a physical activity program for caregivers of older adults.

Sara E. Looby, PhD, ANP-BC, FAAN was the recipient of the Dean's Community Service Award, The Office for Diversity Inclusion and Community Harvard Medical School. Dr. Looby conducts clinical research evaluating endocrine disorders and cardiovascular disease (CVD) in individuals with HIV, particularly women, including menopause and menopause symptoms.

Maurizio Fava, MD , Susan Slaugenhaupt, PhD, Kim Francis, PhD, RN, PHCNS-BC, Jeanette Ives Erickson DNP, RN, NEA-BC, FAAN "Testing the Feasibility of Utilizing Infrared Thermography for Pain Assessment with ELGA Infants: a Pilot Study

2017 Research Awards Supported Through the Munn Center
The Jeanette Ives Erickson Nursing Research Award, funded by the MGH Research Institute, is presented annually to a doctorally prepared nurse researcher who has a passion for advancing nursing science and is dedicated to promoting excellence in patient care. Kim Francis, PhD, RN, PHCNS-BC, is the 2017 Inaugural award recipient. Dr. Francis is the Nurse Director of the Blake 13 Newborn Family Unit. Her research focuses on pain assessment in the neonate and the development of strategies to respond to this challenge. Her funding will address Testing the Feasibility of Utilizing Infrared Thermography for Pain Assessment with ELGA Infants: A Pilot Study.

2017 Yvonne L. Munn Nursing Research Award Recipients
Principal Investigator: Lisa Rattner, BSN, RN-BC
Team: Sue Kilroy, RN, MS, CWS, Theresa, Capodilupo, RN, MSN, NE-BC
Unit: General Surgery, White 7
Mentor: Virginia Capasso, PhD, ANP-BC, ACNS-BC, CWS, The Institute for Patient Care
Project: Decreasing Catheter Dwell Time though Nursing Hand-off and Staff Education, and the Nurse-Driven Protocol for Catheter Removal

(L-R): Susan Kilroy, RN, MS, CSW; Anne Chamberlin, RN; Janiye Baird, RN; Lisa Finnigan, RN; Susan Evangelista, RN; Theresa Capodilupo, RN, MSN, NE-BC; Kristen Antony, RN; Virginia Capasso, PhD, ANP-BC, ACNS-BC, CWS (mentor); Lisa Rattner, BSN, RN-BC (principle investigator); and Jeanette Ives Erickson, DNP, RN, NEA-BC, FAAN. Not pictured: Jennifer Cervante, RN; Kathleen Lopez, RN; Brook McGrath, RN; and Lisa Chandler, RN. "Decreasing Catheter Dwell Time through Nursing Handoff, Staff Education, and the Nurse-Driven Protocol for Catheter Removal"

Principal Investigator: Jamie Ronin, MSN, RN, ACCNS-AG
Team: Susan Gordon, RN, BSN, Margaret Flynn, RN, BSN, CCRN, ACCNS-AG, Jennifer Killmer, BSN, CCRN, Erin Gilmore, RN, BSN, Sue Stengrevics, RN, MSN, ACNS-BC, Nicole Bezreh, RN, BSN, Julia Bandini, PhD(c), Laura Mylott, RN, PhD, ANP-BC (Northeastern University), Vivian Donahue, RN, MSN, ACNS-BC, CCRN
Unit: Cardiac ICU, Ellison 9 in conjunction with Cardiac Surgery ICU, Blake 8
Mentor: Ellen Robinson, RN, PhD, The Institute for Patient Care
Project: Clinical Nurse Involvement in Deliberations about Transplant and Mechanical Cardiac Support Evaluation: Impact on Perceptions of Ethical Climate, Moral Distress, and Ethics Self-Efficacy

(L-r): Margaret Flynn, RN, BSN, CCRN, ACCNS-AG; Julia Bandini, PhD (c); Vivian Donahue, RN, MSN, ACNS-BC, CCRN; Laura Mylott, PhD, RN, ANP-BC; Susan Stengrevics, RN, MSN, ACNS-BC; Ellen Robinson, PhD, RN (mentor); Susan Gordon, RN, BSN; Nicole Bezreh, RN, BSN; Virginia Capasso, PhD, ANP-BC, ACNS-BC, CWS (mentor); Jamie Ronin, MSN,RN, ACCNS-AG (principle investigator); and Jeanette Ives Erickson, DNP,RN, NEA-BC, FAAN.
Not pictured: Erin Gilmore, RN, BSN and Jennifer Kilmer, BSN, CCRN.
"Clinical Nurse Involvement in Deliberations about Transplant and Mechanical Cardiac Support Evaluation: Impact on Perceptions of Ethical Climate, Moral Distress, and Ethics Self-Efficacy."

Nursing research has actively been working collaboratively across disciplines to foster a community of inquiry. Nurse at the MGH actively engage in research initiatives, disseminate findings globally, publish numerous of articles in high impact journals (e.g.) examples and secure ongoing funding (e.g. NIH, NIOSH, ANF). These activities will continue to grow in the coming year.

Obstetrics and Gynecology

Department Report

Jeffrey L. Ecker, MD, Chief

Our department-based research complements our clinical goals to overcome infertility, improve healthcare for both non-pregnant and pregnant women, combat gynecologic cancers, and ease the menopausal transition in women through basic, translational, and clinical research infrastructures.

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 centers.

The Vincent Center for Reproductive Biology's mission is to overcome infertility, improve health care for non-pregnant and pregnant women, combat gynecologic cancers, and ease the menopausal transition in women through basic, translational and clinical research.

Prendergast JM, Galvao da Silva AP, Eavarone DA, Ghaderi D, Zhang M, Brady D, Wicks J, DeSander J, Behrens J, Rueda BR. Novel anti-Sialyl-Tn monoclonal antibodies and antibody-drug conjugates demonstrate tumor specificity and anti-tumor activity. MAbs. 2017 May/Jun;9(4):615-627.
The Sialyl-Thomsen-nouveau antigen (STn or Sialyl-Tn, also known as CD175s) is rarely seen in normal adult tissues, but it is abundantly expressed in many types of human epithelial cancers. Together with his collaborators at SIAMAB Pharmaceuticals, Dr. Rueda identified and characterized novel antibodies that specifically target with high affinity the STn glycan independent of its carrier protein. This specificity provides the potential to recognize a wider array of cancer-specific sialylated proteins. A panel of murine monoclonal anti-STn therapeutic antibodies were generated and their binding specificity and efficacy were characterized in vitro and in in vivo murine cancer models. A subset of these antibodies were conjugated to monomethyl auristatin E (MMAE) to generate antibody-drug conjugates (ADCs). These ADCs demonstrated in vitro efficacy in STn-expressing cell lines and significant tumor growth inhibition in STn-expressing tumor xenograft cancer models.

Bregar A, Deshpande A, Grange C, Zi T, Stall J, Hirsch H, Reeves J, Sathyanarayanan S, Growdon WB, Rueda BR. Characterization of immune regulatory molecules B7-H4 and PD-L1 in low and high grade endometrial tumors. Gynecol Oncol. 2017 Jun;145(3):446-452.
The objective of this investigation was to characterize the expression landscape of immune regulatory molecules programmed death-ligand-1 (PD-L1, B7-H1) and B7-H4 in a cohort of endometrial tumors across the spectrum of grade and histology. PD-L1 expression was observed in both high and low grade endometrial tumors. In the low-grade tumors, PD-L1 expression was associated with MSI status. The high-grade cohort had similar rates of PD-L1 expression compared to low grade MSI tumor, and both were distinct from low grade MSS tumors. High (3+) B7-H4 positive cells were observed in both high and low grade carcinomas. RNA profiling data from confirmed highest CD274 expression in POLE and MSI tumors that was linearly correlated with T cell infiltration, while VTCN1 expression appeared consistent across molecular subtypes. While PD-L1 expression correlated with MSI and high grade tumors, B7-H4 expression was independent of grade, histology and immune cell infiltration. The development and testing of multi-agent therapeutics targeting PD-L1 and B7-H4 may be a novel strategy for endometrial tumors.

Clapp MA, Little SE, Zheng J, Kaimal AJ, Robinson JN. Hospital-level variation in postpartum readmissions. JAMA. 2017 May 23;317(20):2128-2129. OR Wheeler S, Bryant AS. Racial and ethnic disparities in health and healthcare. Obstet Gynecol Clin North Am. 2017 Mar;44(1):1-11.
Readmission rates are used as a quality indicator and linked to reimbursement for certain medical and surgical conditions. Obstetric maternal readmissions have not been rigorously studied as a quality measure, though their use has been proposed. The goal of this study was to determine the potential utility of this metric and its ability to accurately reflect quality by quantifying the variance in hospital postpartum readmission rates and the percentage of the variance that was attributed to the effect of the hospital after controlling for case mix. In this study, postpartum readmissions were rare events and attributable to a variety of causes. Fifty percent of hospitals had postpartum readmission rates of 1% or less; in contrast, well-studied medical and surgical readmission rates exceed 20% for some conditions. The low frequency of readmissions resulted in rate data that were unstable for analysis, especially for lower volume facilities. Furthermore, of the little variability that existed between the hospital readmission rates, less than 1% of this variation was attributed to the hospital, limiting their use as a quality metric. Although a percentage of some indications for readmission may be potentially avoidable, the rarity of events would make studying preventability challenging. In the search for appropriate metrics, these findings caution against the assumption that postpartum readmission rates accurately reflect obstetrical care quality. The adoption of an insufficient quality metric may negatively affect patient care and reimbursement.

Foust-Wright CE, Pulliam SJ, Batalden RP, Berk TK, Weinstein MM, Wakamatsu MM, Phillippe M. Hormone modulation of toll-like receptor 5 in cultured human bladder epithelial cells. Reprod Sci. 2017 May;24(5):713-719. PMID: 27651177.

The objective of this study was to assess the effect of estradiol and progesterone on Toll-like receptor 5 (TLR5) expression and function in human bladder epithelial cells. T24 human urinary bladder (HUB) cells were incubated in hormone-free media for 72 hours. Human urinary bladder cells were then incubated in HF media, estradiol media, progesterone media, or media containing estradiol and progesterone at physiologic concentrations. Following flagellin exposure, cells and media were collected. Toll-like receptor 5 expression and stimulated cytokine release were analyzed using enzyme-linked immunosorbent assays. Results were normalized with cellular protein assays. A TLR5 antagonist was used to confirm that stimulation from flagellin was mediated by TLR5 signaling. This study demonstrated that TLR5 expression and functional activity as measured by IL-6 are modulated by hormones. The increase in TLR5-associated IL-6 may play a role in increasing the rate of symptomatic urinary tract infection. Likewise, low TLR5 functional activity may dampen the response of the innate immune system, thereby lessening the likelihood of a symptomatic bladder infection.

Ophthalmology

Department Report

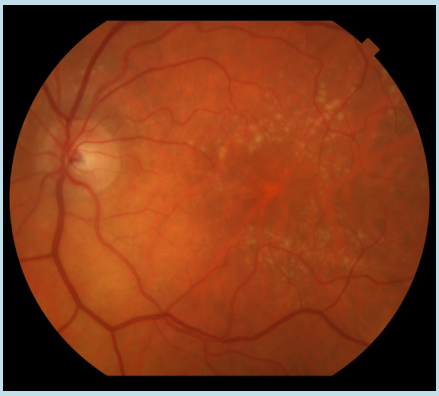
Joan W. Miller, MD, FARVO, Chief

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. With the incorporation of Schepens Eye Research Institute in 2011, the Department is now one of the largest vision research groups in the world. Today, we are well-positioned to bring focused efforts toward prevention, management and rehabilitation of vision-threatening disorders.

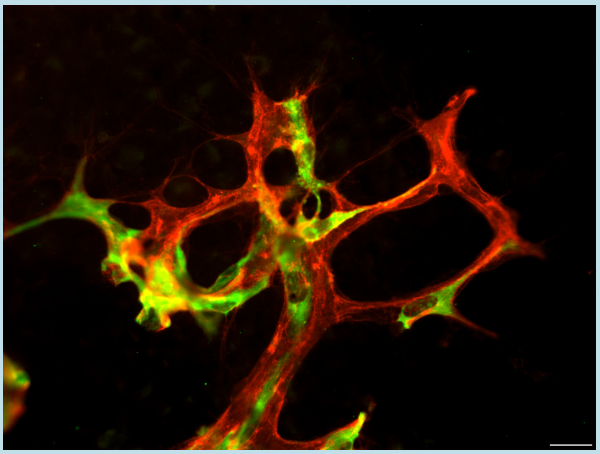
Tackling blinding diseases using a multifaceted, multidisciplinary approach has been the mainstay of the Department's past success in translational medicine. This approach has led to advancements such as proton beam irradiation, photodynamic therapy, anti-VEGF therapies, and the Boston Keratoprosthesis, 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.

Biomarkers for age-related macular degeneration

Research conducted by a team of Mass. Eye and Ear investigators showed that metabolomics can be used to identify potential blood biomarkers for AMD, including its severity stages. Metabolomics is the study of circulating metabolites in our body that reflect our genes and the effect of the environment and, therefore, are thought to closely represent the true functional state of complex diseases, including AMD. In collaboration with the University of Coimbra and colleagues at the Channing Division of Network Medicine of Brigham and Women's Hospital, the researchers—including Inês Laíns, MD, MSc, Deeba Husain, MD, and Joan W. Miller, MD—studied blood samples from 90 patients with AMD and identified 87 metabolites that were significantly different when compared to those without AMD. They also note varying characteristics among the blood profiles at each stage of the disease. The most significant metabolites are involved in lipid metabolism, particularly via the glycerophospholipid pathway. This work supports research suggesting that lipids may be involved in the pathogenesis of AMD, although the exact role of lipids in the disease process remains unclear. The results from this study—published in Ophthalmology (August 2017)—indicate that metabolomics profiling may provide novel insights into the relationship between lipids and AMD. These findings may lead to earlier diagnosis and better prognostic information for patients, and, potentially, new targets for AMD treatment.



Color fundus photograph of a right eye with intermediate AMD. Drusen and pigmentary changes are present in the central macula.



Retinal neovascularization at postnatal day five in a cadherin5 driven CreLoxP system for ribosomal GFP expression. (red=isolectin B4, green=ribosomal GFP in endothelial cells).

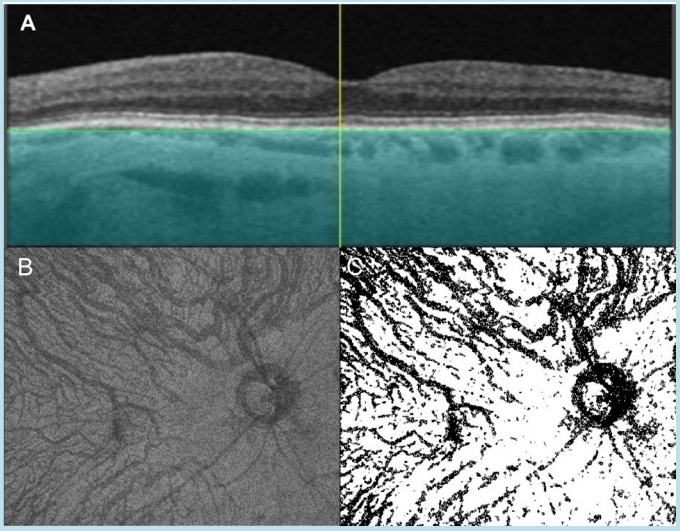
Researchers identify key lipids that resolve abnormal vascular growth in AMD

A research team led by Kip M. Connor, PhD, identified and demonstrated that specific bioactive lipid metabolites from the cytochrome P450 (CYP) pathway, a major family of enzymes, can influence choroidal neovascularization (CNV) and vascular leakage by changing how immune cells are recruited to areas of disease and injury. The report, published in the Proceedings of the National Academy of Sciences (August 2017), suggests that it may be possible to prevent vision loss resulting from abnormal blood vessel growth and inflammation observed in AMD by increasing the expression of specific bioactive lipid metabolites in the retina. AMD is the primary cause of blindness in elderly individuals of industrialized countries and is projected to increase in prevalence ~50% by 2020. In patients with advanced AMD, abnormal blood vessels can start to develop from underneath the light-sensing layer of the eye in a process known as CNV. In light of these considerations, there is an urgent need for new pharmacological or nutritional interventions that are safe over the

long term in both the prevention and treatment of AMD. This research highlights the bioactive properties of CYP-derived lipid mediators in regulating abnormal blood vessel growth and inflammation, which are two fundamental and systemically occurring processes. Specifically, the researchers isolated and characterized two key mediators of disease resolution generated from the CYP pathway: 17,18-epoxyeicosatetraenoic acid (EEQ) and 19,20-epoxydocosapentaenoic acid (EDP). Given the high prevalence and progressive nature of neovascular eye disease, the ability to stabilize bioactive lipids that mitigate or halt disease is of great and increasing therapeutic significance. The hope is that emerging technologies and future studies will expand on this work and ultimately lead to safe, targeted, and cost-effective therapies that markedly improve visual outcomes and quality of life for patients.

Imaging may offer new insights into disease progression of diabetic choroidopathy

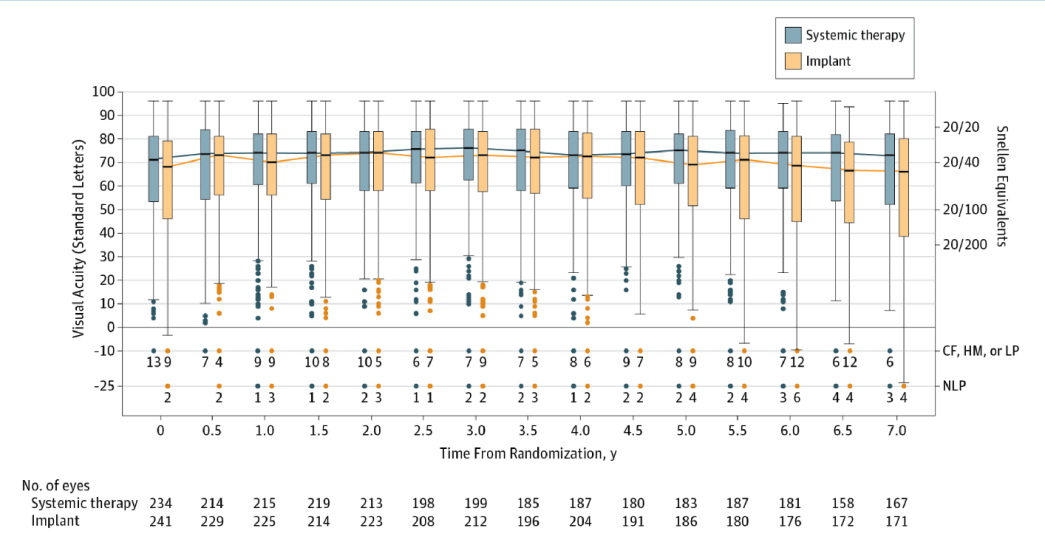
Choroidal vascular density (CVD) and volume (CVV) are significantly reduced in more advanced stages of diabetic retinopathy, according to a report published in the American Journal of Ophthalmology (December 2017). The research team, led by John B. Miller, MD, noted that new imaging modalities, such as swept source optical coherence tomography (SS-OCT), may help researchers understand how the choroidal vasculature contributes to diabetic eye disease. The cross-sectional study used SS-OCT, a novel OCT device that enables imaging the choroid with better resolution, and studied patients with different stages of diabetic retinopathy. CVD and CVV were introduced as new quantitative parameters to assess the choroidal vasculature. Study results demonstrated that, even after accounting for confounding factors, diabetic eyes with diabetic macular edema or proliferative diabetic retinopathy (PDR) demonstrated a reduced CVD, as compared to controls. Additionally, eyes with PDR also demonstrated reduced CVV. These results suggest that vascular abnormalities accumulate with the severity of diabetic retinopathy. This study also emphasizes that a diabetic choroidopathy (i.e. changes in the choroidal vasculature) probably occurs simultaneously with changes in the retinal vasculature, even though it is still not clear if this is a primary or secondary event. Elucidating the relationship between diabetic choroidopathy and retinopathy is essential for a more complete understanding of diabetic eye disease, and to improve its prognosis and treatment.



Representative example of swept source optical coherence tomography (SS-OCT) en face images and image processing. (A) SS-OCT B-scan after flattening of Bruch's membrane. (B) Representative en face SS-OCT image 70 µm below Bruch's membrane – the choroidal vasculature is clearly visible. (C) The same image after binarization.

Systemic therapy outperforms intraocular implant for treating uveitis

For patients with uveitis, systemic therapy consisting of corticosteroids and immunosuppressants preserved vision better, and had fewer adverse outcomes, than a long-lasting corticosteroid intraocular implant, according to a clinical trial funded by the National Eye Institute (NEI). These findings were published in JAMA (May, 2017). According to Writing Committee Chair and Mass. Eye and Ear researcher, John Kempen, MD, PhD, the results are meaningful not only to ophthalmology but to the broader field of medicine given that inflammatory diseases affect many different organs; these results indicated that systemic therapy as administered in the study had a favorable safety profile. Concerns about potential adverse effects of systemic corticosteroid and immunosuppressive therapy drove the development of an intraocular implant to treat uveitis locally. As a result, the Multicenter Uveitis Steroid Treatment (MUST) trial was undertaken to evaluate whether the implant treatment was an improvement over systemic therapy for management of uveitis. These findings offer guidance to clinicians and patients in making informed decisions about uveitis treatment. Specifically, there is good evidence that systemic therapy would be the first choice of treatment for the average patients with intermediate, posterior, or panuveitis. The implant is effective in treating patients where systemic therapy fails to control inflammation or when patients cannot tolerate the oral medications. The duration of control of inflammation following implant treatment was approximately five years, much longer than expected.

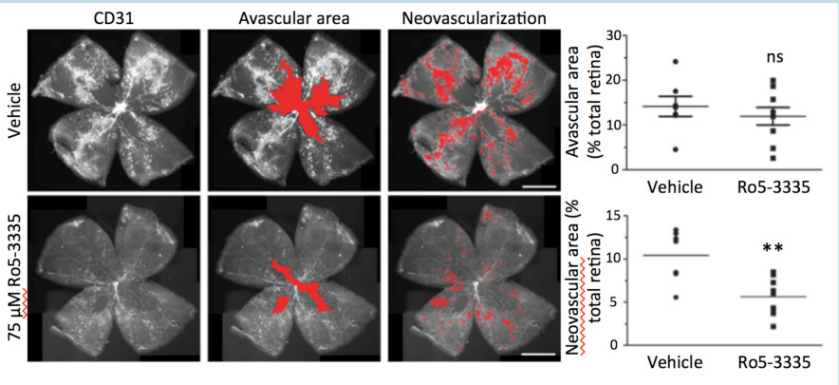


Distribution of Best-Corrected Visual Acuity Among Uveitic Eyes Assigned to Receive Intravitreous Fluocinolone Acetonide Implant or Systemic Therapy. Change from baseline transiently favored implant at six months (P = .03) and favored systemic therapy from year 6 onward (P < .045).

Reproduced with permission from Association Between Long-Lasting Intravitreous Fluocinolone Acetonide Implant vs Systemic Anti-inflammatory Therapy and Visual Acuity at 7 Years Among Patients With Intermediate, Posterior, or Panuveitis. JAMA. 2017; 317(19):1993-2005. Copyright 2017 American Medical Association."

Identification of RUNX1 as a Mediator of Aberrant Retinal Angiogenesis

Proliferative diabetic retinopathy (PDR) is a common cause of blindness in the developed world's working adult population and affects those with type 1 and type 2 diabetes. Mass. Eye and Ear investigators Joseph Arboleda-Velasquez, MD, PhD, and Leo Kim, MD, PhD led a team of researchers who identified a novel therapeutic target for retinal neovascularization, or abnormal blood vessel growth in the retina, a hallmark of PDR or advanced diabetic eye disease. The transcription factor RUNX1 was found in abnormal retinal blood vessels; by inhibiting RUNX1 with a small molecule drug, the researchers achieved a 50 percent reduction of retinopathy in preclinical models. Current treatments to control retinal neovascularization require injecting very large proteins, including antibodies, into the eyes of patients, as frequently as once a month. These findings—featured on the cover of Diabetes (July 2017)—open the door for novel modalities of treatment based on small molecules that could cross biological barriers on their own. The study authors are hopeful that inhibiting RUNX1 may present a more targeted opportunity for managing the retinopathy of certain eye conditions—perhaps earlier in the disease process, before the abnormal blood vessels develop. Future studies will evaluate the role of RUNX1 and its interaction with VEGF, as well as other diseases of aberrant angiogenesis such as choroidal neovascularization, the primary pathological feature of wet age-related macular degeneration.



Inhibition of RUNX1 with Ro5-3335 in the oxygen-induced retinopathy (OIR) mouse model. Anti-Runx1 treatment resulted in a selective ~46% reduction in aberrant neovascular tufts, while the avascular region remained unaffected in a mouse model of oxygen- induced retinopathy. (scale bar = 1mm).

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

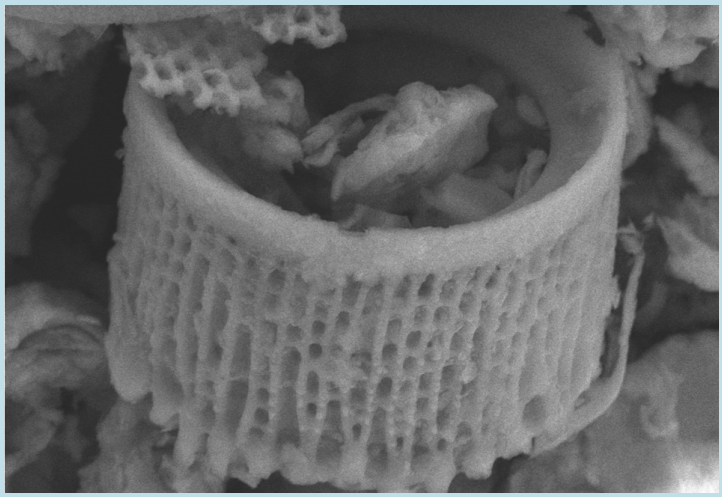
The focus of our department's research continues to be a thematically driven translational research program that is intimately integrated with our clinical program(s). The research is organized the research into two centers: The Skeletal Biology Research Center (SBRC), directed by Dr. Zach Peacock, and The Center for Applied Clinical Investigation (CACI), directed by Dr. Meredith August.

Skeletal Biology Research Center (SBRC) on Thier 5, focuses on translational science performed on bone biology and rare tumor biology. 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 Temporomandibular joint repair, using nanotechnology, in a mouse model. We are also studying the effects of marijuana on tooth movements and bone, in a rat model, developed by Dr. Katie Klein.

Center for Applied Clinical Investigation (CACI) 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, implantology and medication related osteonecrosis of the jaws (MRONJ), maxillofacial pathology, orofacial pain and temporomandibular joint surgery and Obstructive sleep apnea outcomes. The center serves to study outcomes (retrospective and prospective) on treatment protocols developed in the department. We have initiated QI/Safety headed by Dr. Ed Lahey and, Education /Simulation research headed by Dr. John Tannyhill.

This year was used to plan, organize and create new collaborations. Under the direction of our research AD, Dan Salvati, we have re-designed and obtained new equipment. The tissue culture room will open shortly. With the help of our fellows Dr. Fernando Guastaldi and Jose Sandra DaSilva, we have restarted our bone tissue engineering experiments in an autologous, animal model. Dr. Baboucarr Lowe, our PhD candidate, is working on scaffold printing for these projects. Dr. Lowe has also developed biosilica nanotachnology, for TMJ in vivo generation. We have 9 research fellows (7in SBRC and 2 in CACI) working very hard on multiple projects.
New collaborations include the department of Pathology, Drs. Iafrate, Faquin and Rivera, (Genetics of Rare Jaw Tumors); Infectious Disease, Dr. Fusco (effects of ZIKA in the osteoblasts; Oncology, Dr. Raje, (genetics of bone metabolism and MRONJ) and Dermatology, Dr Yakir Levin (tissue engineering of attached gingiva)

We hope that these strong foundations will result in a productive research year, which eventually will translate into improved patient care.



This is a microscopic view of a diatom frustule used for the development of functionalized nanoparticles for intra-articular regeneration of temporomandibular joint with stem cells.

Otolaryngology

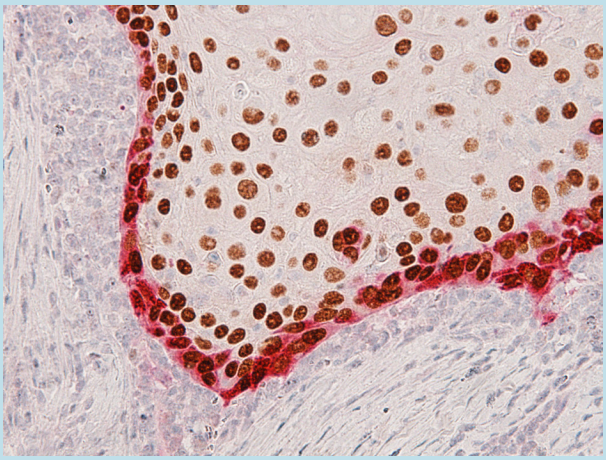
Department Report

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 prevention, management, and rehabilitation of human communication disorders. From advancements in using gene therapy against hearing loss to FDA-approved clinical trials for chronic rhinosinusitis, we strive to improve outcomes and find new treatments for our patients.

Invasive cells in head and neck tumors predict cancer spread

Head and neck tumors that contain cells undergoing a partial epithelial-to-mesenchymal transition—which transforms them from neatly organized blocks into irregular structures that extrude into the surrounding environment—are more likely to invade and spread to other parts of the body, according to a study led by Derrick T. Lin, MD, and Sid Puram, MD, from Massachusetts Eye and Ear, in collaboration with Massachusetts General Hospital and the Broad Institute of MIT and Harvard. In a report published in Cell, the researchers analyzed more than 6,000 individual cells from head and neck squamous cell carcinomas via single-cell RNA-sequencing. Through their analysis, the research team created a comprehensive atlas of cells present in head and neck cancer. They also characterized a unique structural transition involving cancer cells and normal cells in their environment that allows tumors to spread. The findings provide important clues as to how head and neck cancers metastasize, and may have implications for other common cancers as well.



Head and neck tumor stained for markers of cancer (brown) and p-EMT transition (red), demonstrating cells having undergone a unique transition at the tumor's outer edge.

CRISPR therapy preserves hearing in progressive deafness model

In collaboration with the Broad Institute of MIT and Harvard, Harvard University, and Howard Hughes Medical Institute, Zheng-Yi Chen, PhD, of Massachusetts Eye and Ear, developed a CRISPR-Cas9 genome-editing therapy to prevent hearing loss in a mouse model of human genetic progressive deafness. The therapy delivers a CRISPR-Cas9 gene-editing protein complex directly into the sound-sensing hair cells via lipid rafts to disrupt an autosomal dominant mutation that would otherwise cause the cells to die. The work represents a significant step toward genome-editing to halt progression of genetic hearing loss. Delivering the Cas9 protein itself locally, instead of DNA elements that the cell can use to build Cas9, improved the DNA specificity and potential safety of the treatment.

Patients with severe chronic rhinosinusitis show improvement with Verapamil treatment

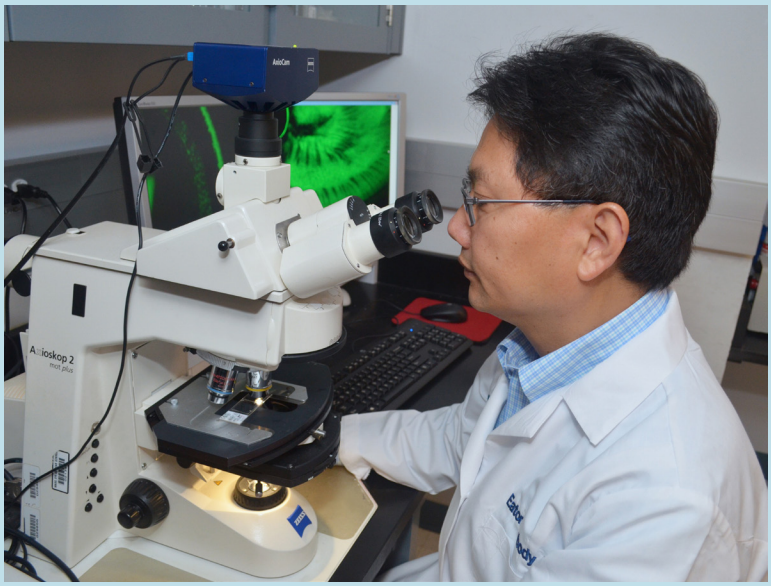
A clinical trial studying the use of Verapamil, a drug currently in use for cardiovascular disease and cluster headache, in alleviating chronic rhinosinusitis (CRS) with nasal polyps revealed significant improvement in the symptoms of this subset of patients. Led by Benjamin S. Bleier, MD, FACS, of Massachusetts Eye and Ear, it is the first study of its kind to explore treatment for CRS by inhibiting P-glycoprotein, a protein pump within the nasal lining that Mass. Eye and Ear researchers previously identified as a mechanism for these severe cases of CRS marked by the presence of nasal polyps. The clinical trial results, which are published in the Journal of Allergy and Clinical Immunology: In Practice, suggest that Verapamil represents a promising novel therapy for the treatment of CRS with nasal polyps.

Connectome-wide phenotypical and genotypical associations found in focal dystonia

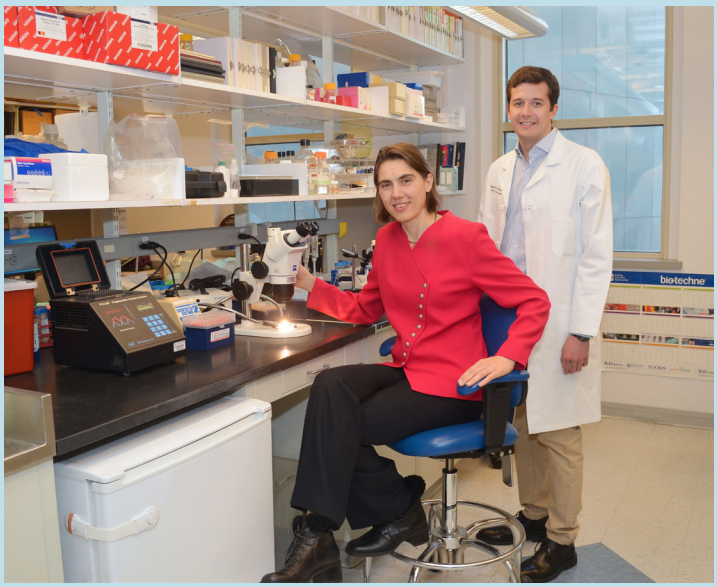
Laryngeal dystonia (LD), or spasmodic dysphonia, is a movement disorder that selectively affects the production of speech due to impaired voluntary control of vocal fold movements. Early studies have pointed to segregated changes in brain activity and connectivity and only recently, the notion that dystonia pathophysiology may lie in abnormalities of large-scale brain networks has appeared in the literature. In support of this emerging view, a team of researchers including Kristina Simonyan, MD, PhD, of Massachusetts Eye and Ear, conducted detailed investigation of the architecture of large-scale functional brain networks in a uniquely large population of 90 LD patients and 32 healthy subjects. Their findings provide a comprehensive atlas of functional topology across different phenotypes and genotypes of focal dystonia. As such, this study constitutes an important paradigm-shifting step towards defining dystonia as a large-scale network disorder for understanding of its causative pathophysiology and the identification of disorder-specific markers.

A synthetic AAV vector enables safe and efficient gene transfer to inner ear

Efforts to develop gene therapies for hearing loss have been hampered by the lack of safe, efficient, and clinically relevant delivery modalities. In a study led by Konstantina M. Stankovic, MD, PhD, FACS, and Lukas Landegger, MD, PhD, of Massachusetts Eye and Ear, in collaboration with Luk H. Vandenberghe, PhD, and Jeffrey R. Holt, PhD, researchers demonstrated the safety and efficiency of Anc80L65, a rationally designed synthetic vector, for transgene delivery to the mouse cochlea. Ex vivo transduction of mouse organotypic explants identified Anc80L65 from a set of other adeno-associated virus (AAV) vectors as a potent vector for the cochlear cell targets. Round window membrane injection resulted in highly efficient transduction of inner and outer hair cells in mice. The ability of Anc80L65 to target outer hair cells at high rates, a requirement for restoration of complex auditory function, may enable future gene therapies for hearing and balance disorders.



Dr. Zheng-Yi Chen in his laboratory at Mass. Eye and Ear. Photo by Garyfallia Pagonis.



Dr. Tina Stankovic (left) and Dr. Lukas Landegger (right) in the Molecular Neuro-Otology and Biotechnology Laboratory at Mass. Eye and Ear. Photo by Garyfallia Pagonis.

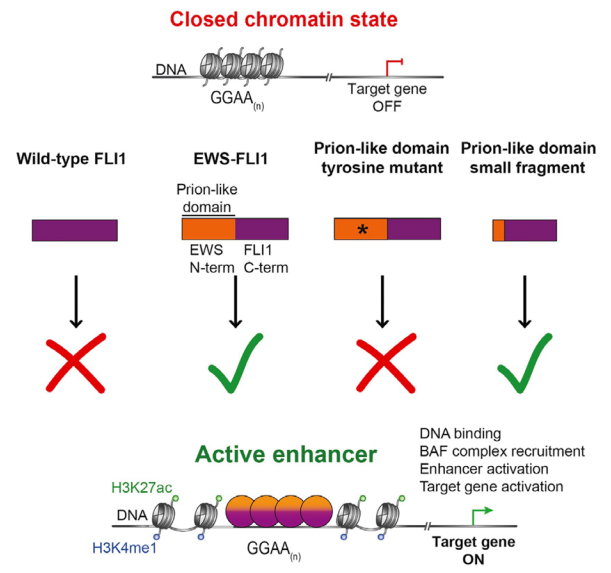
David N. Louis, MD, Chief

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 scientific areas makes this a very exciting time in the field of pathology. Laboratory-based scientific research is a major component and activity 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 robustly grown over the past 16 years, 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 identified 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 significance 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 fields, enabling them to continue advancing our understanding and diagnosis of human diseases.

Decoupling genetics, lineages, and microenvironment in IDH-mutant gliomas by single-cell RNA-seq. Venteicher AS, Tirosh I, Hebert C, Yizhak K, Neftel C, Filbin MG, Hovestadt V, Escalante LE, Shaw ML, Rodman C, Gillespie SM, Dionne D, Luo CC, Ravichandran H, Mylvaganam R, Mount C, Onozato ML, Nahed BV, Wakimoto H, Curry WT, Iafrate AJ, Rivera MN, Frosch MP, Golub TR, Brastianos PK, Getz G, Patel AP, Monje M, Cahill DP, Rozenblatt-Rosen O, Louis DN, Bernstein BE, Regev A, Suvà ML. Science. 2017 Mar 31;355(6332).

This study performed by the Suva lab of MGH Pathology represents the largest effort ever undertaken to characterize clinical tumor samples with single-cell RNA-sequencing technologies. It is the first study leveraging these techniques in IDH-mutant gliomas, tumors whose biology has been difficult to dissect due to the scarcity of animal and cellular models. The goal of this work was to precisely characterize the genetics, cell lineages, phenotypes and microenvironments driving IDH-mutant gliomas. The resulting findings revealed that two distinct subtypes of IDH-mutant gliomas, known as astrocytoma and oligodendroglioma, are actually driven by similar types of stem cells and follow similar differentiation programs. This helps resolve a longstanding debate regarding the histogenesis of these tumors and defines for the first time their stem cell programs. Interestingly, significant differences were also observed in the microenvironments of these gliomas, specifically, the amounts of immune cells such as microglia and macrophages present in each tumor. New granularity of these immune cells was also discovered, identifying myeloid cells with mixed phenotypes that had not been previously appreciated in gliomas. These methodology and analyses provide critical insights in IDH-mutant gliomas and a general framework to dissect human malignancies.

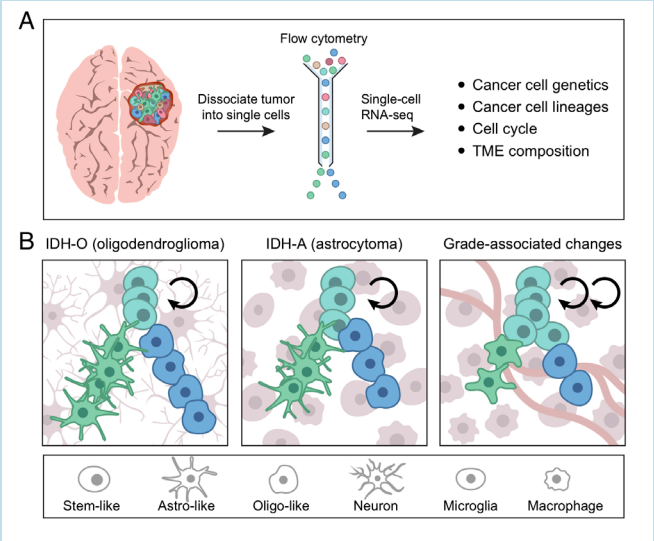


Single-cell RNA-seq of IDH-mutant gliomas reveals tumor architecture. (A)Clinical gliomas samples are dissociated and analyzed by single-cell RNA-seq. (B) IDH-mutant oligodendroglioma and IDH-mutant astrocytoma differ in genetics and the composition of their tumor micro-environment but are both primarily composed of three main types of malignant cells: cycling stem-like cells, and non-cycling differentiated astrocyte-like and oligodendrocyte-like cells. Tumor progression is associated with increased proliferation, decreased differentiation and increase in macrophages over microglia in the tumor micro-environment.

Boulay G, Sandoval GJ, Riggi N, Iyer S, Buisson R, Naigles B, Awad ME, Rengarajan S, Volorio A, McBride MJ, Broye LC, Zou L, Stamenkovic I, Kadoch C, Rivera MN. Cancer-Specific Retargeting of BAF Complexes by a Prion-like Domain. Cell. 2017 Sep 21; 171(1): 163-178.e19.

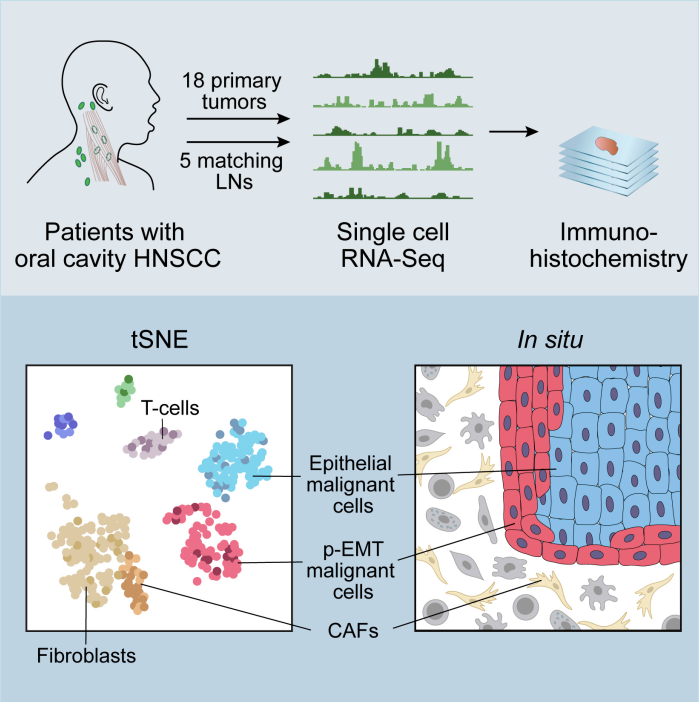
Disordered proteins are often involved in important biological processes but are poorly understood. In the pediatric bone cancer Ewing sarcoma, the disordered prion-like protein EWS is fused to the ETS transcription factor FLI1 to form an oncogenic fusion protein that is the main oncogenic driver of this tumor type. Using epigenome profiling methods, the Rivera lab of MGH Pathology had previously shown that EWS-FLI1

functions as a pioneer factor to establish de novo active enhancers at GGAA microsatellite repeats. In this new study, the Rivera lab compared the function EWS-FLI1 to wild-type FLI1 and found that the phase-transition properties of the EWS prion-like domain are required to activate GGAA repeat enhancers. Tyrosine mutants that are unable to undergo phase transitions are inactive at GGAA repeats while the addition of even a small intact fragment of disordered prion-like portion of EWS is sufficient to confer wild-type FLI1 with the ability to activate these sites. These results thus link the phase transition properties of EWS to a tumor specific oncogenic gene expression program and suggest that similar mechanisms may be critical contributors to gene regulation in cancer and other diseases.



The prion like domain of the EWS-FLI1 oncogenic fusion protein is required for enhancer activation. The Ewing sarcoma oncogenic fusion protein EWS-FLI1 operates as an abnormal transcription factor and activates a large set of target genes by recruiting chromatin regulators, including the BAF complex, to induce new enhancers at GGAA repeats. This neomorphic property of EWS-FLI1 is not shared by the wild-type ETS factor FLI1 and is dependent on the phase-transition properties of the EWS prion-like domain. Tyrosine mutants that are unable to undergo phase transitions are inactive at GGAA repeats while the addition of even a small intact fragment of disordered prion-like portion of EWS is sufficient to confer wild-type FLI1 with the ability to activate these sites. These results link the phase transition properties of EWS to a tumor specific oncogenic gene expression program and suggest that similar mechanisms may be critical contributors to gene regulation in cancer and other diseases.

Puram SV, Tirosh I, Parikh AS, Patel AP, Yizhak K, Gillespie S, Rodman C, Luo CL, Mroz EA, Emerick KS, Deschler DG, Varvares MA, Mylvaganam R, Rozenblatt-Rosen O, Rocco JW, Faquin WC, Lin DT, Regev A, Bernstein BE. Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor Ecosystems in Head and Neck Cancer. Cell. 2017 Dec 14; 171(7): 1611-1624.e24.

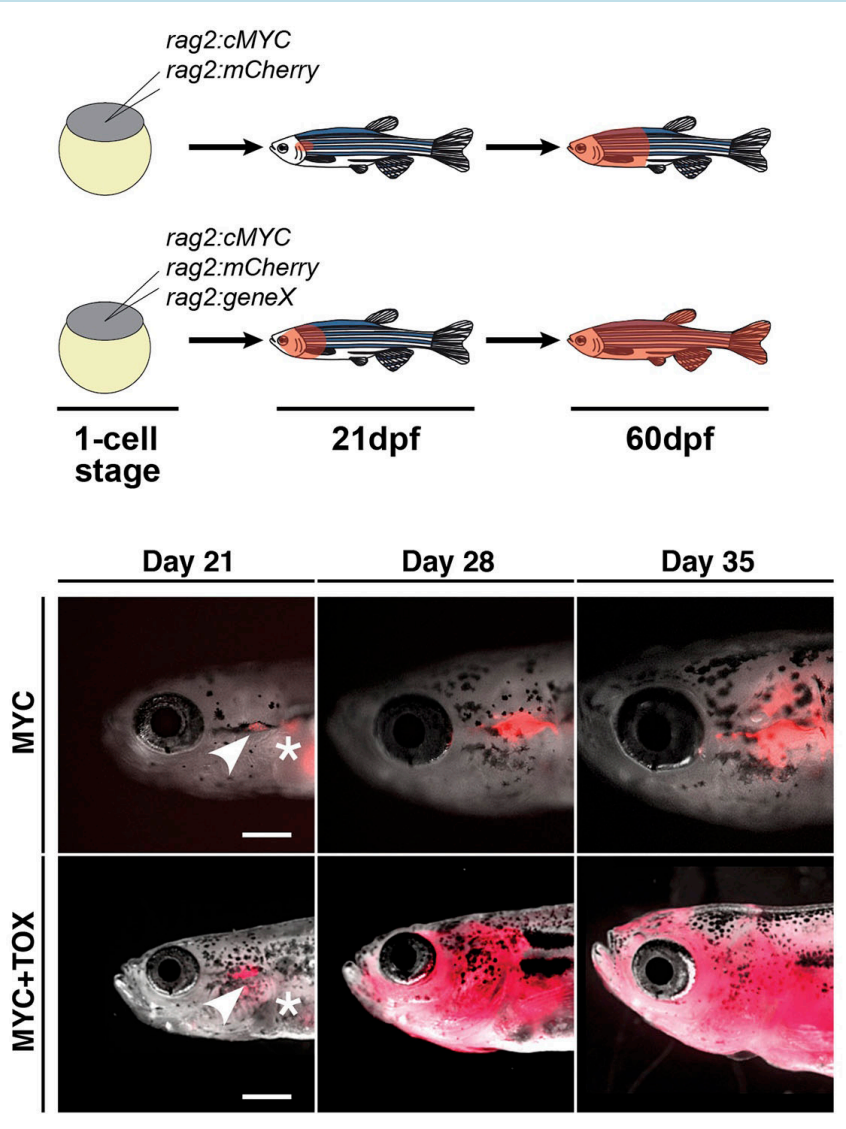


The Bernstein lab in MGH Pathology with colleagues at the Mass Eye and Ear Institute and the Broad Institute have completed a detailed single cell atlas of head and neck squamous cell carcinomas, defining the heterogeneous landscape of cancer cells, immune cells and stroma in primary tumors and metastases. The team identified a subpopulation of malignant cells that express a partial epithelial-to-mesenchymal (p-EMT) program that appear to drive invasion and metastasis in this disease. This work suggests new diagnostic methods for predicting cancer spread based on biomarkers in the primary tumor, as well as new avenues for therapeutically targeting metastasis programs.

Single cell RNA-sequencing identifies programs driving invasion and metastasis in head and neck squamous cell carcinoma. Transcriptome profiles of ~6,000 single cells from 18 head and neck squamous cell carcinoma (HNSCC) patients, including matched pairs of primary tumors and metastases were obtained. Cells expressing a partial epithelial-to-mesenchymal (p-EMT) program spatially localized to the leading edge of primary tumors in close proximity to cancer-associated fibroblasts. Integration of single-cell transcriptomes with bulk expression profiles for hundreds of tumors established p-EMT as an independent predictor of nodal metastasis, grade, and adverse pathologic features.

TOX Regulates Growth, DNA Repair, and Genomic Instability in T-cell Acute Lymphoblastic Leukemia. Lobbardi R, Pinder J, Martinez-Pastor B, Theodorou M, Blackburn JS, Abraham BJ, Namiki Y, Mansour M, Abdelfattah NS, Molodtsov A, Alexe G, Toiber D, de Waard M, Jain E, Boukhali M, Lion M, Bhere D, Shah K, Gutierrez A, Stegmaier K, Silverman LB, Sadreyev RI, Asara JM, Oettinger MA, Haas W, Look AT, Young RA, Mostoslavsky R, Dellaire G, Langenau DM. Cancer Discov. 2017 Nov;7(11):1336-1353.

Using an innovative transgenic screen in zebrafish, the Langenau lab of MGH Pathology has identified a protein called thymocyte selection-associated high mobility box protein (TOX) as the major oncogenic driver responsible for causing genomic DNA alterations and transforming normal T cells into aggressive leukemia. TOX is also required for leukemia cell growth in human disease and thus is a new, previously unexplored therapeutic target in this disease. Importantly, TOX is expressed in 95% of human T cell acute lymphoblastic leukemia suggesting TOX is a major oncogenic driver in the vast majority of patients with this disease. Using a wide array of functional analyses, TOX was found to be involved in the impairment of Non-Homologous End Joining (NHEJ) repair, a condition which is well known to cause genomic instability. Collectively, this work has uncovered important roles for TOX in regulating elevating genomic instability during leukemia initiation and sustaining leukemic cell proliferation following transformation.



A transgenic screen identifies TOX as a collaborating oncogenic driver in T cell acute lymphoblastic leukemia. Zebrafish were injected with MYC along with putative oncogenes identified to be amplified, over-expressed, or mutationally activated in human T-ALL (gene X). From this work, TOX was found to synergize potently with MYC to accelerate leukemia onset (bottom panels).

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 30 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. We have in these last six years carried out more clinical studies, involving more study participants, than any other center in Boston. Two studies, Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) and the Resolution of Allergy to Milk Protein (RAMP), have 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). In addition to a research concentration in Food Allergy, Dr. Perdita Permaul leads a project focused on the interaction between childhood obesity and allergic inflammation. The Division enjoys strong collaborations with academic and industry groups at BWH (The Channing Laboratory), BCH, MIT, The Broad Institute, Sanofi and others.

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.

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 (for example, Marfan syndrome and Loeys Dietz syndrome). 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

The Division of Pediatric Critical Care Medicine focuses on three areas of investigation in which we have achieved national and international recognition: 1) acute brain injury; 2) innovative technology; and 3) global health.

1. Acute brain injury: our faculty have established proof of principle that repetitive mild concussion in adolescent mice induces increased hyperphosphorylated human Tau protein in several regions of mouse brain that are also affected by chronic traumatic encephalopathy in NFL players. These findings will be leveraged to uncover mechanisms of tau phosphorylation as well as downstream mechanisms of neurodegeneration in an attempt to understand mechanisms contributing to development of chronic traumatic encephalopathy (CTE) in football players and war fighters subjected to repetitive traumatic brain injury. Pilot studies in the NFLPA grant have also demonstrated long-term fMRI changes in brain connectivity and response to CO2 inhalation may be physiological biomarkers of brain injury after repetitive sub-concussion threshold TBI. These studies could help to validate use of fMRI as a potential test for concussion recovery. The group has also focused on mechanisms of cognitive outcome in repetitive concussion and contusion models and has found that endothelial cells are a significant source of IL-1 beta and IL-18 in concussion and contusion models, and that genetic inhibition of IL-1R1 or caspase-1 exerts opposite effects on cognitive recovery in these models with protection in adolescent and adult concussion models. The group believes the significance is that in clinical trials, patients with different forms of TBI (e.g., concussion vs. contusion) may respond differently to genetic variations or possibly to therapeutic agents. The findings in adult models are under review at Annals of Neurology. Similar findings in an adolescent mouse repetitive concussion model are ready for manuscript submission at this time again to Annals of Neurology. In addition to this work, Dr. Whalen has continued his work on programmed cell death and functional outcome following intracerebral hemorrhage (ICH) in humans. In a manuscript published in Stroke (2017, 48:2549-2556) his lab showed that receptor interacting protein kinases (RIPKs) mediate programmed necrosis as well as functional outcome in a mouse intracerebral hemorrhage model. A small molecule RIPK1 inhibitor also reduced acute cell death. The results are the first proof of concept, using genetic and pharmacological tools, that RIPKs are involved in programmed cell death and functional outcome and that RIPK1 is in fact a therapeutic target for ICH in humans. Our division has been involved in several multi-center studies including the ADAPT (site PI) and TRACK II TBI (co-investigator) studies. For the investigators of the Approaches and Decisions in Acute Pediatric Traumatic Brain Injury (ADAPT) study, we have published a manuscript in J Neurotrauma (2017, 34:2220-2229) describing the distribution of Glascow Coma Scale (GCS) scores in children, the relationship between injury characteristics with the GCS score, and the association between the tripartite stratification of the GCS on mortality in children with severe TBI. Results of this analysis showed that overall, GCS score at the time of intracranial pressure (ICP) monitor placement was strongly associated with mortality across the pediatric age range. The hope is that this work may help in the development of models with GCS and other factors to allow identification of subtypes of children after severe TBI for future studies. Following passage of Massachusetts state legislation in 2010 imposing the strictest statewide age restrictions for Off-Road Vehicle (ORV) riding in the United States, the MGH Trauma and Injury Prevention Outreach Program sought to determine the overall impact of the new law. They performed a retrospective study investigating population-based rates of emergency department visits and inpatient hospital discharges for ORV-related injuries in children <18 years of age before and after the legislation's implementation. Results of this study published in Pediatrics (2017 Oct; 140(4)) demonstrated for the first time in this country that a comprehensive law, including restrictions on age, engine size, and private land use has led to a decrease in ORV-related injuries in children. Publication of these results could help this legislation to serve as a model for other state laws.

2. Innovative technology: Our division continued its longstanding efforts to explore innovative uses of telemedicine to improve patient care in the pediatric ICU setting. In a manuscript published in the Journal of Pediatrics (2017 Mar), our faculty shared the results of a proof-of-concept study indicating that remote parent participation in PICU rounds via telemedicine when parents are unable to be present at their child's bedside is feasible, enhances parent-provider communication, and offers parents reassurance. This innovative use of technology directly answers the call to healthcare providers from the Institute of Medicine and the American Hospital Association to develop programs using today's technology to promote patient- and family-centered care and to provide emotional support to families.

3. Global health: The division's global health research initiatives include exploration of innovative technology solutions for utilization in resource-limited settings. Two examples include 1) a meta-analysis published in Tropical Medicine International Health (2017, 22:1072-1080) on the utility of reagent strip leukocyte esterase assay for the diagnosis of meningitis in resource-limited settings; and 2) publication of a study evaluation a low-cost bubble continuous positive airway pressure system designed for resource-limited settings in Respiratory Care (2017 Oct).

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 molecular approaches to beta cell regeneration. 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 concern 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 internationally-known academic research division continues to be 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; 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. This research leverages clinical and community partnerships.

Genetics and Metabolism
The Division of Medical Genetics and Metabolism at MGHIC is dedicated to understanding the genetic basis of developmental and congenital disorders affecting the entire life course. We are actively engaged in basic science at the cellular and sub-cellular level at the bench and as well in translational and clinical studies to inform counseling, diagnostic and management services to help patients and physicians 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 world renown 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. Active clinical trials are also underway with lysosomal storage diseases and mitochondrial diseases. The MGH Genetics Division has been at the forefront of applying clinical whole exomic sequencing for diagnosis and new gene discovery in selected patients. Our services impact every field of pediatric and adult medicine.

Global Health
The Division of Global Health at MassGeneral Hospital for Children was founded in March 2010 and includes faculty, research fellows, postgraduate and undergraduate trainees and staff members. The primary goal of the Division is to build and foster international partnerships for interdisciplinary research, education and service to reduce health disparities and achieve optimal health for children and adolescents in resource-limited settings. Our faculty focus on developing innovative solutions to prematurity, birth asphyxia, neonatal sepsis, childhood pneumonia, diarrhea, and HIV in Africa, Asia, Central and South America by conducting high quality research, as well as developing and testing innovative technology to improve the quality of care provided to the world's children.

Hematology/Oncology
The Pediatric Hematology and Oncology program continues to focus on building excellence in multi-disciplinary clinics for our oncology and

hematology patients and expanding our clinical and lab-based research efforts. The Brain tumor, long-term survivor, and Hemophilia clinics are prime examples of this multidisciplinary effort. All three programs show increased growth with respect to new patient accruals. In addition to our therapeutic clinical trials we also have important companion studies examining quality of life and neurocognitive sequelae for our patients with brain tumors. We have recently become members of a Neuroblastoma and Medulloblastoma Translational Research Consortium and are participating in several novel clinical trials. We are collaborating with investigators in Pathology and the Cancer Center at MGH in several different research projects. Our joint research efforts with Dr. Miguel Rivera in Pathology have focused on the molecular pathogenesis of Ewing's sarcoma and medulloblastoma. We have an exciting new initiative with Dr. Shannon Stott in the Cancer Center to examine peripheral blood for exosomes and circulating tumor cells from patients with brain tumors and sarcomas. We continue our research with Dr. Jain in Radiation oncology examining the influence of the microenvironment in various pediatric solid tumors and novel approaches to treating medulloblastoma.

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. In 2017, our collaborative research project with Drs. Jacob Hooker and Nicole Zurcher (Martinos Center), which is aimed to identify an "inflammatory subtype" of autism, has produced very exciting preliminary findings. First, 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 brain 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). Importantly, based on this work, we have secured funding for the ongoing support of Dr. Nicole Zurcher (Instructor in Radiology), via a philanthropic donation. 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

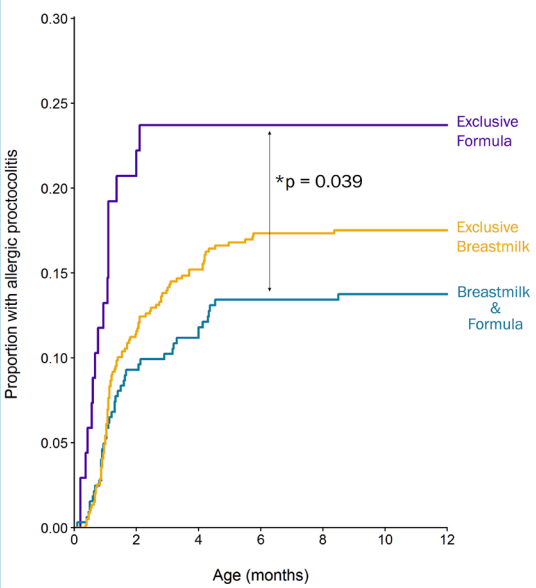
The research efforts in the Neonatology and Newborn Medicine Unit are multifaceted and range from basic science to epidemiology. All research projects share a common mission, which is to advance scientific knowledge aimed at improving the care and treatment of our very vulnerable patients and their families. 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 including the use of human pluripotent stem cells to better understand how genetic disorders and prematurity affect human development and efforts to create new strategies and treatment to mitigate their negative impact; 2. Neuroprotection strategies, including an examination of those factors that affect neurodevelopmental outcomes following hypoxic post-natal insults; 3. interventions to mitigate the effects of substance abuse disorders pre and post natum

Nephrology

The Nephrology Division has a major focus on the molecular biology of rare genetic disorders affecting the regulation of mineral ion homeostasis, with a particular emphasis on the different forms of pseudohypoparathyroidism type Ib (PHP1B) and hypoparathyroidism, and the regulation of phosphate. In addition we continue to pursue studies exploring the renin-angiotensin system and hypertension.

Pulmonary

The research focus of the Pulmonary Division encompasses 4 areas. The first 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 a novel whole exome and genetic panel , which allow for rapid and multiple gene analysis. We defined the spectrum mutations in a protein called ABCA3 that cause interstitial lung disease. The second areais an effort to develop new approaches to the treatment of Pseudomonas infections in the airway of patients with Cystic Fibrosis by defining the mechanisms that induce airway inflammation. The third area, is clinical research looking at the use of correctors and potentiators of CFTR to treat cystic fibrosis. The fourth area, focuses on genetic correctors for Duchenne's Muscular Dystrophy. In a landmark publication, Dr. Kinane demonstrated how eteplirsen reduced pulmonary function decline in patients with Duchenne's Muscular Dystrophy.



Kaplan-Meier curve using Cox regression for survival analysis. Subjects followed for mean follow-up time of 18.2 months.

Kaplan-Meier curve using Cox regression for survival analysis. Subjects followed for mean follow-up time of 18.2 months.

Science Initiative at the Broad Institute.

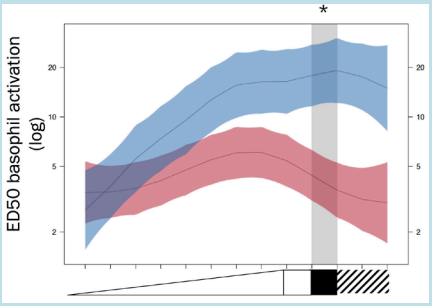
Notable Achievements 2017

Allergy and Immunology Risk Factors for the Development of Allergic Proctocolitis

From the Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) cohort, we have for the first time prospectively defined the cumulative one year incidence of allergic proctocolitis (AP) 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.

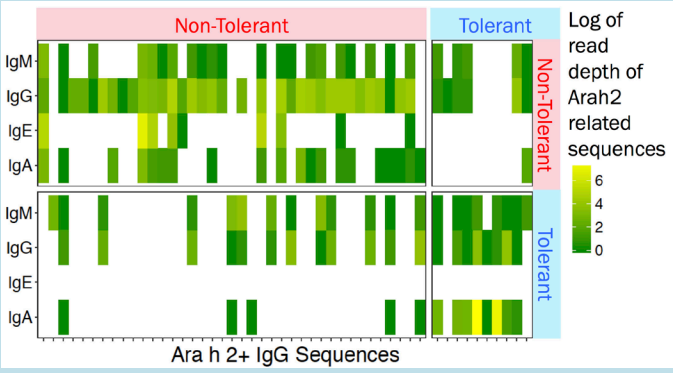
Breast-feeding from the time of initial feeding when combined with formula was associated with almost half the rate of AP ($p<0.05$). Mode of delivery, perinatal antibiotic exposure, and presence of siblings were not associated with AP (not shown), however eczema as well as a family history of food allergies, bloody stools or diet intolerance/feeding difficulties all were significantly associated with infant AP ($p<0.05$, not shown).

Longitudinal evaluation of microbiota composition is now underway in collaboration with Ramnik Xavier as part of the newly established Food Allergy



Ex vivo basophil sensitivity decreases in subjects who achieve sustained post OIT efficacy.

Mechanism of Immune Tolerance during Oral Allergen Immunotherapy



Ara h 2-specific repertoires are distinct in subjects with and without sustained clinical tolerance post OIT. ($p < 0.001$). The repertoire of non-tolerant subjects is broader and enriched for IgE-species whereas in tolerant subjects, the repertoire is more narrow and enriched for IgA.

Oral immunotherapy (OIT) is an investigational treatment of peanut and other food allergies that raises the threshold of peanut consumed without a reaction for the patients who tolerate it (~85%), but most (>50%) lose the benefit rapidly if they stop regular exposure. Non-IgE antibodies have been hypothesized to play a protective role and in vitro demonstrate mechanisms by which they can be suppressive. However, measured in bulk, all OIT patients experience induction of allergen-specific IgG, despite the clinical heterogeneity described.

In the context of the two clinical trials referenced above, we have been evaluating the hypothesis that this paradox can be explained by functional differences in the induced IgG, including its clonal specificity – the repertoire of antibodies that make up the overall concentration, which is what is routinely measured in bulk.

Sarita Patil, now a newly independent investigator (2018) has shown that the BCR repertoire assessed by sequencing and its function are distinct between patients with transient versus sustained OIT-induced clinical efficacy.

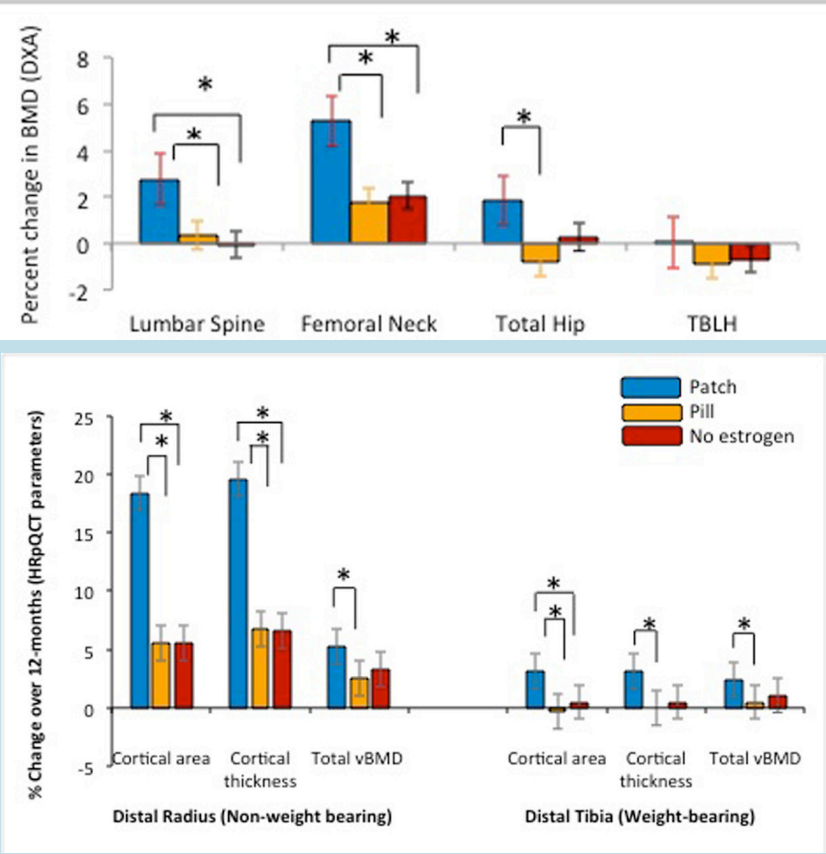
Endocrinology

In the past year, Dr. Misra's laboratory completed an important randomized controlled trial of transdermal 17-β estradiol vs. oral ethinyl estradiol vs. no estrogen in 14-25 year old oligoamenorrheic athletes, and showed significant improvements in bone density, geometry and structure in those who received the transdermal estradiol patch compared to the oral pill (Figure 1). Participants randomized to the pill had significant reductions in IGF-1 (a bone trophic hormone important for adolescent bone accrual), associated with a reduction in bone formation markers, and increases in sex hormone binding globulin (which may reduce levels of bioavailable gonadal steroids). These data are potentially paradigm shifting and were presented at a platform presentation at the American Society of Bone Mineral Research. The group has also shown in a different study that and that metabolic outcomes are comparable following Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) in children with morbid obesity, however, RYGB has a slight edge over VSG, particularly for weight outcomes.

Further, Dr. Stanford has demonstrated in the largest study to date that weight loss pharmacotherapy serves as a useful adjunct to bariatric surgery in patients with inadequate weight loss or weight regain, and that even when consumers have exposure to employer wellness programs that target BMI, their health insurance often excludes obesity treatments.

Dr. Stanley and Dr. Misra were co-authors on positions papers that were the result of a long consensus process but will change the paradigm for the management of (i) children with lipodystrophy and (ii) adolescents with functional hypothalamic amenorrhea respectively.
Currently the faculty includes two researchers with R01 funding, and three with K23 funding. Faculty members were recipients of multiple awards, including the following:

- Deborah Mitchell: Rising Star Award, ASBMR 2016
- Vibha Singhal: Young Investigator Award, ASBMR 2016; Early Investigator Award, Endocrine Society 2017; Janet MacArthur Award for Excellence in Clinical Research, Women in Endocrinology 2017
- Charumathi Baskaran: Early Investigator Award, Endocrine Society 2017
- Fatima Stanford: Massachusetts Medical Society Women's Health Award 2017; Harvard Medical School Amos Diversity Award 2017; Emory University Inaugural Top 40 Under 40 2017



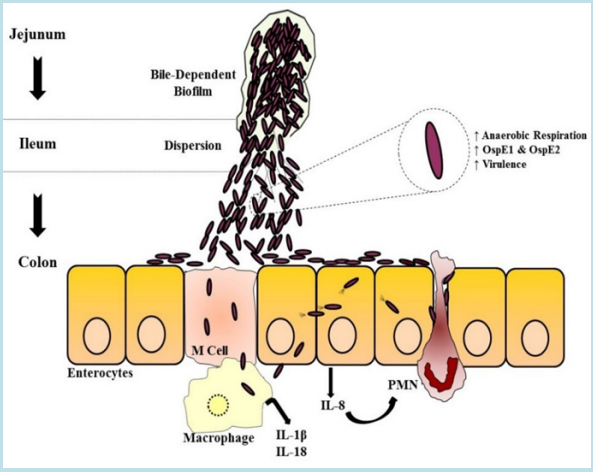
Percent change in bone density and geometry in oligo-amenorrheic athletes randomized to the estradiol patch, oral pill or no estrogen

Ackerman KE, Slattery M, Singhal V, Baskaran C, Campoverde Reyes K, Toth A, Lee H, Bouxsein M, Klibanski A, Misra M. Transdermal 17-β Estradiol has a Beneficial Effect on Bone Parameters Assessed using HRpQCT Compared to Oral Estrogen-Progesterone Combination Pills in Oligo-amenorrheic Athletes: a Randomized Controlled Trial. Book of Abstracts. ASBMR 2017

Gastroenterology, Hepatology & Nutrition Mucosal Immunology and Biology Research Center

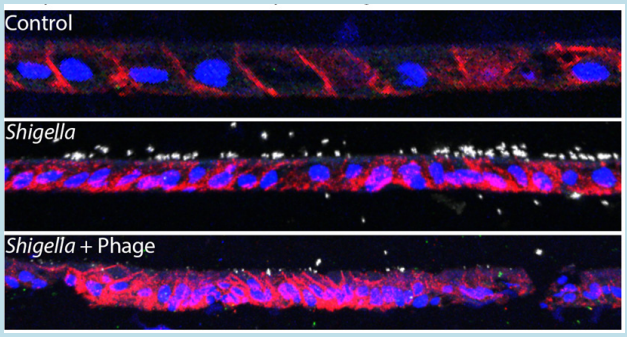
Researchers at the MIBRC have been utilizing novel techniques and approaches to study critical aspects of global health. Human-specific bacterial pathogens such as Shigella and Salmonella enterica serovar Typhi cause significant morbidity and mortality around the globe each year. Despite years of research, successful vaccines have not been developed and antibiotic resistance has complicated treatment. First, in recognizing a need to understand how bacterial pathogens

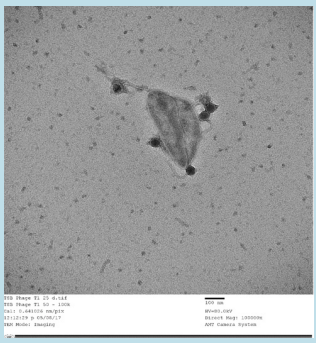
exploit host signals during infection, MIBRC researchers have demonstrated the mechanism by which S. flexneri resists bile salts exposure in the small intestine and uses such exposure as a trigger for biofilm formation, which increase the ability of the pathogen to resist antibiotics. The studies also demonstrated that the loss of bile salts, which normally occurs as 95% of bile is recycled back into circulation in the terminal ileum, enables a hypervirulent Shigella to disperse the biofilm for subsequent infection of the colonic epithelium. Researchers have also identified, for the first time, adherence factors expressed by S. flexneri following bile salts exposure (manuscript submission in process), which have important implications for vaccine development. Second, analysis of early events in S. Typhi infection of human tissue isolated from donors has demonstrated that the bacteria repress host gene expression, coordinate specific virulence gene expression, and regulate cytokine secretion to evade recognition by the innate immune system (revised manuscript submission in process). Interestingly, the S. Typhi host-pathogen interaction differed from the S. Typhimurium interaction, which has enhanced our understanding of S. Typhi infection and will allow us to pursue the development of new therapeutics to control infection. Third, researchers have utilized the novel human organoid-derived epithelial model developed at the MIBRC, which adequately represents the cellular architecture of the colon and small intestine, to assess Shigella and Salmonella infection in a human-based model (manuscript in preparation). This novel culture model will help to evaluate the complex mechanisms of host-pathogen interactions and will provide new insights for novel therapeutic development. Finally, we are working with collaborators at MIT to develop engineered pathogen-specific bacteriophages to specifically target these enteric bacteria while preserving commensal organisms as a practical treatment option and alternative to antibiotics, especially for children suffering from environmental enteropathy. Phage have been tested against Shigella following bile salt exposure using our organoid monolayer model. In all and as a result of our novel approaches and methodologies, we are utilizing the most accurate human-like environment to study the natural infection process of Shigella and Salmonella to date and are pursuing innovative therapeutic design strategies to combat these pathogens on a global scale.



Model of Shigella infection following bile exposure. During small intestine transit, bile exposure induces transcriptional changes, bile resistance mechanisms, and biofilm formation. Biofilm dispersion occurs in the terminal ileum. Bile-induced transcriptional changes, such as increased anaerobic respiration and induction of osp and ipaH virulence genes, enable Shigella to efficiently adapt to the colonic environment, attach and invade epithelial cells, and establish infection. Reference: Nickerson KP, Chanin RB, Sistrunk JR, Rasko DA, Fink PJ, Barry EM, Nataro JP, and Faherty CS. Infect Immun. 2017 May 23;85(6). pii: e01067-16. PMID: 28348056.

Analysis of bacteriophage efficacy against Shigella flexneri.
Left: Confocal immunofluorescence analysis of uninfected control (top), 2457T-infected (middle), and 2457T-infected, phage treated (bottom) human epithelial organoid-derived monolayers. Staining: anti-Epcam (red) for enterocytes, DAPI nuclear stain (blue), and the biotin-conguated anti-Shigella antibody (white). Bacterial adherence and invasion were detected, which were reduced with phage treatment. Plating for bacterial recoveries demonstrated complete lysis of S. flexneri by the phage (data not shown).
Right: Transmission electron microscopy image (10,000X) of the T1-like bacteriophage attached to a dying S. flexneri cell isolated from broth cultures following bile salts exposure.

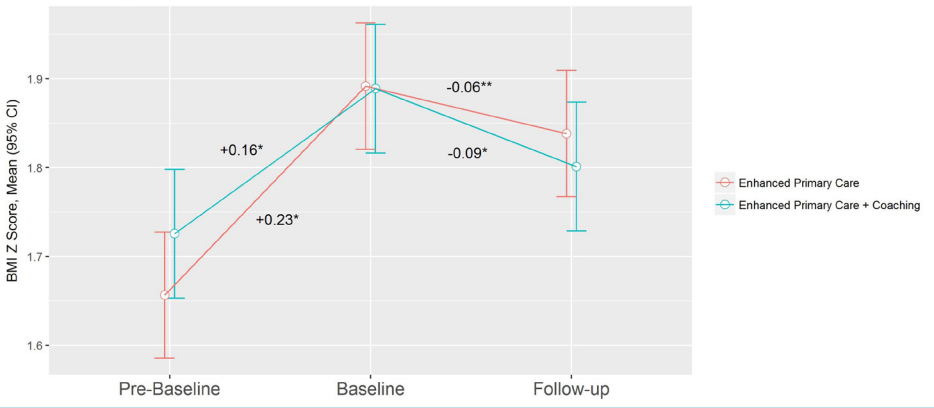




General Academic Pediatrics

Connect for Health: Design of a clinical-community childhood obesity intervention testing best practices of positive outliers

Childhood overweight and obesity place a significant burden on morbidity and quality of life. Clinical interventions to reduce obesity have been somewhat effective but are often limited in their effectiveness due to the social and environmental barriers that impede improvement in obesity related behaviors. Dr. Elsie Taveras and her research team conducted Connect for Health, a randomized controlled trial that used novel approaches to the delivery of care in 6 pediatric primary care practices of Harvard Vanguard Medical Associates and leveraged clinical and community resources to improve body mass index (BMI) and family-centered outcomes. The intervention was built on the practices of positive outlier families, families who have succeeded where many others have not to change health behaviors, improve BMI and develop resilience in the context of adverse built and social environments. The study also utilized geographic information systems and community mapping, interactive text messaging and video conferencing for study visits to tailor the intervention to the individual's environment and needs. Connect for Health randomly assigned 721 patients ages 2-12 years old to one of two groups: 1) enhanced primary care or 2) enhanced primary care plus contextually tailored, individual health coaching. In both groups, clinicians received alerts when patients had a BMI > 85th percentile and clinical decision support tools for pediatric weight management and parents received educational materials, a Neighborhood Resource Guide and monthly text messages. Additionally, in the enhanced primary care + coaching group, parents received twice-weekly text messages and 6 telephone or video contacts with a health coach. At 1 year, children in both groups showed improvements in BMI z-score and some family centered outcomes, though being in the group receiving health coaching did not have significantly greater effects on BMI or the family centered outcomes than enhanced primary care alone. The intervention components were feasible to deliver, acceptable to parents, and did not have adverse effects on parents' perceptions of their children's health care services. The next step will be to disseminate the intervention in other healthcare systems.



Adjusted Mean BMI Z-Score Changes from Pre-Baseline (1-Year Prior to Baseline), Baseline, and 1-Year Follow-Up (N=560)

Clinical effectiveness of the Massachusetts Childhood Obesity Research Demonstration initiative among low-income children.

The Massachusetts Childhood Obesity Research Demonstration (MA-CORD) project was a multifaceted initiative to prevent childhood obesity among low-income children aged 2-12 years in two federally qualified community health centers (FQHCs). FQHCs implemented: (1) pediatric weight management training for providers and staff, (2) electronic decision supports for clinicians, (3) on-site Healthy Weight Clinics for child weight management, (4) community health worker integration, and (5) healthful clinical environment changes. A demographically matched FQHC served as the control site. Compared to children in the control site (n = 2,286), children in one FQHC (n = 1,368) had a significant decline in BMI z scores following the start of the intervention (−0.16 units/y; 95% confidence interval: −0.21 to −0.12). No evidence of an effect was found in the other intervention FQHC (n=111).

Taveras EM, Perkins M, Anand S, Woo Baidal JA, Nelson CC, Kamdar N, Kwass JA, Gortmaker SL, Barrett JL, Davison KK, Land T. Clinical effectiveness of the Massachusetts Childhood Obesity Research Demonstration initiative among low-income children. Obesity (Silver Spring). 2017 Jul;25(7):1159-1166.PubMed Central PMCID: PMC5506684.

Pediatric Accountable Care Organizations: Insight From Early Adopters

Accountable Care Organizations (ACOs) have emerged as one of the main new strategies for improving care and lowering costs in the delivery of health care. Although there has been much experimentation in the development of ACOs for adult populations, including the pioneering work of the MGH focused on frail elderly populations, little work has described pediatric experiences with ACOs. During his time as president and a member of the executive committee of the American Academy of Pediatrics (AAP), Dr. Perrin led efforts to strengthen practice and payment reform in pediatrics. Dr. Perrin directed a study through the AAP of pediatric ACO developments, including in-depth case studies of five pioneer pediatric ACOs, a pediatric ACO summit co-led with Leavitt Partners (a leading health care organization and financing consulting group), and a market scan of pediatric ACO growth. This work culminated in a publication in Pediatrics describing early experiences with

pediatric ACOs, contrasting their experience with what is known about adult ACO development, and providing a series of recommendations to help ACOs improve pediatric care. This experience emphasized the importance of physician leadership and the need for up-front investment in team development, clinician training, and incentivizing change. None of the pediatric ACOs could fund initial development costs without substantial support from hospitals. All pediatric ACOs developed methods to identify particularly costly and complex patients and applied case management strategies to improve their care. They also all provided training for network primary care pediatricians in quality assessment and improvement and in development of team care models. All pediatric ACOs also recognized the need for behavioral health integration in primary care settings, although they applied different models for integration. The study identified areas needing different pediatric specifications – standard ways to measure care quality, payment that recognizes that value for care in child health differs substantially from value in adult care, as well as the need for hospital or other financing to achieve success.

Perrin JM, Zimmerman E, Hertz A, Johnson T, Merrill T, Smith D. Pediatric accountable care organizations: Insight from early adopters. Pediatrics, 2017; 139: e20161840.

Innovative Health Care Financing Strategies for Children and Youth With Special Health Care Needs
Especially with the recognition of the need to control the growth of health care costs as well as improve health outcomes for Americans, much effort has gone to move payment systems from fee for service (FFS) (paying for each specific service provided) to paying for value (offering incentives for quality or improved outcomes). Most organizations have moved away from strict FFS arrangements to some form of enhanced payment for meeting certain quality metrics or in some cases toward forms of payment capitation, where providers are paid for populations cared for creating incentives to diminish use of unnecessary and expensive procedures or treatments. Much work has led to measures of value and their implementation in adult health care. Much less work has taken place in pediatrics, yet the value proposition for pediatrics differs substantially from that for adults. Pediatric care very much emphasizes prevention, yet the payoff for prevention, other than for immunizations, often takes places a few to many years after the intervention. Short-term benefits do accrue from good pediatric care, and improved care for the small number of children who engender high expenditures can lead to short-term savings. Nonetheless, many of the benefits of good pediatric care – lower special education costs, improved school performance, lower rates of substance use and incarceration in adolescence, and lower rates of chronic disease in adults – all occur several to many years later. For children with special health care needs – chronic health conditions – the issues are even more complex. What improvements are needed for children with arthritis, sickle cell disease, or mental health conditions? The American Academy of Pediatrics led an effort to describe the state of the art in value-based payments for children with special health care needs in pediatrics, published in a supplement to Pediatrics. Dr. Perrin, given his prominence in pediatrics, quality assessment, and childhood chronic conditions, provided an introduction and overview of the supplement.

Perrin JM. Innovative financing strategies for health care services for children and youth with special health care needs (CYSHCN). Pediatrics, 2017; 139: S85-S88.

Autism Intervention Research Network on Physical Health and the Autism Speaks Autism Treatment Network
The joint autism network comprised of the Autism Intervention Research Network on Physical Health (AIR-P) and the Autism Speaks Autism Treatment Network (ATN) seeks to improve the health and quality of life of children with autism spectrum disorder (ASD). Dr. Kuhlthau is the PI of the AIR-P grant and the co-director of the clinical coordinating center of the joint network. The network is comprised of 12 multidisciplinary autism clinics in North American. Guided by family advisors, ATN/AIR-P conducts research projects to further evidence and creates clinical guidelines to improve and standardize care. The joint network has made fundamental differences to the ways we study, diagnose, and treat ASD. The network emphasizes family engagement and improving care for underserved populations. ATN/AIR-P centers also engage in quality improvement activates as part of the Autism Learning Network, which provides a collaborative laboratory for developing and testing interventions and accelerating the adoption of effective interventions and system management approaches into practice.

A randomized, placebo controlled trial of metformin for the treatment of overweight induced by antipsychotic medication in young people with ASD: Open-label extension.
This open-label extension followed a 16 week, double-blind random control trial studying the use of Metformin for weight stabilization among children with autism spectrum disorder currently taking atypical antipsychotics. In the original RCT, 61 children and adolescents ages 6-17 who were prescribed atypical antipsychotics were randomized into either a control group or an intervention group that would receive Metformin for weight stabilization. The extension study enrolled 52 participants from the acute trial, 22 of whom had been on Metformin and 30 who had been on placebo. BMI decreased and body composition improved for those who had originally been on the placebo but were switched to Metformin in the open-label trial. Those who were on Metformin through both studies maintained their lowered BMI but did not see any further decrease during the open label extension. This study supports the findings of the original RCT and also suggests the feasibility of using Metformin as a longer-term solution to weight gain issues in this population. This adds further evidence that Metformin may be an appropriate weight stabilizer for children with autism spectrum disorder who are experiencing weight gain from atypical antipsychotic medication use.

Anagnostou E, Aman MG, Handen BL, Sanders KB, Shui A, Hollway JA, Brian J, Arnold LE, Capano L, Hellings JA, Butter E, Mankad D, Tumuluru R, Kettle J, Newsom CR, Hadjiyannakis S, Peleg N, Odrobina D, McAuliffe-Bellin S, Zakroysky P, Marler S, Wagner A, Wong T, Mackin EA, Veenstra-VanderWeele J. Metformin for treatment of overweight induced by atypical antipsychotic medication in young people with autism spectrum disorder: A randomized clinical trial. JAMA Psychiatry. 2016 Sept 1; 73(9): 928-37.

Handen, B.L., Anagnostou, E., Aman, M.G., Sanders, K.B., Chan, J., Hollway, J.A., Brian, J., Arnold, L.E., Capano, L., Williams, C., Hellings, J.A., Butter, E., Mankad, D., Tumuluru, R., Kettel, J., Newsom, C.R., Peleg, N., Odrobina, D., McAuliffe-Bellin, S., Marler, S., Wong, T., Wagner, A., Hadjiyannakis, S., Macklin, E.A., Veenstra-VanderWeele, J. A randomized, placebo controlled trial of metformin for the treatment of overweight induced by antipsychotic medication in young people with ASD: Open-label extension. Journal of the American Academy of Child and Adolescent Psychiatry. 2017 October, Volume 56, Issue 10, Pages 849-856.e6.

A Prospective Study of the Concordance of DSM-IV and DSM-5 Diagnostic Criteria for Autism Spectrum Disorder.
As the DSM-IV transitioned to the DSM-5, diagnostic criteria for many disorders, including autism spectrum disorder (ASD), evolved. Previous studies measuring concordance between the two diagnostic standards looked only retrospectively at already diagnosed individuals, or compared the DSM-IV with an early draft of the DSM-5. This study aimed to discern parity between the two diagnostic standards and to determine if children with an ASD diagnosis under old criteria would be diagnosed again under DSM-5 criteria. DSM-5 criteria showed excellent specificity and good selectivity comparative to the DSM-IV standards. There was some discordance, however, as 20% of children who met criteria for Asperger's under the DSM-IV did not meet for ASD diagnosis under the DSM-5. Similarly, 70% of children who met criteria for Pervasive Developmental Disorder Not Otherwise Specified did not meet criteria for ASD under DSM-5 standards. There was also greater diagnostic discordance among children who were female or had a higher IQ. The findings of this study have far reaching clinical implications, as DSM-5 criteria are more stringent and could overlook more subtle or ambiguous symptoms. Understanding the ways in which this update will change diagnoses, and thus eligibility for treatment, for these children is essential in ensuring that all children with ASD are receiving appropriate care.

Mazurek, M.O., Lu, F., Symecko, H., Butter, E., Bing, N.M., Hundley, R.J., Poulsen, M., Kanne, S.M., Macklin, E., & Handen, B.L. (In Press). A prospective study of the concordance of DSM-IV and DSM-5 diagnostic criteria for autism spectrum disorder. JADD. doi: 10.1007/s10803-017-3200-7.

Associations of Quality of Life with Health-related Characteristics among Children with Autism
Previous studies about a child with Autism Spectrum Disorder's (ASD) quality of life focus primarily on the behavioral problems associated with the disorder. This study examined the relationship between a child with ASD's quality of life and both behavioral and physical health conditions such as sleep and digestive problems. The study found that gastrointestinal issues, including constipation, acid reflux, and pain, were associated with a lower quality of life. Bipolar disorder and worse sleep quality were also related to a lower quality of life. These associations were consistent over time, suggesting that the impacts behavior and physical health have on quality of life will not lessen without intervention. Therefore, clinicians should screen for these factors as they work with families and children on treatment plans.

Kuhlthau, KA, McDonnell, E, Coury, DL, Payakachat, N, Macklin, E. Associations of quality of life with health-related characteristics among children with autism. (2017). Autism.

Maternal Substance Use Disorders and Infant Outcomes in the First Year of Life among Massachusetts Singletons, 2003-2010.
Substance abuse treatments for pregnant women and their infants are insufficient and inadequate. While maternal substance use disorders (SUD) are generally known to be harmful for their newborns, previous efforts to more specifically characterize those risks have been limited - due to restricted or biased study samples, inadequate methodology for ascertaining SUD, and reluctance of providers or women to identify SUD during pregnancy. This current study is part of a series of methodologically enhanced MA population-based epidemiologic studies examining the impact of maternal SUD on the health of women, newborns and infants through their first year of life. These multi-year studies examine the maternal and infant outcomes for all MA births from 2003-2010 - using their birth certificates, associated hospitalization utilization data (MA PELL Data System), and linked MA Bureau of Substance Abuse Services participant treatment data. Women with SUD are identified through an innovative and more expansive women-centric methodology utilizing a wide-range of health and treatment data bases, especially ED visits, up to five years prior to the targeted birth event (Derrington et al 2015). This current study builds upon from the prior Kotelchuck et al study (2016) that documented the widespread prevalence of SUD among MA births and its negative impact on birth outcomes, and the limited number of women with SUD receiving any SUD treatment services, plus the positive impact of SUD treatment on birth outcome. This current study follows those same SUD exposed newborn infants longitudinally through the first year of life, and after controlling for maternal characteristics and preterm birth, documents the continued impact of SUD exposure across a wide range of neonatal clinical conditions, including more intrauterine growth restriction, cardiac, respiratory, neurologic, infectious, hematologic, and feeding/nutrition problems; prolonged hospital stay, higher mortality and increased hospitalization over the first year of life. This study provides important clinical information for treating

children of mothers with at MGH and throughout the State during the current SUD crisis; and it adds to the call for more clinical and public health services for the mothers with SUD and their infants.

Hwang SS, Diop H, Liu CL, Yu Q, Babakhanlou-Chase H, Cui X, Kotelchuck M. Maternal Substance Use Disorders and Infant Outcomes in the First Year of Life among Massachusetts Singletons, 2003-2010. J Pediatr. 2017 Dec;69-75. PMID: 29050752

Lessons Learned: Implementation of Pilot Universal Postpartum Nurse Home Visiting Program, Massachusetts 2013-2016.
Universal newborn home visiting is one of the cornerstones of the European Maternal and Child Health (MCH) and social welfare system. Yet in the United States today, home visiting is limited, occurring mostly through isolated freestanding programs serving targeted high-risk populations. Developing universal newborn home visiting programs has been a long-standing dream of the MCH community. This paper describes the practical implementation experiences of the Massachusetts Department of Public Health's (MDPH) Welcome Family Program – a universal home visitation program that offers a one-time visit by a nurse to new mothers up to eight weeks postpartum - being piloted in four communities across MA. MGH leads its evaluation (Kotelchuck PI). Welcome Family program served over 3000 families in its first three years. This paper synthesizes its initial implementation successes and challenges related to outreach and enrollment, program operations, and linkages with community resources. Overall, the initial start-up experiences were mixed. Early challenges included insufficient referrals to a new program (the hospital-based nurse recruitment system didn't function as planned) and more limited maternal willingness to participate than anticipated– resulting in substantial under enrollment given its universal participation goals. Second, the actual home visits were effectively implemented and well received, and continuously refined over time. Third and finally, the Welcome Family program did not yet serve as an effective entry point into the existing MA system of early childcare, nor did it even have sufficient capacity to serve all women giving birth in the targeted communities. The MDPH and local Welcome Family implementation agencies initiated a series of CQI initiatives and tested several innovative strategies to address some of the early program deficits. While universal home visiting programs would appear to be hard to implement, MDPH remains committed to the success of Welcome Family and its expansion statewide. Practical lessons learned from the Massachusetts pilot can inform other states' efforts to enhance their early childhood systems of care through expanding universal home visiting.

Stetler K, Silva C, Manning SE, Harvey EM, Posner E, Walmer B, Downs K, Kotelchuck M. Lessons Learned: Implementation of Pilot Universal Postpartum Nurse Home Visiting Program, Massachusetts 2013-2016. Matern Child Health J. 2017 Nov 8. PMID: 29119476

Father's Role in Preconception Health.
Knowledge of the importance of men's preconception health and health care for reproductive outcomes and men's own health across the life course is very limited. This conceptual and research agenda setting paper grew in part out of an NICHD-led, multi-agency federal research agenda setting conference on Paternal Involvement in Pregnancy Outcomes. This conference was notably innovative in expanding the traditional Paternal/Fatherhood paradigm to include a new conceptual focus on Men's Preconception Health. Dr. Kotelchuck, having written previously on men's preconception health (along with Dr. Lu, the Director of the federal Maternal and Child Health Bureau), made the keynote presentation– from which this paper was derived. This essay introduces the new concept of men's preconception health and health care, and then explores six direct and indirect ways that men's preconception health and health care influences reproductive outcomes for the infant and the mother, as well as for men's own health and development—planned and wanted pregnancies (family planning); enhanced paternal biologic and genetic contributions; improved reproductive health biology for women; improved reproductive health practices and outcomes for women; improved capacity for parenthood and fatherhood (psychological development); and enhanced male health through access to primary health care. Given that research on men's preconception health and health care is very limited and often siloed, this essay proposed a research agenda to advance this topic in three broad domains, using the Richmond and Kotelchuck policy development framework: increasing the basic epidemiology and risk factor knowledge base; implementing and evaluating men's preconception health/fatherhood interventions (addressing clinical health care, psychological resiliency/maturation, and social determinants of health); and fostering more fatherhood health policy and advocacy research. This essay provides a new conceptual framework for the substantial recent increase in research and practice initiatives to actively include fathers in reproductive, pediatric, and early child development programs nationally and more specifically here at MGH.

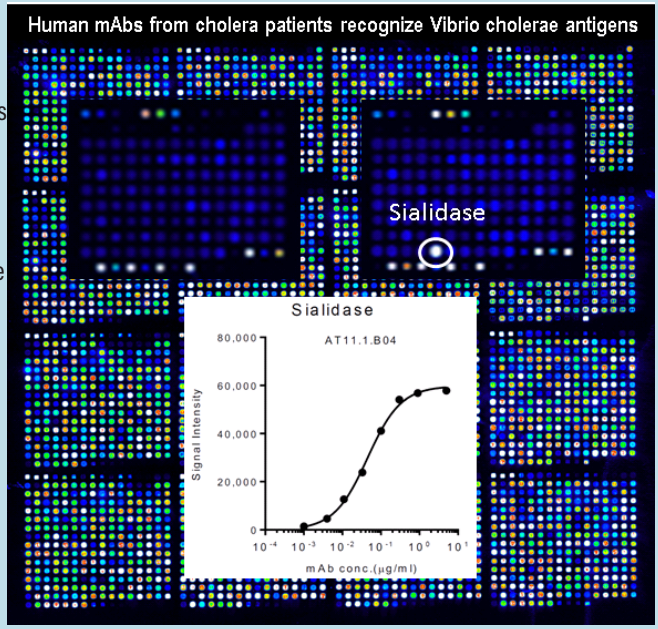
Kotelchuck M, Lu M. Father's Role in Preconception Health. Matern Child Health J. 2017 Nov;2025-2039. PMID: 28983715

Global Health
Advances in cholera – steps forward towards a better understanding of the human immune response and better cholera vaccine. (IMAGE – lightbrite)
Dr. Jason Harris, an NIH funded investigator, and a recipient of this years MGH Center for Global Health's Service Award, assumed the role of director of the division of pediatric global health in October 2017. His group has collaborated with investigators in Bangladesh and Haiti, and over the past year has made notable findings that have advanced our understanding of the mechanisms of immunity against Vibrio cholerae,

the cause of 3 million cases of severe diarrhea and approximately 100,000 deaths annually. Their recent work examining the B repertoire of V. chorea infection using both a novel antigen array and single-cell/ single antibody based screening approach was published as an editor's choice article in mBio at the end of 2016. The study demonstrates that the human immune response against cholera is directed primarily at three dominant antigens including a novel sialidase antigen, but that the functional antibacterial activity of the response is derived from highly specific antibodies which target at the O-specific polysaccharide in a serotype specific manner.

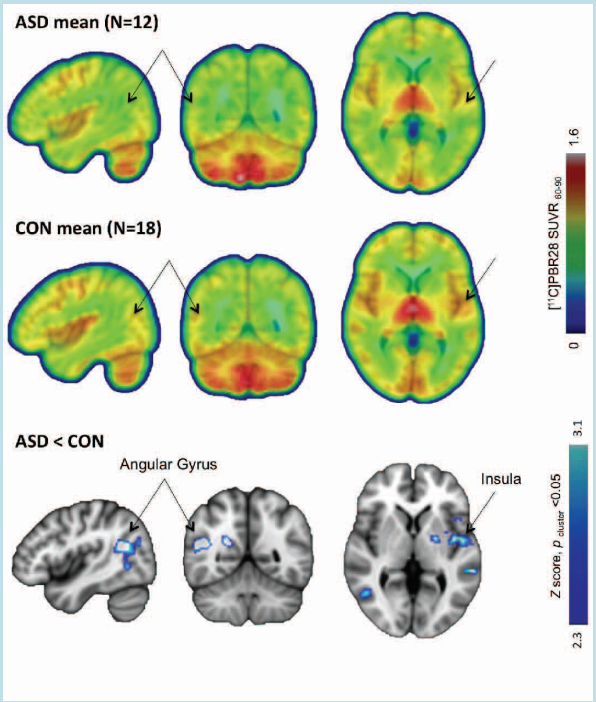
Kate Powis, MD, an NIH funded investigator, and international leader in the area of pediatric HIV infection organized the 3rd HIV-Exposed Uninfected Workshop in Paris with sponsorship from the World Health Organization and the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER). The conference was attended by over 200 participants.

Peter Moschovis, MD, MPH, led a study of a new point of care, smartphone-based diagnostic application to diagnose pneumonia by analyzing the sound of a patient's breathing. While the app didn't perform as well in diagnosing pneumonia as hoped, the data was used to create refinements in the approach and a follow-up study is now underway.



A Vibrio cholerae proteome array containing 3,647 ORFs were expressed by in vitro translation, and spotted onto nitrocellulose-coated glass slides where their expression was confirmed as shown in the background image. These arrays were initially probed with pools of MAbs of unknown specificity and a targeted array of potential hits was probed with individual MAbs identifying V. cholerae sialidase as a major target of the human immune response to cholera (shown in the inset images).

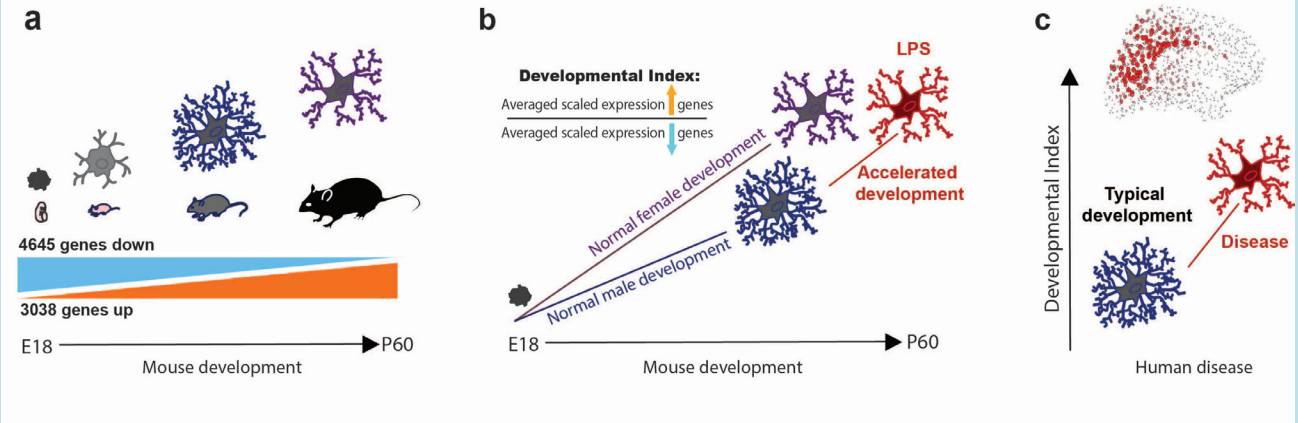
Lurie Center



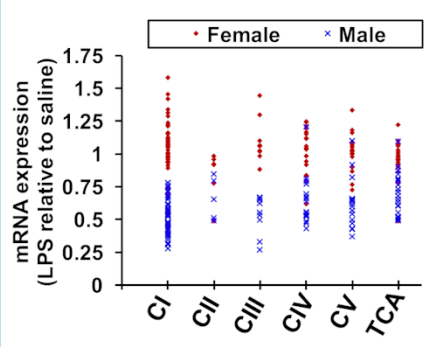
Decreased TSPO expression in individuals with ASD

Evidence of a sex difference in microglial cell development in mice and post-mortem human brain, and greater reactivity to immune activation in males. (Hanamsagar et al., GLIA, 2017)

Voxelwise whole brain analysis showing decreased [11C]PBR28 SUVR in individuals with ASD (N=12) compared to CON (N=18) in insular cortex and angular gyrus. Data are shown at MNI coordinates +44, -54, +2). Group means are shown in top (ASD) and middle (CON) panels. Statistical maps are shown in the lower panel and show data threshold at Z>2.3, cluster corrected at p<0.05.

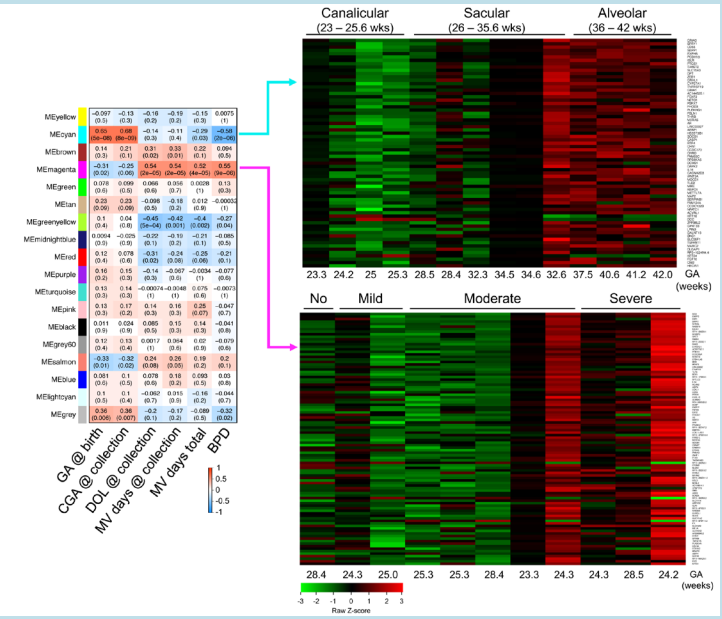


Microglia, the primary immune cells of the brain, were purified from the developing brains of male and female mice and transcriptionally profiled. Genes that monotonically increased or decreased over normal development were identified and compared between males and females. (b) Plotting the relative number of genes that increase over development vs decrease over development in healthy mice, and in response to an immune challenge with the bacterial mimic LPS reveals that female microglia develop more quickly than male microglia, and that LPS accelerates development only in males. (c) Analysis of the same microglial genes identified in mice in postmortem human brain reveals that accelerated microglial development is associated with several neurological diseases, including ASD. The sex bias in microglial development may explain some of the sex bias in ASD, with greater incidence in males. E=embryonic day, P=postnatal day



Mitochondrial gene expression differs between male and female microglia. 2hr following saline or LPS injection, transcriptomic analyses were performed on microglia isolated from hippocampus of mice. mRNA expression of female (red) and male (blue) ETC subunits (Complex I-V: CI-CV) and TCA cycle genes. Every point is an individual gene. n = 5-7 per

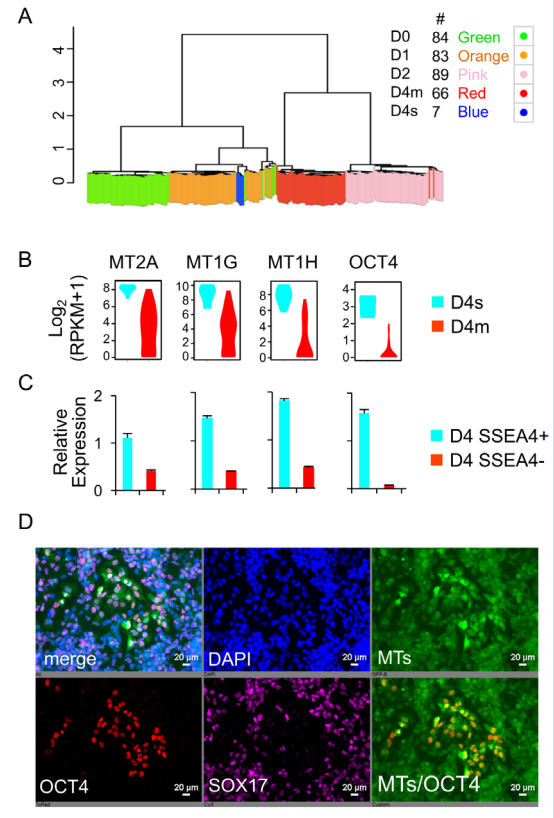
TSPO is a mitochondrial protein that may indicate a change in metabolism in cells. As described above, we have demonstrated for the first time using [11C]PBR28 PET imaging, that translocator protein 18 kDa (TSPO), a protein whose expression is hypothesized to depend on glial activity states, is strikingly decreased in its expression in adults with ASD compared to healthy controls, in several brain regions. TSPO is expressed on the outer mitochondrial membrane of cells with enrichment in microglia (and less so in astrocytes), and is a validated marker for glial cells, but virtually nothing is known about what TSPO expression means for the function of glia, or their mitochondria, and its potential implications for ASD. The aim of our ongoing work is to determine the role of TSPO in mitochondrial function in microglia vs. other neural/glial cell types. Our preliminary data (Figure 3) shows that mitochondrial genes are dramatically different in expression between male and female immune cells (microglia). We believe these data have relevance for the sex bias in ASD.



Neonatology and Newborn Medicine

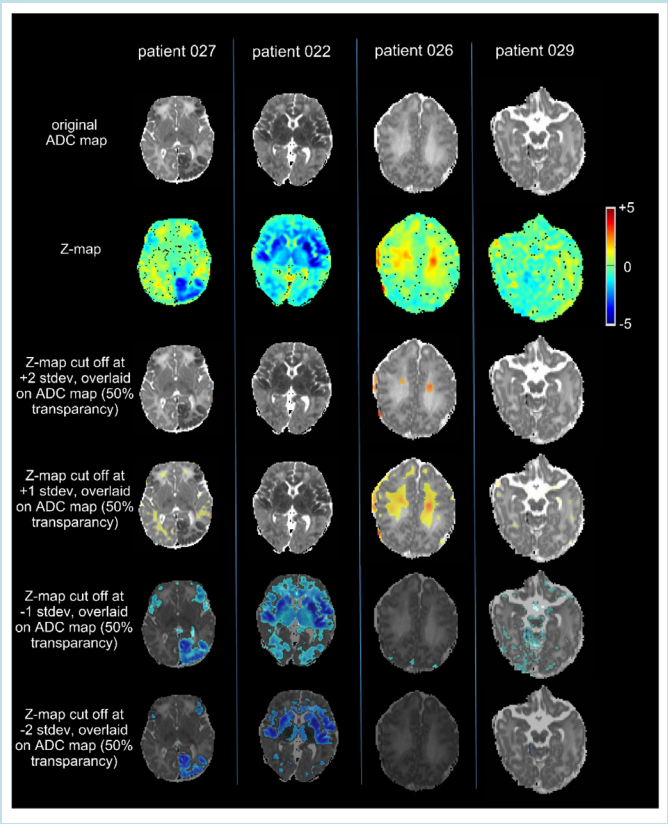
Trachel aspirate-derived mesenchymal stromal cells reveal transcriptional dynamics of lung development in preterm infants

Bronchopulmonary dysplasia (BPD) is the most common long-term pulmonary complication associated with extreme preterm birth. A major challenge to development of adequate prevention and treatment strategies is limited understanding of BPD endotypes—subsets of patients with distinct pathobiological mechanisms. 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 lines. WGCNA identifed 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. Within the GA module, gene ontology (GO) and protein-protein interaction analysis (STRING) identified developmental stage-specific signaling pathways (e.g., TGF-beta, FGF, and Wnt/beta-catenin) and transcription factors (Foxf2, Twist2, GRHL1). Within the BPD module, GO and STRING analysis identified a strong enrichment of various extracellular matrix components (e.g. LOXL1, COL6A1, ITGA7) known to be part of a functionally interconnected network perturbed in BPD. The transcriptomes of tracheal aspirate-derived MSCs show a clear association with late stage human lung development in preterm newborns and the severity of BPD. The translational potentials of our findings are important because tracheal-aspirate derived MSCs represent a novel ex-vivo system to study the premature human lung. Further studies are necessary to investigate the predictive potential of the MSC molecular landscape and to validate it as a biomarker for BPD.



Single-Cell RNA Sequencing Reveals Metallothionein Heterogeneity during hESC Differentiation to Definitive Endoderm

Differentiation of human pluripotent stem cells toward definitive endoderm (DE) is the critical first step for generating cells comprising organs such as the gut, liver, pancreas and lung. This in-vitro differentiation process generates a heterogeneous population with a proportion of cells failing to differentiate properly and maintaining expression of pluripotency factors such as Oct4. RNA sequencing of single cells collected at four time points during a 4-day DE differentiation identified high expression of metallothionein genes in the residual Oct4-positive cells that failed to differentiate to DE. Using X-ray fluorescence microscopy and multi-isotope mass spectrometry, we discovered that high intracellular zinc level corresponds with persistent Oct4 expression and failure to differentiate. This study improves our understanding of the cellular heterogeneity during in-vitro directed differentiation and provides a valuable resource to improve DE differentiation efficiency.



Neonatal brain imaging—first dataset to launch the Partners Clinical Imaging Bank

Hypoxic-ischemic encephalopathy (HIE) affects 1-3 per 1000 live births and is a leading cause of neurologic morbidity and mortality in childhood. The etiology of HIE is complex and is often multi-factorial with potential contributing factors from the fetus, placenta, maternal health, intrapartum events, and early resuscitative care. Identifying risk factors through a more detailed understanding of the clinical course and from quantitative imaging biomarkers may lead to improved prognostication paradigms that can aide medical providers and families in management decisions in this high-risk patient population. Over the last decade, Therapeutic hypothermia (TH) has been shown to improve neurodevelopmental outcomes in infants with HIE and is considered standard therapy. The MGH Neonatal Intensive Care Unit (NICU) implemented the TH protocol in February 2009; however, the impact of this intervention on institutional HIE clinical and imaging data have not been rigorously evaluated to date.

We have created a comprehensive database of the patients with HIE treated at MGH from 2003-2017. Our clinical and imaging repository was used as the first dataset to launch the Partners Clinical Image Bank (CIB), a portal for researchers to access imaging and clinical data through RPDR. This database encompasses the potential risk factors resulting in HIE, details of their NICU stay through expert chart review, imaging data reviewed by neuroradiologists, and developmental outcome for those still in the Partners electronic healthcare records system. Our goal is to quantify the extent to which clinical data and imaging biomarkers can determine the long-term developmental outcomes of these infants.

Psychiatry

Department Report

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, 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 23 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 FY17, the department had more than $65 million in research support, continuing its record of successful funding despite an increasingly challenging funding environment.

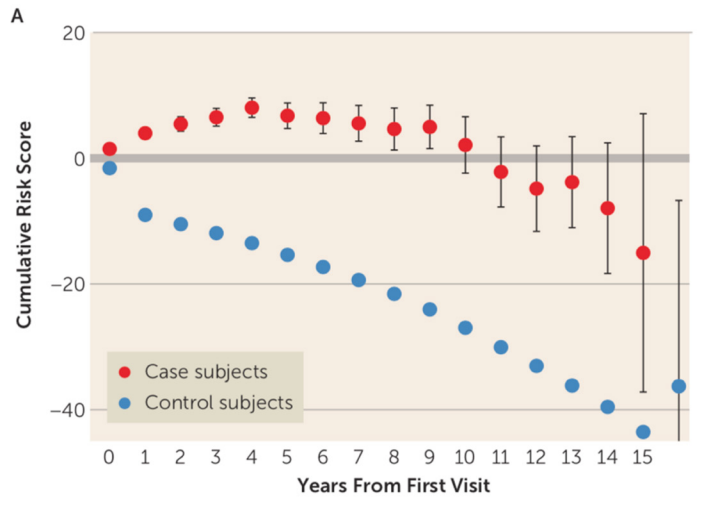
Professional Education: The Department of Psychiatry offers in-depth postgraduate education that trains the next generation of mental health professionals. For our colleagues at MGH and across the globe, our experts share the latest clinical and research advances to help improve access to and quality of psychiatric care. Each year, we train 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, clergy 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.

Last year, the Psychiatry Academy began another new program, Mass General Visiting. Visiting's goal is to reduce the risks and disparities associated with physician shortages in health care systems, with goals to: improve patient outcomes, strengthen education and provide quality leadership. We utilize our expertise to provide customized solutions for provisional clinical services, telehealth, interim leadership personnel, continuing medical education, and clinical and financial consultation.

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. 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.

Achievements

Barak-Corren et al 2017: Predicting Suicidal Behavior From Longitudinal Electronic Health Records.
Suicide is one of the leading causes of death worldwide, and the second leading cause of death among young people. Most people who die by suicide are seen by clinicians in the year prior to their death, making healthcare systems an important setting for suicide risk prediction and prevention. Unfortunately, there is no accepted algorithm that clinicians can use to combine information about the multiple factors that may indicate high risk for a suicide attempt in the near future. Thus, clinicians are left to use their intuition as a guide, which unfortunately is no better than chance at predicting suicidal behaviors. The growing adoption of electronic health records (EHRs) has created a powerful opportunity to develop new tools for identifying patients who may be at risk of self-harm. Here, we leveraged data commonly available in EHRs



Suicidal behavior risk scores over time: Classifier separates cases (red) from (controls) early and progressively overtime.

to develop and validate a model aimed at predicting suicide attempts or death by suicide in the Partners Healthcare System. Using data spanning 15 years from more than 1.7 million patients and integrating thousands of variables, our Naïve Bayes Classifier models were able to identify nearly half of all suicides and suicidal behaviors an average of 3–4 years in advance. Validation of the prediction tool in 5 independent health systems is in progress with the goal of developing an EHR-based clinical alert system to help reduce the risk of suicide attempts or death.

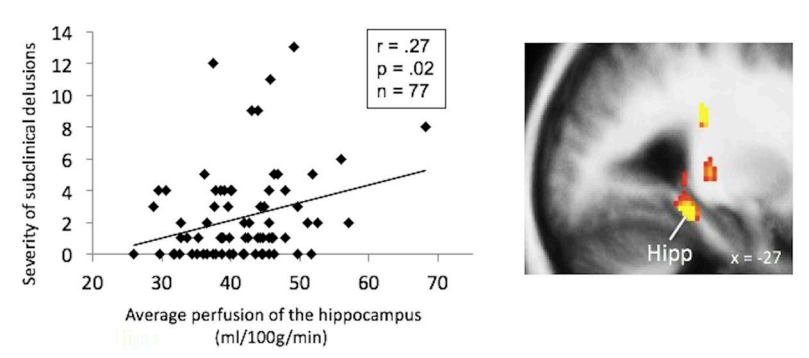
Barak-Corren Y, Castro VM, Javitt S, Hoffnagle AG, Dai Y, Perlis RH, Nock MK, Smoller JW*, Reis BY. Predicting Suicidal Behavior From Longitudinal Electronic Health Records. Am J Psychiatry. 2017 Feb 1;174(2):154-162.

Qian et al. 2017: APOE-related risk of mild cognitive impairment and dementia for prevention trials: An analysis of four cohorts.
The gene APOE-e4 is associated with increased risk and earlier onset of Alzheimer's dementia. With lifetime risk estimated as high as 50-67%, those with two copies of this gene ("APOE-e44") are being targeted for prevention trials. Dr. Deborah Blacker of MGH Psychiatry was asked to develop more refined estimates of APOE-e44-associated risk that would allow potential participants in a prevention trial to compare the risk of developing Alzheimer's to any risk associated with the study drug. Working with first author Dr. Jing Qian at U. Mass Amherst and biostatistical colleague Dr. Rebecca Betensky, along with a team of twelve other investigators across seven institutions, Dr. Blacker examined prospective data from 16,844 individuals, 292 with APOE-e44, from four different samples of cognitively normal older individuals aged 60-75. Five-year risk of dementia or mild cognitive impairment within groups based on number of copies of APOE-e4 and age was highly variable across the four samples, but risk to age 85 ("lifetime risk") was more consistent, ranging from 31-40% for those with APOE-e44. The study showed how differences in age, ethnicity, education, and family history of dementia within the samples, along with differences in screening and assessment methods, can lead to substantial differences in risk estimates across different studies. Understanding that risk of Alzheimer's dementia in those with APOE-e44 is lower than previously estimated may be valuable to those receiving results from medical or "recreational" genetic testing, those considering joining prevention trials, or to those designing observational or intervention studies in this population.

Qian J, Wolters FJ, Beiser A, Haan M, Ikram MA, Karlawish J, Langbaum JB, Neuhaus JM, Reiman EM, Roberts JS, Seshadri S, Tariot PN, Woods BM, Betensky RA, Blacker D. APOE-related risk of mild cognitive impairment and dementia for prevention trials: An analysis of four cohorts. PLoS Med. 2017;14(3):e1002254. Epub 2017/03/23. doi: 10.1371/journal.pmed.1002254. PubMed PMID: 28323826; PMCID: PMC5360223.

Wolthusen et al 2017: Neuroimaging evidence for the continuum model of psychosis.
Delusions are a defining symptom of psychotic disorders. Recent epidemiological studies suggest that delusion-like beliefs may be on an etiological continuum and share some pathophysiological mechanisms with delusions in psychotic disorders, given their common risk factors. However, there have been few studies that have tested whether patterns of brain activity associated with subclinical delusions are similar to those observed in patients with psychotic disorders, such as schizophrenia. A recent study conducted at the MGH/HST Athinoula A. Martinos Center for Biomedical Imaging tested whether overactivity of the hippocampus, which has been frequently observed in schizophrenia, is also present in individuals with subclinical, non-impairing delusional beliefs. Using arterial spin labeling functional magnetic resonance imaging (ASL fMRI), this study showed that the severity of subclinical delusions predicted the resting activity (perfusion) of the hippocampus bilaterally in a cohort of 77 individuals without psychiatric illness. The observation of hippocampal overactivity in association with psychotic experiences in non–help-seeking, relatively healthy individuals indicates that at least some aspects of this psychosis-related neural phenotype can be observed and studied in populations that are not affected by the typical confounds associated with having a serious mental illness. Given the overall consistency of findings across studies using a wide range of methods, hippocampal overactivity may also represent a useful target for testing potential novel interventions, both in animal models of psychosis and clinical trials.

Wolthusen RPF, Coombs G, Boeke EA, Ehrlich S, DeCross SN, Nasr S, Holt DJ (2017). Correlation between levels of delusional beliefs and perfusion of the hippocampus and an associated network in a non-help seeking population. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. Advance online publication, 13 July 2017, doi: 10.1016/j.bpsc.2017.06.007



The scatter plot (left panel) displays a significant correlation (corrected for effects of potential confounds, such as age, hippocampal volume, levels of depressive and anxiety symptoms, and signal-to-noise ratio) between hippocampal perfusion (average of both hemispheres) and total Peters et al. Delusions Inventory (PDI) score in a non-help-seeking, healthy cohort. The results of a voxelwise regression analysis conducted in the same dataset (right panel), in which total PDI score was used as a regressor, confirmed the correlation. Hipp, hippocampus.

Jay S. Loeffler, MD, Chief

Clinical, translational, and laboratory-based biology research are critical components of the MGH Department of Radiation Oncology. Presently, there are four main pillars of research within the Department of Radiation Oncology including the Cellular and Molecular Radiation Oncology Laboratory, the Edwin Steele Laboratory, the Medical Physics Research Group, and the Proton Research Group. It is anticipated that research conducted in these areas will lead to improved approaches to radiation therapy in cancer treatment and further understanding the mechanisms of radiation-induced cancer, leading to development of novel targets for cancer therapy and new preventative approaches.

- In FY17 the Department of Radiation Oncology maintained 37 active clinical trials (with an additional 3 that were completed) and 280 clinical trial accruals.
- Rakesh Jain, PhD, of the Steele Lab, was recognized as One of the Most Cited Authors by Cancer Research.
- Dai Fukamura, PhD, of the Steele Lab, was elected as a fellow of the American Institute of Medical and Biological Engineering (AIMBE).
- Zohreh Amoozgar, PhD, of the Steele Lab, received the 2017 Tosteson Fellowship Award for her project on understanding the role of T-regulatory cells in shaping brain tumor microenvironment and therapeutic responsiveness to immunotherapy. This understanding should provide insight for other combinatorial regimens that specifically target T regulatory cells, and thus enhance therapeutic responsiveness to current immunotherapies. Importantly, this study has the potential to translate to viable clinical trials.
- Hadi Tavakoli Nia of the Steele Lab has received the F32 NRSA Fellowship Award from the National Institutes of Health (NIH) and National Cancer Institute (NCI) for his work titled, "Alleviating Solid Stress to Overcome Immunotherapy Resistance in Metastatic Breast Cancer.
- In February 2017, "Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer" authored by MGH Radiation Oncology's Drs. William Shipley and Anthony Zietman, along with 19 co-authors from the NCI clinical trial group NRG / RTOG was published in the New England Journal of Medicine.
- Alphonse G. Taghian, MD, PhD, FASTRO,director of Lymphedema Research Program, has been honored as a Fellow of the American Society for Radiation Oncology (ASTRO). An ASTRO fellow designation honors individuals who have been active, emeritus or international members of the society for at least 15 years, given the equivalent of 10 years of service to ASTRO, and significantly added to the field of radiation oncology in the areas of research, education, patient care, or service and leadership.
- The American Association for Women Radiologists (AAWR) has chosen Dr. Nancy Tarbell as the 2017 recipient of the Marie Sklodowska-Curie Award. This award is given to an individual who has made outstanding contributions to the field of radiology/radiation oncology.
- In October 2017, the Lustgarten Foundation Pancreatic Cancer Interception Translational Research Team was announced as one of the four new pancreatic and lung cancer Stand Up to Cancer teams. Team members include: Dave Ryan, Ted Hong, David Ting, Ryan Corcoran, Carlos Fernandez, Cristina Ferrone, and Beow Yeap. Special recognition should also go out to Rakesh Jain and his entire team who provided the scientific rationale for the project and provided the early pre-clinical science.
- In June 2017, Dr. Herman Suit was recognized by Giants of Cancer Care for his contribution to the field of Radiation Oncology. The Giants of Cancer Care award celebrates pioneers, innovators, and future generations of leaders who have been selected by their peers for their remarkable achievements in oncology research and clinical practice.
- Rakesh Jain, PhD, receives Life-Time Achievement in Cancer Research Award from the American Association of Indian Scientists in Cancer Research (AAISCR).
- Department of Radiation Oncology hosted a research retreat on September 14, 2017 titled Immunotherapy and Radiation Medicine. The key note speaker, Dr. Nir Hacohen's, discussion, "Learning the rules of human immunity and applying them to therapy" led seamlessly into talks by Drs. Ted Hong, Rakesh Jain, and Harald Paganetti on Immuno-Oncology Research.
- The Radiation Oncology Nursing team's poster abstract titled "Engaging Staff in Interdisciplinary Ethics Rounds," was accepted for the National Nursing Ethics Conference.

Radiology

Department Report

James A. Brink, MD, Chief

The Department of Radiology provides excellence in patient care, teaching and research. The research mission of the Department includes primary research within radiology and extensive collaborative research with investigators from most Departments and Centers at MGH. Our strategic priority is the continuous development of intellectual and physical resources to enable researchers within and outside of Radiology to translate their research goals into clinical applications.

Primary Radiology research includes: 1) instrumentation and algorithm development for data acquisition and analysis including machine learning, to discover and/or measure novel biological processes and structures; 2) design and synthesis of molecular agents (PET, MR, optical) for assessment of receptors, abnormal proteins and other biological targets of disease; 3) assessment of novel instrumentation and molecular imaging agents in preclinical disease models and in clinical research; 4) translation of these discoveries, in concert with industry, into patient care and; 5) development and application of analytic tools to support economically-based assessment of medical imaging technologies and outcomes research. Our research enterprise is achieved through three Radiology Centers (The Martinos Center, The Gordon Center and The Center for Clinical Data Science); The Institute of Technology Assessment; several research Programs including the Cardiac MR PET CT Program (a joint radiology cardiology program) and a Program in Neuroprotection. The Department also operates three 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.

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 (FY17 > $70M) received. Over 200 Radiology faculty members serve as principal investigators on one or more grants, either from the NIH or other funding sources, with total research funding over $100M for 2017. Through its research Centers, major Programs and Core facilities, the Department has significantly enabled the research efforts of many investigators in Cardiology, Emergency Medicine, Neurology, Oncology, Pathology, Psychiatry, Radiation Medicine, Surgery and other MGH Departments.

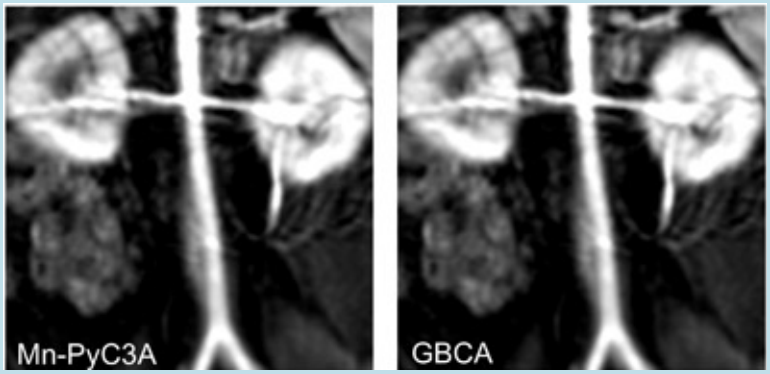
Martinos Center for Biomedical Imaging: Director, Bruce Rosen, MD, PhD

In late 2017 Larry Wald, the Director of the Magnetic Resonance Physics & Instrumentation Group at the Martinos Center, was awarded a grant through the National Institutes of Health's BRAIN Initiative that will support design and construction of the first magnetic particle imaging (MPI) scanner for imaging of the human brain. Once completed and validated, the technology will offer an exciting new means to study activity in the brain. Ultimately, it could replace functional MRI as the premier functional neuroimaging tool. The award follows a 2014 BRAIN Initiative grant—one of the first announced by NIH—which funded work by Dr. Wald and his group assessing the potential of MPI: examining the barriers to its use for neuroimaging in humans and, through simulations, testing the performance of various MPI scanner designs. An MGH Research Scholar Award, which Dr. Wald received the following year for the project "Magnetic Particle Imaging for Breast Cancer Screening and Monitoring," afforded further opportunities to explore the potential of the emerging technology.

In a study reported in April in the journal Brain, a team of investigators led by the Martinos Center's Vitaly Napadow explored the relationship between acupuncture and the alleviation of pain in carpal tunnel syndrome. The functional MRI study looked at real and sham acupuncture and found that, while both alleviated the symptoms of carpal tunnel, real acupuncture also improved outcomes by remapping the areas of the brain associated with pain. Importantly, these changes in the brain proved to be predictors of long-term symptom relief in carpal tunnel patients. The study also offered insight into the differences between real and sham acupuncture. Sham acupuncture may produce a stronger placebo effect than a pill, for example, because it sends inputs to the brain via skin receptors and is coupled with a specific ritual. Nonetheless, the symptom improvement produced by sham treatment for conditions like carpal tunnel may derive from entirely different mechanisms than those elicited by real acupuncture, which might more specifically target carpal tunnel syndrome pathophysiology.

Manganese-based MR contrast agent may be safer alternative to gadolinium-based agents. In November, The Martinos Center's Peter Caravan and colleagues reported a potential alternative to gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging. In a paper published online in the journal Radiology, they described the manganese-based agent Mn-PyC3A and showed in a primate model that it produced contrast enhancement of blood vessels equivalent to that of gadolinium-based agents, which carry significant health risks for some patients.

The researchers developed the manganese-based agent based on two properties of the element: its ability to produce an MR signal comparable to that of GBCAs and the fact that that manganese is an essential element, and intake of small amounts is required for vital bodily functions. Because of this, the body has natural mechanisms to process and excrete excess manganese. In contrast, any gadolinium that is released from GBCAs is likely to be retained in the body indefinitely.



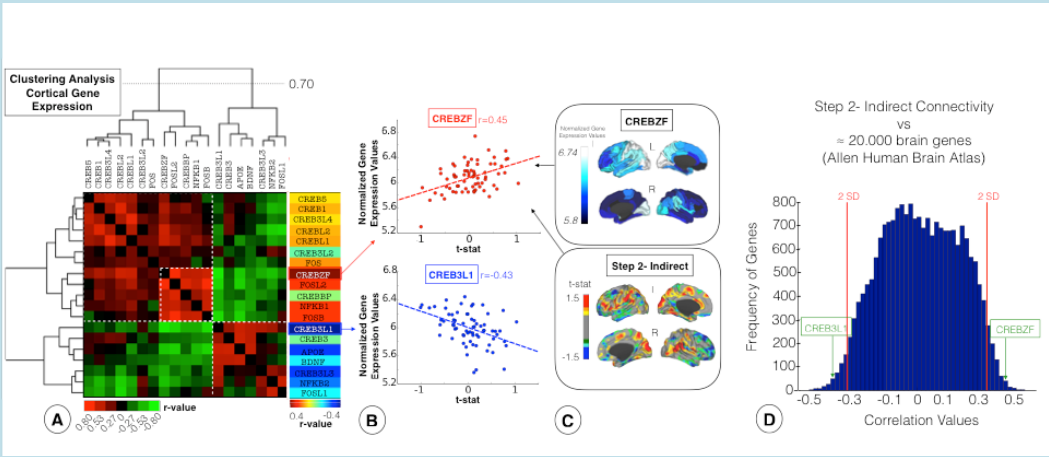
A contrast-enhanced MR abdominal image showing the abdominal aorta, renal arteries and kidneys of a baboon made with manganese-based agent Mn-PyC3A (left) shows comparable detail to an image of the same animal made using a gadolinium-based contrast agent (right) (Eric Gale, PhD).

Gordon Center for Medical Imaging: Director, Georges El Fakhri, PhD

This has been an exciting year for the Gordon Center for Medical Imaging with the funding of the first P41 Biomedical Technology Resource Center in the US in the field of PET (there are 25 BTRC currently funded by NIBIB). The grant provides long term funding for the Center for developing PET/MR technologies and evaluating their medical impact.

Hak Soo Choi, PhD and his team have published a novel and high impact work in Accounts of Chemical Research [49(9):1731-1740] that describes the design principles of site-specific fluorescence contrast agents that represent a versatile arsenals to surgeons for real-time intraoperative navigation as well as image-guided targeted therapy. NIR fluorescence imaging combined with targeted NIR fluorophores can simultaneously guide surgeons with the real-time delineation of diseased tissue while preserving vital tissues. Admittedly, NIR imaging technology has been slow to enter clinical use mostly due to the late-coming development of truly breakthrough contrast agents for use with current imaging systems. Dr. Choi has developed a versatile library of tissue-specific targeted NIR fluorophores targeting pancreatic, thyroid and other cancers which offers clinicians an array of possibilities that will improve intraoperative success and long-term post-operation prognosis.

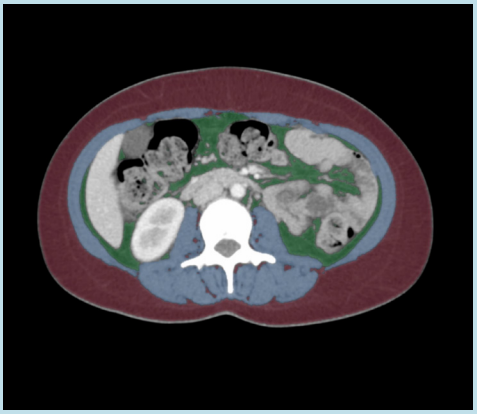
Ortiz-Terán et al. (PNAS [114(26):6830-6835] has opened a new field at the intersection of genetics and neuroimaging, with potential therapeutic implications in the field of neuroplasticity in children with blindness. It is the first scientific research characterizing how brain gene expression profiles map onto brain regions exhibiting functional connectivity neuroplastic reorganization following sensory deprivation in blind children. Specifically, the brain areas showing the most reorganization were areas expressing the highest rates of CREB-family gene expression levels. This suggests that neuromodulation efforts to facilitate adaptive plasticity should be targeted towards these higher-order cortical areas and related genetic profiles. This work has been awarded a prize at the MGH research day of 2017.



Brain plasticity-gene expression relationships in blindness. (A) An analysis of the relationship between transcription levels of neuroplasticity-related genes from a canonical human brain atlas. A coexpression matrix is shown based on the spatial similarity of transcription levels between genes. The green (positive correlation) and red (negative correlation) colors represent similarity in the expression between gene's cortical expression. (B) An analysis of the relationship between gene expression profiles and main connectivity changes in blind individuals. The x axis represents the blind-sighted step 2 connectivity difference. The y axis represents the gene expression score. (C) The spatial distribution of the CREBZF gene (Top) and functional connectivity changes in the indirect connectivity (Bottom) represented in cortical maps. (D) A histogram is displayed presenting the location of CREBZF and CREB3L1 among all topological similarities between ~20,000 genes.

The MGH BWH Center for Clinical Data Science: Director, Mark Michalski, MD

The CCDS is focused on the full life cycle of research and development for machine learning enabled clinical applications, from early stage



CT slice showing automatically segmented muscle (blue), peripheral (red) and visceral (green) fat with mean DICE coefficients of 0.96 ± 0.04, 0.97 ± 0.06 and 0.94 ± 0.07, respectively.

fundamental research, to prototype development, through to clinical validation and commercialization. The CCDS has developed more than a dozen machine learning algorithm models internally, and translated several applications into the clinical arena. Example applications include detection and characterization of stroke from CT and from MRI studies; level-by-level spinal vertebrae and disc localization from MRI; muscle, visceral and subcutaneous fat segmentation on CT images for population health studies (Figure); vital sign monitoring in acute care settings.

Additionally, the CCDS has developed a variety of tools to facilitate machine learning research. These include data access, de-identification and curation tools; web-based textual report as well as image pixel data annotation tools; a machine learning algorithm validation pipeline; and clinical integration applications. The Center makes its significant compute infrastructure available to researchers in the PHS community.

MGH Institute for Technology Assessment: Director, Pari Pandharipande, MD, MPH

In 2017, the MGH Institute for Technology Assessment (ITA) once again experienced a productive year of policy-relevant accomplishments in decision science and health outcomes research. Dr. Chin Hur and Dr. Jagpreet Chhatwal – together with a multicenter team from MGH – used a state-transition model to compare the benefits, harms, and costs of bariatric surgery for adolescents with severe obesity. They leveraged published results from the Teen-Longitudinal Assessment of Bariatric Surgery study. Under a societal willingness-to-pay threshold of $100,000/quality-adjusted life year, they found that bariatric surgery was not cost-effective under a time horizon of three years, but was under a horizon of five years. They also provided critical insight into those factors that most influenced their results – e.g., short-term costs of bariatric surgery, and risks of late complications, specific to the adolescents – underscoring the need for further, longitudinal data collection to evaluate these important outcomes.

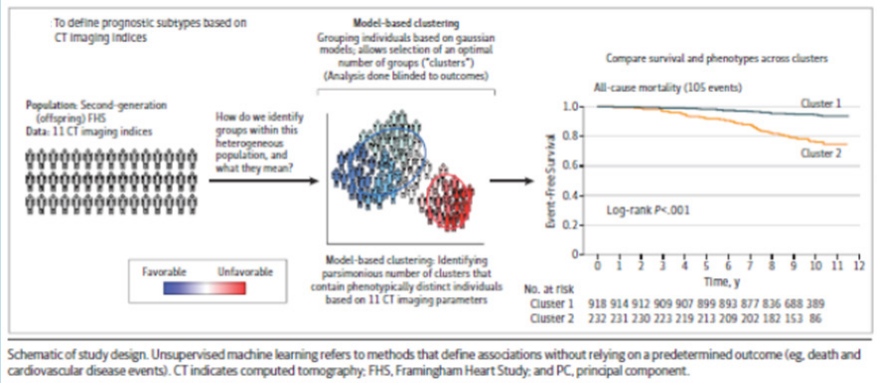
In addition, the ITA's focus on cancer modeling and imaging continues to grow. As an example, Dr. Pandharipande and Dr. Amy Knudsen – together with a team of national experts on incidental findings – used decision-analytic modeling techniques to determine the effects of patient age and comorbidity level on life expectancy (LE) benefits associated with imaging surveillance of low-risk incidental findings detected on CT or MRI. They focused on two common findings, complex renal cysts (Bosniak IIF) and pancreatic side-branch intraductal papillary mucinous neoplasms (SB-IPMNs). Their results exposed the substantial extent to which age and comorbidity affect the LE benefits achievable from surveillance. For example, five-year follow-up of Bosniak IIF cysts in the youngest, healthiest cohort evaluated (60-year-old women with no comorbidities) was projected to yield a 6.5-month LE benefit. For a cohort of the same gender/age but with severe comorbidities, this estimate was 3.9 months. In 80-year-old women, corresponding estimates were 2.8 and 1.5 months, respectively. The results underscore the importance of patients' individual circumstances and preferences in follow-up decisions (JAMA Surgery 2017; 152(2): 136-141).

Cardiac MR PET CT Program: Director, Udo Hoffmann, MD, MPH

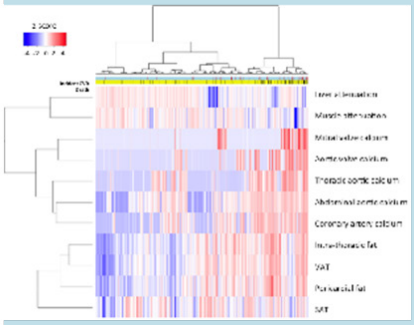
For the MGH Cardiac MR PET CT program 2017 was another successful year using advanced multimodality imaging technology to answer key biological questions such as 1) the link between inflammatory and immune activation with advanced coronary atherosclerosis and heart failure in patients with HIV, rheumatoid arthritis, and cancer and 2) the brain heart axis and how psychosocial stress promotes CVD.

Dr. Ravi Shah and colleagues used unsupervised machine learning to identify a healthy multiorgan cardiometabolic phenotype based on 11 quantitative CT–based measures of atherosclerosis, adiposity, liver and muscle composition in >1100 participants of the Offspring Cohort of the Framingham Heart Study. A healthy phenotype was associated with a 2-fold increased hazard of death at 10 years, robust to adjustment for age, sex, risk factors, and individual phenotypes. Machine learning may evolve as a tool to improve primary prevention and identify new therapeutic targets, especially in in elderly asymptomatic Americans. Shah RV et al. Association of Multiorg Phenomap of Cardiovascular Health. JAMA Cardiology 2017.

The PROMISE trial continues to shape the evidence base for the power of non-invasive cardiovascular testing. Dr. Hoffmann and colleagues demonstrated in more than 9000 patients with stable chest pain randomized to anatomic vs. functional testing that the discriminatory ability of



Schematic of study design. Unsupervised machine learning refers to methods that define associations without relying on a predetermined outcome (eg, death and cardiovascular disease events). CT indicates computed tomography; FHS, Framingham Heart Study; and PC, principal component.



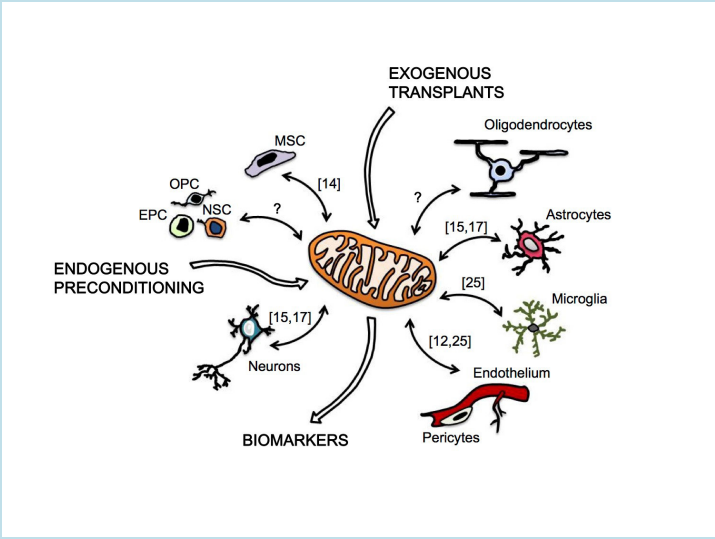
Hierarchical Clustering of 11 CT derived phenotypes

coronary CTA in predicting cardiovascular events was significantly higher as compared to stress testing (c-index, 0.72; 95% CI, 0.68–0.76 versus 0.64; 95% CI, 0.59–0.69; P=0.04). Hoffmann U et al. Prognostic Value of Noninvasive Testing. Circulation 2017.

In a translational setting, Dr. Ahmed Tawakol extended prior observations linking amygdala activity to increased inflammation, to assessment of inflammatory and immune activity in HIV-infected tissues such as lymph nodes and the arterial wall. The work demonstrated that while lymph node and arterial inflammation was increased in HIV, inflammatory activity in these tissues was not related. Moreover, measures of HIV disease activity were strongly associated with LN inflammation but not with arterial inflammation. These data suggest that LN and arterial inflammation do not share underlying pathways of immune activation and that therapeutic interventions that reduce viral disease activity may not predictably reduce arterial inflammation in HIV or its downstream consequence. Tawakol A et al. Association of Arterial and Lymph Node Inflammation With Distinct Inflammatory Pathways in HIV. JAMA Cardiology, 2017.

Program in Neuroprotection Research: Unit Chief, Eng H. Lo, PhD

The Program in Neuroprotection Research is focused on experimental and translational research in stroke, brain injury and neurodegeneration. We collaborate widely within and outside of MGH using a combination of in vivo imaging tools and molecular biology methods. Over this past year, we have continued to pursue the phenomenon of extracellular mitochondria transfer as a mechanism of "help-me signaling" between different CNS cell types. Our latest findings suggest that extracellular mitochondria can be detected not only in cell and animal models, but also in human cerebrospinal fluid, where they may correlate with clinical outcomes after brain injury.



Mitochondrial transfer has been reported in mesenchymal stem cells, neurons, astrocytes, microglia and endothelial cells. Transplant of exogenous mitochondria may offer novel ways to augment neurorepair after CNS injury. To complement transplant approaches, extracellular mitochondria may also be preconditioned to further amplify therapeutic benefit. Finally, insofar as extracellular mitochondria may reflect intracellular metabolism, they may also represent a novel class of biomarkers in the CNS.

Chou et al, Extracellular mitochondria for therapy and diagnosis in acute central nervous system injury. JAMA Neurol 2017.
Chou et al. Extracellular mitochondria in cerebrospinal fluid and neurological recovery after subarachnoid hemorrhage. Stroke 2017.

Ragon Institute of MGH, MIT and Harvard

Department Report

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 immunology. The Institute was founded with an original commitment of expendable funds of $10 million per year for 10 years from Terry and Susan Ragon. They have since made an additional commitment to extend this funding through 2023, as well as an endowment to insure the long-term viability of the Institute. With ten faculty using innovative methods to address the challenges of various human diseases, along with additional Associate Members, the Institute is well positioned to make significant contributions to the field of immunology, and more specifically to the global effort to develop an HIV/AIDS vaccine. What makes us 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.

New Imaging Facilities

In the past year, the Ragon Institute Imaging Facility has undergone a significant expansion in instruments and technical support, providing cutting edge technologies and services to the Institute and MGH research community through access, training, and consultation in high-end flow cytometry, imaging flow cytometry, cell sorting, advanced microscopy applications, and image analysis. New instruments include two new cell sorters, a custom upgraded TissueFAXS slide scanner to 10-color fluorescence capability for both tissue and cell culture imaging (the first of its kind), installation of a Zeiss Lightsheet 3D imaging system for high speed imaging of larger whole samples, a Zeiss Elyra PS1/LSM780 confocal/super resolution system, and an Olympus FV1000 dual two-photon system for live tissue imaging. Cell sorting, flow cytometry and microscopy are also available in a state of the art BSL3 facility. These systems afford MGH investigators cutting edge high-throughput tissue scanning, super resolution, 3D imaging, and live deep tissue imaging, which are accessed through core services or through collaboration with Ragon Institute investigators. In the past year, Core instrumentation was used to contribute to the work of over 70 principal investigators from MGH, MIT, Harvard, and surrounding academic and industry groups, generating over $500,000 in core income and contributing to dozens of publications.

Start of the Ragon-supported clinical efficacy trial

In November of 2017, we initiated a clinical efficacy trial in South Africa of a novel preventive HIV vaccine regimen developed by researchers at the Ragon Institute of Massachusetts General Hospital (MGH), MIT and Harvard, Beth Israel Deaconess Medical Center (BIDMC), and Partners. The vaccine regimen being tested was originally developed by Ragon Institute founding member Dan H. Barouch, MD, PhD, and is designed to induce immune responses to the many different strains of the virus found in the world. Called the Imbokodo trial from the Zulu word for "rock" – echoing a South African proverb that refers to the strength of women and their importance in the community – the new study will involve 2,600 women in southern Africa. The trial is being supported by the Ragon Institute, the National Institutes of Health and the Gates Foundation, and Janssen Pharmaceuticals. Optimism is based on Ragon Institute-supported testing in several animal models, which showed greater than 90% per exposure protection.

Detection and treatment of Fiebig stage I HIV-1 infection in young at-risk women in South Africa: a prospective cohort study

Dong, KL, Moodley A, Kwon DS, Ghebremichael MS, Dong M, Ismail N, Ndhlovu ZM, Mabuka JM, Muema DM, Pretorius K, Lin N, Walker BD, Ndung'u T. Detection and treatment of Fiebig stage I HIV-1 infection in young at-risk women in South Africa: a prospective cohort study. Lancet HIV. 2017 Sep 29. pii: S2352-3018(17)30146-7. doi: 10.1016/S2352-3018(17)30146-7. [Epub ahead of print] PubMed PMID: 28978417.

In order to define the initial battle between virus and host just as HIV infection is starting, and the impact of immediate treatment, we established a cohort of uninfected women in South Africa who were followed twice weekly for evidence of acute infection. 945 uninfected women were enrolled and followed twice weekly through a research site established at a shopping mall in an impoverished township near Durban, in order to avoid stigma associated with attending a medical clinic. At each visit they participated in an empowerment curriculum including life skills, job readiness training, interview skills, computer training, and HIV prevention education, with the goal of employment at the end of a year in the program. At each visit, they were tested for HIV infection by finger prick for HIV RNA. 42 women were diagnosed with acute HIV infection (incidence 8·2 per 100 person-years, 95% CI 5·9–11·1), of whom 36 (86%) were diagnosed in Fiebig stage I infection with a median initial viral load of 2·97 log10 copies per mL (IQR 2·42–3·85). 23 of these 36 women started ART at a median of 1 day (1–1) after detection, which limited the

median peak viral load to 4·22 log10 copies per mL and prevented CD4 T cell destruction. 385 women completed the 48 week socioeconomic intervention, of whom 231 were followed up for 1 year. 87% were placed in jobs, returned to school, or started a business. The study shows that frequent HIV screening combined with a socioeconomic intervention facilitated sampling and risk assessment before and after infection. In addition to detection of acute infection and immediate treatment, we established a cohort optimized for prevention and cure research.

A switch from canonical to noncanonical autophagy shapes B cell responses
Martinez-Martin N, Maldonado P, Gasparrini F, Frederico B, Aggarwal S, Gaya M, Tsui C, Burbage M, Keppler SJ, Montaner B, Jefferies HB, Nair U, Zhao YG, Domart MC, Collinson L, Bruckbauer A, Tooze SA, Batista FD. A switch from canonical to noncanonical autophagy shapes B cell responses. Science. 2017 Feb 10;355(6325):641-647. doi: 10.1126/science.aal3908. PubMed PMID: 28183981.

The recruitment of Dr. Facundo Batista to become Associate Director of the Ragon Institute has further enhanced our basic science mission, and his laboratory is already having a profound impact. In a study by Dr. Batista just published in Science, his group addressed the role of autophagy in immune responses. Autophagy is a natural, regulated process within cells that leads to breakdown of unnecessary or dysfunctional components of the cell. Despite its importance in a variety of cellular and pathophysiological situations, its role in immune responses has remained elusive. Dr. Batista's group showed that among B cells, germinal center (GC) cells exhibited the highest rate of autophagy during viral infection, and showed that this happened through an unexpected non-canonical pathway. Their results advance the field of fundamental B cell biology and vaccinology by defining this mechanism that controls B cell differentiation and fate.

Ragon Institute Employees - 400 Technology Square in Cambridge, MA

Surgery

Department Report

Keith D. Lillemoe, MD, Surgeon-in-Chief

Mission

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 particular interest.

Center for Transplantation Sciences (CTS)

The CTS is a multidisciplinary research center working at the interface between basic science and clinical applications in transplantation immunology and related fields with Joren C. Madsen, MD, DPhil, and James F. Markmann MD, PhD, serving as co-directors. The mission of the CTS 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 is a clinically driven enterprise built upon decades of collaborative clinical, basic science, and engineering activities at MGH and MIT. Clinically inspired engineers, physicians, and human biologists use creative scientific approaches to improve diagnostics and therapeutics for patient care worldwide.

Within this MGH Center, and under the same roof, the most promising discovers are nurtured and supported into therapies, devices, and diagnostics in a direct and rapid fashion. 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, Harald Ott, MD, and their teams 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. Dr. Ott and his research lab focuses on developing novel strategies to generate personalized solid organ grafts for transplantation and to repair damaged organs in vivo and ex vivo.

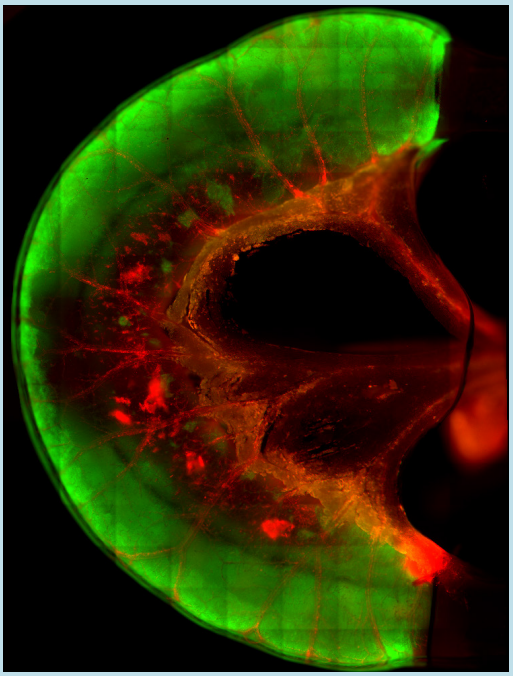
Codman Center for Clinical Effectiveness in Surgery

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.

Achievements

New protocol expands transplant tolerance application
The first report of successful transplantation tolerance induction in live donor kidney recipients in 2008 by the MGH team was a precedent setting accomplishment for the field. The protocol relied on a week of pretransplant conditioning followed by a combined live donor kidney and bone marrow transplant. Immunosuppression was successfully weaned in 70% of patients in the first iteration of the protocol, with the first recipient now 15 years post-transplant and 14 years without immunosuppression with a perfectly functioning kidney.

The tremendous success of the regimen has prompted research to modify the regimen to allow it to be used with deceased donor organs where a week of pretransplant conditioning is not logistically feasible. In the lab of Dr. Tatsuo Kawai, Center for Transplantation Sciences, delayed tolerance is now routinely achieved in non-human primates by performing kidney transplants with standard immunosuppression and after waiting 4-6 months, then conditioning the patient and administering donor bone marrow. 6/6 NHP recipients treated with novel conditioning regimens in this way have accepted their kidneys after complete immunosuppression withdrawal. This work provides the foundation for the first clinical trial of delayed tolerance induction in deceased donor kidney recipients that the team hopes to begin later this year.



A decellularized loop of rat small bowel after repopulation, with stem-cell-derived human epithelial cells (green) lining the intestine and endothelial cells (red) lining the blood vessels. (Credit: Kentaro Kitano, MD, MGH Center for Regenerative Medicine)

Human Stem Cell Based Engineered Intestine
Using human induced pluripotent stem cells (iPSCs), Dr. Harald Ott's research team has bioengineered functional small intestine segments that, when implanted into rats, were capable of deliver nutrients into the bloodstream. The study successfully bridged the gap between differentiation of single cells – driving stem cells to become a specific cell type – and the generation of tissue that shows a higher level of function – in this instance vascular perfusion and nutrient absorption in the context of transplantable tissue grafts. While previous studies have reported successful differentiation of organoids – millimeter-small units of tissue – from iPSCs, the team developed a technology that enabled these smaller units of tissue to form larger-scale grafts that someday could be used as implanted replacement organs.

Several gastrointestinal diseases, including Crohn's disease, may lead to removal of all or part of the small intestine, leading to a condition called short bowel syndrome. While it sometimes can be treated with special diets, many patients need to rely on intravenous nutrition. While small bowel transplantation is a feasible treatment option, its availability is very limited because of the organ shortage. For example, while 127 transplants were performed in the U.S. in 2015, as of October 4, 2017, 273 patients remained on the waiting list.

As with previous studies from Ott's team, this study utilizes a procedure he developed in 2008 for stripping the living cells from a donor organ with a detergent solution and then repopulating the remaining extracellular matrix scaffold with organ-appropriate types of cells. His team has decellularized animal kidneys, lungs and hearts; generated functional rat kidneys and lungs, and last year regenerated functional heart muscle in decellularized human hearts. In this study, the MGH team used that same approach to decellularize 4 cm segments of rat small intestine and confirmed the applicability of the procedure to larger animals in segments of pig intestine.

Developing stem cell therapy as a novel treatment for neurointestinal diseases
Neurointestinal diseases are characterized by abnormalities of the enteric nervous system and include conditions such as Hirschsprung disease, gastroparesis, esophageal achalasia, and others. These diseases cause significant morbidity. Current therapies aim only to treat the symptoms but don't address the underlying enteric neuronal abnormality.

Ryo Hotta MD, PhD, working in the lab of Allan Goldstein, MD, has developed efficient methods of isolating, culturing, and expanding neuronal stem cells from the rodent and human intestine. Transplantation of these cells into mouse models of Hirschsprung disease demonstrates their survival, proliferation, and differentiation, as well as active neuronal signaling. The Goldstein lab has recently established a novel model of colonic dysmotility and delayed gastric emptying by delivering diphtheria toxin to transgenic mice whose enteric nervous system expresses

the toxin receptor. These new models of neurointestinal disease are serving as a platform for testing the effects of neuronal stem cell therapy on restoring gut function in these animals. These studies are currently supported by R01 funding from the NIH. A corporate-sponsored research agreement is currently underway to move these experiments to large animal models with the goal of proving feasibility for human clinical trials.

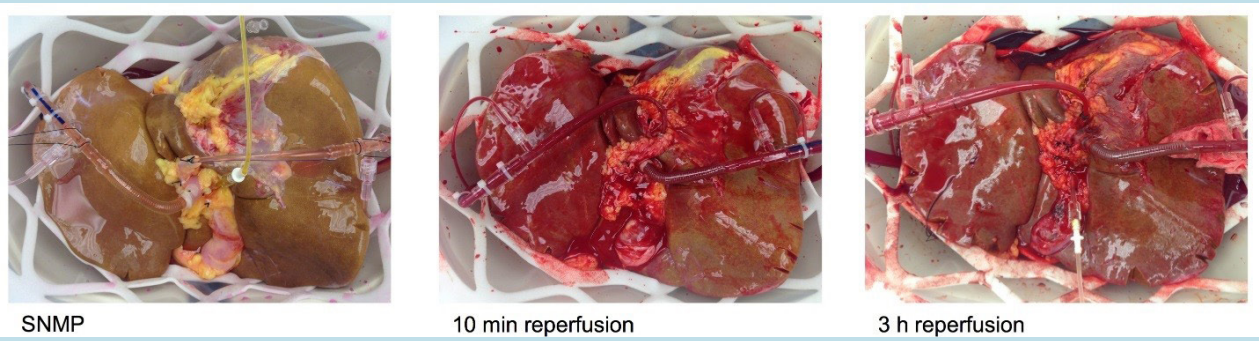
Enzyme treatment reduces alcohol-induced liver damage in mouse models

An intestinal enzyme previously shown to keep bacterial toxins from passing from the gastrointestinal system into the bloodstream may be able to prevent or reduce the liver damage caused by excess alcohol consumption. Richard Hodin, MD, and his research team, used oral doses of intestinal alkaline phosphatase (IAP) to prevent the lover damage in mouse models of both binge drinking and chronic alcohol consumption. The study also provides the first evidence of an expanded role of the liver's stellate cells in alcoholic liver disease.

Previous research by Hodin's group revealed that IAP helps to maintain a healthy intestinal microbial population. In addition, the enzyme's anti-inflammatory properties have been shown to prevent the development of metabolic syndrome in mice fed a high fat diet. These beneficial effects of IAP are thought to relate to its ability to detoxify LPS and since LPS is believed to play a role in alcohol-induced liver inflammation, the MGH team investigated whether oral IAP supplementation could prevent alcoholic liver disease. While mice that did not receive the enzyme before or during an alcohol dose were found to have elevations in their liver enzymes and developed a fatty liver, IAP supplementation prevented those effects. Activation of the hepatic stellate cells was also prevented by pretreatment with IAP. Importantly, the IAP supplementation had to occur prior to or at the same time as the alcohol consumption, whereas if it was after alcohol dosing there were no protective effects.

How to tell a good organ from bad?

With recipient safety a priority, a key issue in transplantation of marginal organs is ensuring an organ is transplantable. By studying energy cofactor levels in donor livers before and after reperfusion during transplant, Dr. Heidi Yeh and collaborators found that energy charge, a measure of the availability of high energy phosphate bonds, accurately predicts graft function and is strongly correlated to early allograft dysfunction. They also reported the development and validation of a simulated ex vivo transplant model to mimic the function of livers post-transplant.



A liver through 3 hours of subnormothermic machine perfusion.

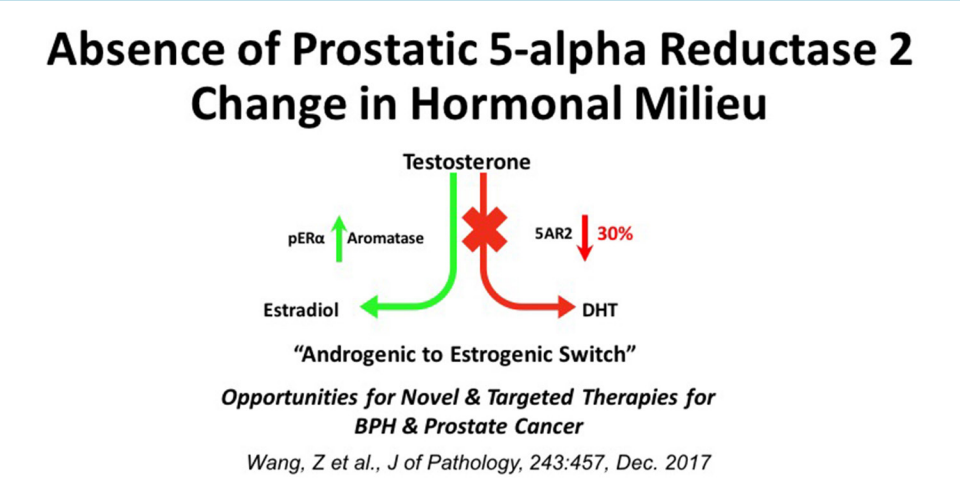
This study is a continuation of work from 2016, where the transplant team, headed by James Markmann, MD, PhD, and Heidi Yeh, MD, has been collaborating with the Center for Engineering in Medicine group led by Korkut Uygun, PhD, to develop ex vivo machine perfusion to improve the quality of organs prior to transplantation. The group utilizes discarded human livers to evaluate therapeutic interventions that may improve their quality sufficiently to make them transplantable. The group utilizes discarded human livers to evaluate therapeutic interventions that may improve their quality sufficiently to make them transplantable. Because of the heterogeneity of discarded human livers, they have developed a novel technique of splitting the discarded livers into functionally identical lobes, in order to provide a perfect control for evaluating the impact of the intervention being tested (see Fig 2). The investigators have also studied nearly 50 discarded human kidneys and found that a large proportion make urine and clear metabolites during normothermic perfusion and by criteria developed by other groups, would be transplantable.

Michael L. Blute, Sr., MD, Chief

The Department of Urology is committed to advancing urologic research through impactful translational research. 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 form NIH and Department of Defense.

Achievements:

1. Penis Transplantation: First US Experience.Cetrulo CL Jr, Li K, Salinas HM, Treiser MD, Schol I, Barrisford GW, McGovern FJ, Feldman AS, Grant MT, Tanrikut C, Lee JH, Ehrlichman RJ, Holzer PW, Choy GM, Liu RW, Ng ZY, Lellouch AG, Kurtz JM, Austen WG Jr, Winograd JM, Bojovic B, Eberlin KR, Rosales IA, Colvin RB, Ko DSC. Ann Surg. 2017 May 15. doi: 10.1097/SLA.0000000000002241. [Epub ahead of print]
2. Androgenic to oestrogenic switch in the human adult prostate gland is regulated by epigenetic silencing of steroid 5α-reductase 2.Wang Z, Hu L, Salari K, Bechis SK, Ge R, Wu S, Rassoulian C, Pham J, Wu CL, Tabatabaei S, Strand DW, Olumi AF. J Pathol. 2017 Dec;243(4):457-467. doi: 10.1002/path.4985. PMID: 28940538 [PubMed - indexed for MEDLINE]
3. 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. 2017 Dec 14. pii: S0302-2838(17)31034-5. doi: 10.1016/j.eururo.2017.12.002. [Epub ahead of print] PMID: 29249291 [PubMed - as supplied by publisher]
4. Cessation of Ureteral Colic Does Not Necessarily Mean That A Ureteral Stone Has Been Expelled. Hernandez N, Mozafarpour S, Song Y, Eisner BH. J Urol. 2017 Oct 26. pii: S0022-5347(17)77794-4. doi: 10.1016/j.juro.2017.10.032. [Epub ahead of print] PMID: 29107030 [PubMed - as supplied by publisher]
5. Zimmern P, De E Editors. Native Tissue Repair for Incontinence and Prolapse. Case-based technique with video demonstrations. Springer International Publishing Switzerland. Copyright 2017. 317 pages. DOI 10.1007/978-3-319-45268-5



5-alpha Reductase 2 is the key enzyme that regulates development and growth of prostate gland. The Olumi lab has discovered that expression of 5AR2, an enzyme once thought to be ubiquitously expressed, is epigenetically regulated, and is absent in 30% of normal adult men. In the setting when there is an "androgenic to estrogenic switch" in the prostate gland, better targeted therapies can be used for management of prostatic disases.